VOLUME 42 APRIL 15, 1977 NUMBER 8 JOCEAH

THE JOURNAL OF Organic Chemistry

PUBLISHED BIWEEKLY BY THE AMERICAN CHEMICAL SOCIETY

THE JOURNAL OF Organic Chemistry

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Published biweekly by the American Chemical Society at 20th and Northampton Sts., Easton, Pa. 18042. Second class postage paid at Washington, D.C., and at additional mailing offices.

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Notice to Authors last printed in the issue of January 7, 1977

JOCEAH 42(8) 1267–1484 (1977)
ISSN 0022-3263

THE JOURNAL OF Organic Chemistry®

VOLUME 42, NUMBER 8 APRIL 15, 1977

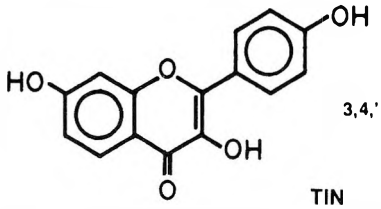
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3,4,' 7-Trihydroxyflavone (THF)

TIN

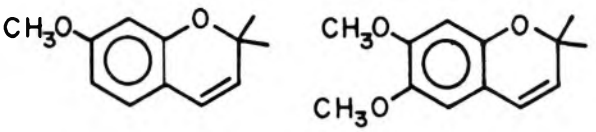
THF is 3 to 15 times more sensitive than the other commonly used tin reagents such as ammonium 6-nitro-2-naphthylamine-8-sulfonate, flavanol, or oxine-5-sulfonic acid. The method is simple and shows excellent tolerance to most common elements. The detection limit is 0.007μg (7ng) with a precision of 2% on 1 μg (100ng) quantities. Suitable for both mineral and tissue samples. T.D. Filer Anal. Chem., 43 1753-1757 (1971)

THORIUM

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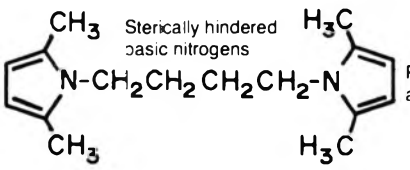
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W. S. Bowers, T. Ohta, J. S. Cleere and P. A. Marsella, Science 193, 542-547 (1976).

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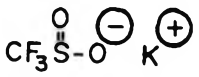
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Reactive π excessive aromatic rings

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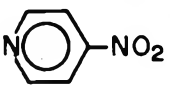
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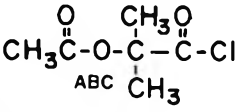
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High

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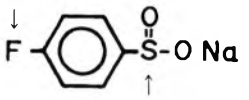


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THE JOURNAL OF Organic Chemistry®

VOLUME 42, NUMBER 8

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APRIL 15, 1977

Studies on the Total Synthesis of Steroidal Antibiotics. 2. Two Convergent Schemes for the Synthesis of Tetracyclic Intermediates[1]

Robert E. Ireland,* Pierre Beslin,[2] Rudolf Giger, Urs Hengartner,[3] Herbert A. Kirst, and Hans Maag

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Received October 1, 1976

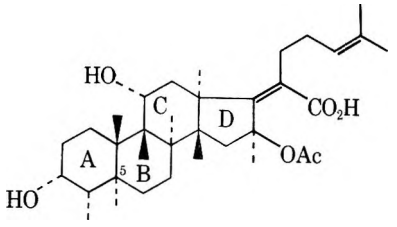
Two synthetic schemes are outlined for the construction of tetracyclic intermediates with the syn-trans-anti-trans backbone characteristic of the fusidic acid nucleus. Both entail the use of the α-methylene ketone **14** as the source of the C/D rings. One approach utilizes the conjugate addition of *m*-methoxybenzylmagnesium chloride as the means for the introduction of the remnants of the A/B ring system, as well as the placement of the C-8 angular methyl group. Modification of the aromatic ring through Birch reduction and then the Eschenmoser hydrazone

Robert E. Ireland,* Pierre Beslin, Rudolf Giger, Urs Hengartner, Herbert A. Kirst, and Hans Maag: Studies on the Total Synthesis of Steroidal Antibiotics. 2. Two Convergent Schemes for the Synthesis of Tetracyclic Intermediates.

Page 1267. Substituent at positions 4, 8, 10, and 14 (steroid numbering) in all formulas, I through **34**, unless otherwise specified, should be taken to represent methyl groups. Angular substituents at other positions should be taken to represent hydrogens.

w, versatile annelation procedure is demonstrated
le in the Diels–Alder condensation with acrylates.
om the adducts allows for introduction of the C-8
f the enone **13** through aldol-type closure of the B
isidic acid type intermediates (**30**) as well as tricy-
ined. Means are also presented for the conversion
rans-syn-trans structures characteristic of fusidic

An integral part of any program concerned with the total synthesis of the steroidal antibiotic fusidic acid (**1**)[4] must be the development of means for the construction of the highly



1

strained *trcns-syn-trans*-perhydrophenanthrene system that represents the A, B, and C rings of this molecule. In such an arrangement, the B ring is fixed in a full boat conformation, and isomerization at either of the obvious synthetically accessible C-5 and C-9 positions leads to a more stable structure. The system thus dictates precise stereochemical control during synthesis and greatly circumscribes the methodology that is suitable.

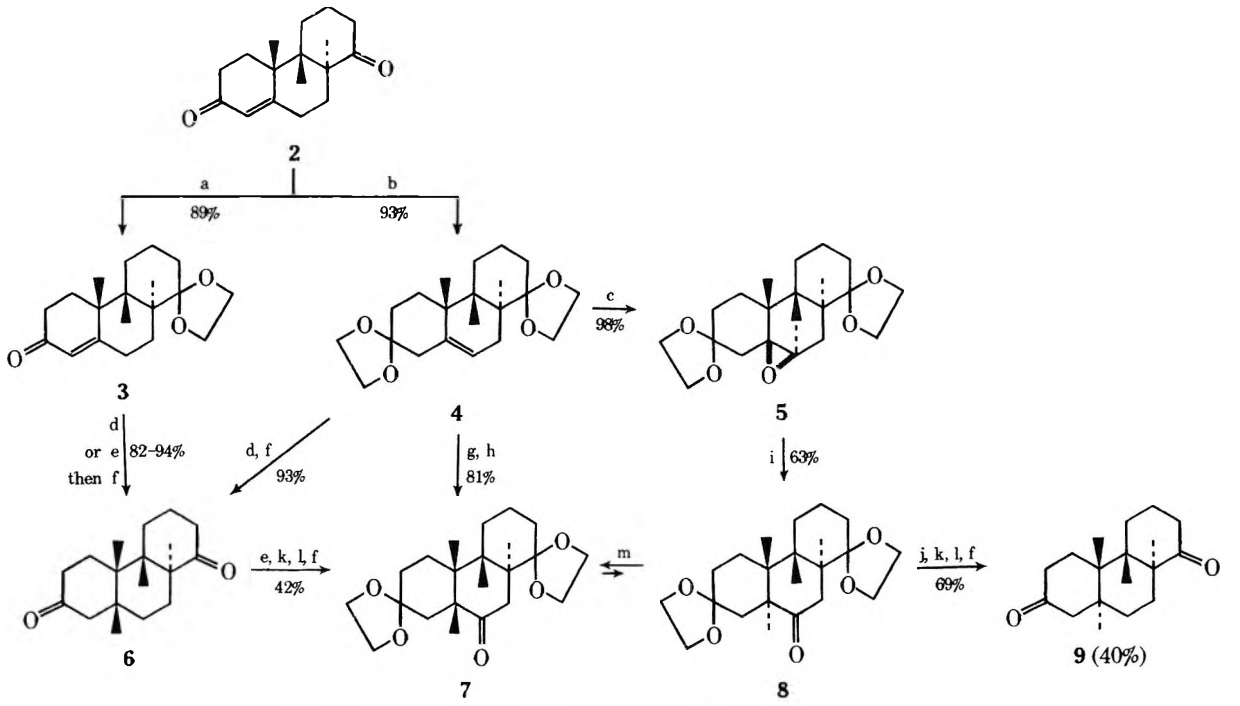
To explore the problems posed by this system a tricyclic model was investigated[5] first. The purpose of this work was the development of a scheme for the reduction of the readily accessible Δ^4-3-ketone system to the desired A/B-trans structure. Thus, the transformation of the enedione **2**[6] (Chart I) to the trans-syn-trans diketone **9** was pursued. From the results[5] of reduction of the enone **2** by either metal in ammonia or catalytic hydrogenation, it became apparent that direct saturation of the double bond in this system leads only to A/B-cis fused material. Even catalytic hydrogenation of the 5(6) double bond in the intermediate bisketal **4** results[5] in only the cis isomer. The propensity for such syn-trans tricyclic systems to interact with reagents on the β face of the molecule is understandable from models in which it is apparent that the B ring is already in a virtual boat conformation. The α-C-8 methyl group very effectively shields the α side of the C-5 carbon toward approach by any external reagent.

To overcome this problem a sequence (Chart I) was used in which the desired C-5 α hydrogen was introduced by the intramolecular rearrangement of the oxide **5**. Despite the multistage nature of this process the overall yield of the diketone **9** was quite acceptable in view of the strain introduced. In retrospect it is particularly interesting that in this tricyclic system none of the product of C-9 methyl group migration could be identified as a result of rearrangement of the oxide **5**. The ketone function at C-6 in the diketal **8**, while efficiently removable without isomerization at C-5 for the fusidic acid (**1**) scheme, could be viewed as an asset for a potential helvolic acid[7] synthesis.

With this sequence available work was initiated on the synthesis of a tetracyclic analogue of the enone **2** with fusidic acid (**1**) as the ultimate objective. The basic approach employed was patterned after the later stages of the synthesis of the enone **2**[6] in which the syn relationship between the C-9 H and the C-10 CH_3 was established through the reductive methylation[8] of an intermediate α,β-unsaturated ketone. For this work the unsaturated ketone required was the tricyclic bisketal **13** (Chart II), and two different schemes were explored for its synthesis.

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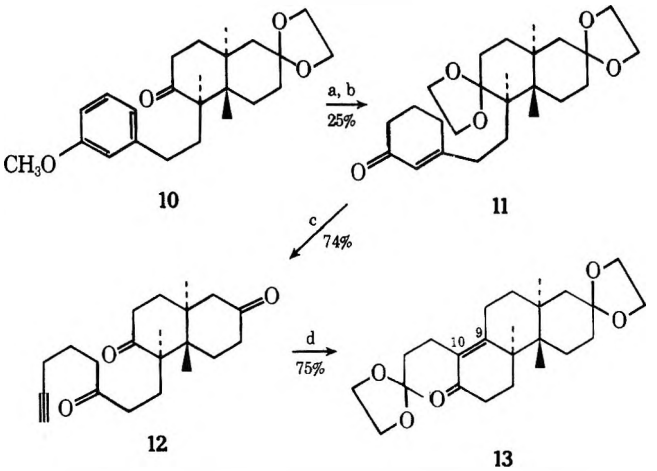
Chart I. Synthesis of *trans-syn-trans-* and *cis-syn-trans*-Perhydrophenanthrene System[a]



[a] a, $(CH_2OH)_2$, H^+, CH_2Cl_2–*n*-C_5H_{12}; b, $(CH_2OH)_2$, H^+, C_6H_6; c, *m*-$ClC_6H_4CO_3H$, CH_2Cl_2; d, H_2, Pd/C, EtOH; e, K or Li, NH_3, THF; f, H_3O^+, acetone; g, B_2H_6, THF; H_2O_2, OH^-; h, CrO_3·2Pyr, CH_2Cl_2; i, BF_3-Et_2O, CH_2Cl_2; j, $LiAlH_4$, Et_2O; k, *n*-BuLi, DME, Et_3N; $ClPO(N(CH_3)_2)_2$; l, Li, $EtNH_2$, THF, *t*-BuOH; m, NaOH, C_2H_5OH.

The first approach (Chart II) began from the ketone **10** in which the aromatic ring was envisaged as the ultimate source of the A ring in the desired tetracyclic ketone **30** (Chart IV). The conversion of this aromatic ring to a saturated carbon

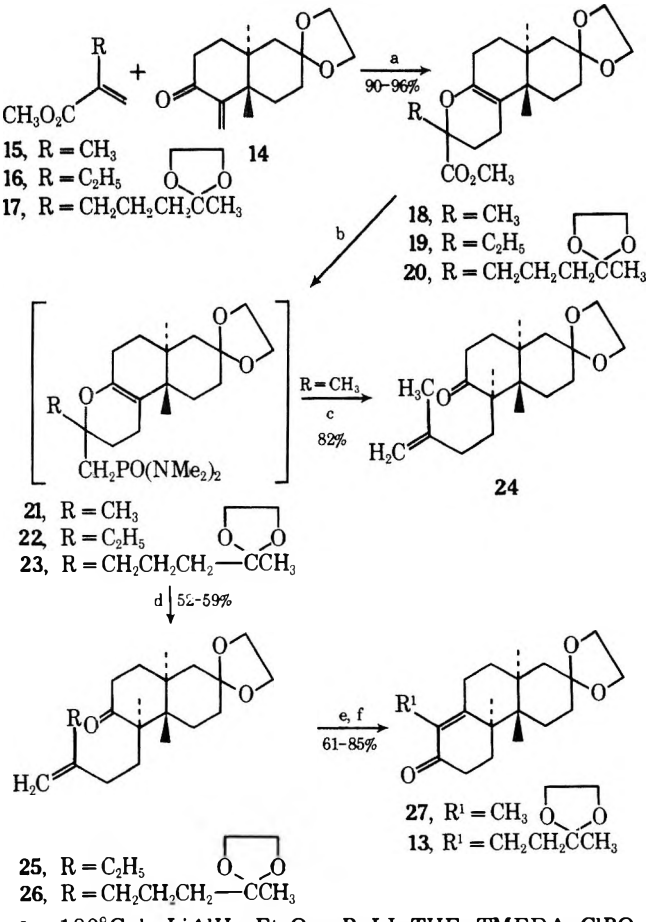
Chart II. Conjugate Addition Approach to the Synthesis of Enone 13[a]



[a] a, $(CH_2OH)_2$, $C_6H_5CH_3$, *p*-TsOH; b, Li, NH_3, THF–*t*-BuOH; 5% aqueous $(CO_2H)_2$; Al_2O_3 (activity II); c, H_2O_2, NaOH, CH_2Cl_2, 0°C; R_2NNH_2, C_6H_6, Δ; H_3O^+; d, 0.18 N KOH, H_2O–CH_3OH; $(CH_2OH)_2$, C_6H_6, *p*-TsOH; $HqSO_4$, 1% H_2SO_4, CH_3OH; $(CH_2OH)_2$, C_6H_6, *p*-TsOH.

chain without oxidative loss of carbon entailed first Birch reduction sequence to the enone **11** and then Eschenmoser cleavage[10] of the derived epoxy ketone with aminodiphenylaziridine.[11] A similar sequence was recorded recently in the total synthesis of (±)-shionone.[12] After aldol-type condensation to form the B ring, hydrolysis of the terminal acetylene[13] and selective ketalization of the saturated ketones afforded the desired α,β-unsaturated ketone intermediate **13** in 14% overall yield [7% from the α-methylene ketone **14** (Chart III) common to both approaches]. While this sequence accomplished the intermediary objective, the frequent necessity to protect carbonyl functionality led to an unsatisfying overall yield as a result of the numerous manipulations required.

Chart III. Diels–Alder Approach to the Synthesis of Enone 13[a]



[a] a, 180°C; b, $LiAlH_4$, Et_2O; *n*-BuLI, THF–TMEDA, $ClPO(NMe_2)_2$; c, Li, CH_3NH_2; H_2O; d, Li, $(C_6H_5)_2$, THF; CH_3I; e, O_3, CH_3OH; CH_3SCH_3; f, 0.18 N KOH, H_2O–CH_3OH.

A second approach (Chart III) to the synthesis of the unsaturated ketone **13** was shown to have broader general application as well as to provide the desired ketone **13** in higher overall yield. This scheme, like the foregoing route, relies on the α-methylene ketone **14**[9] as a substrate for both the addition of the carbon chain destined to become the A and B rings and the generation in the process of the masked enolate used to introduce the second of the vicinal angular methyl groups characteristic of these triterpenoids. The Diels–Alder condensation between the α-methylene ketone **14**[9] and various methyl α-substituted acrylates admirably served this purpose. An important facet of this reaction is that while the acrylate dienophile is used best in a fivefold excess over the α-methylene ketone **14**,[9] unreacted dienophile may be recovered very efficiently in reusable condition—a necessary feature for this condensation to be the core reaction in a convergent synthesis in which *both* the α-methylene ketone **14**[9] and the acrylate **17**, for instance, are valuable materials.

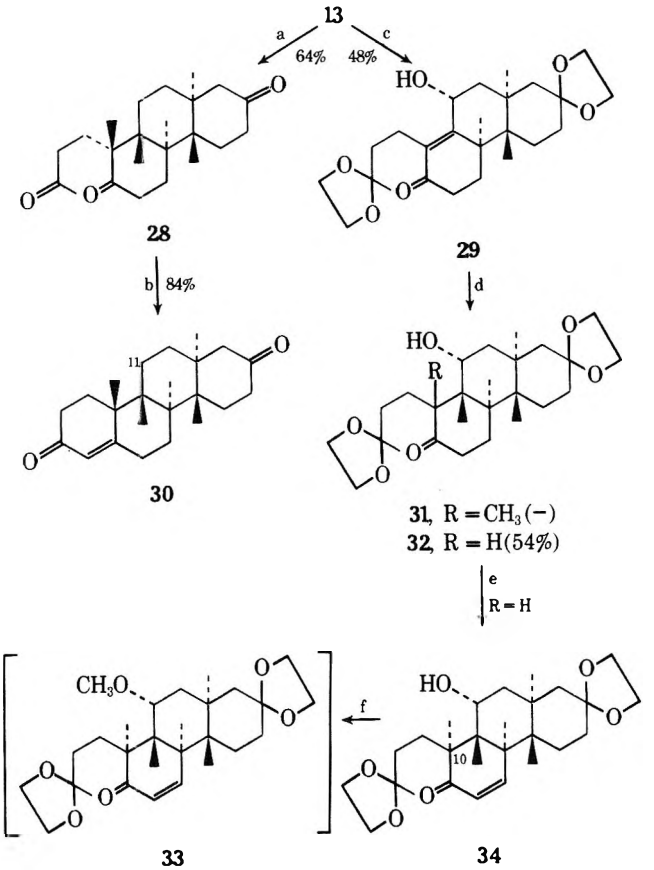
The planned subsequent cleavage of the dihydropyran ring so as to generate the desired enolate initially presented some difficulties. It was necessary to carry out this cleavage under conditions such that the enolate formed was not protonated and then reenolized to the more stable isomeric enolate. In addition, it was necessary to arrange the cleavage reaction in a manner such that the carbomethoxyl bearing carbon of the esters **18–20** became ultimately a ketone function. The cleavage sequence chosen made use of the recently developed phosphorodiamidate grouping[14] as a means for the final deoxygenation with fragmentation of the carbomethoxydihydropyran system. However, reduction of the primary phosphorodiamidates **21–23** was unsuccessful in ammonia and overreduction of the terminal methylene group generated by the fragmentation took place in ethylamine. While a solution to the latter overreduction problem was found when methylamine was used as a solvent, this solvent was too basic to permit direct methylation of the enolate generated by the fragmentation reaction, and only the ketone **24** was readily available from the phosphorodiamidate **21** under these conditions. In order to effect both fragmentation and then direct methylation, the phosphorodiamidates **22** and **23** were reduced with the biphenyl radical anion in tetrahydrofuran solution. The reductive fragmentation process took place efficiently as evidenced by the good yield of the derived enol acetate formed by trapping the intermediate enolate with acetic anhydride. The limitation on the overall yield of the process again appears to be the methylation of this intermediate enolate which leads not only to the desired ketones **25** and **26** but also to the corresponding β-methylated ketone (cis methyl groups, 5–14%) and the methyl enol ether (14–12%).

Final completion of the tricyclic construction was accomplished by ozonization of the terminal methylene group and then aldol-type condensation. The α,β-unsaturated ketone **13** was available in 45% overall yield from the methylene ketone **14**[9] by this scheme, which represents a significant improvement over the foregoing aromatic approach.

Further modification (Chart IV) of the α,β-unsaturated ketone **13** followed two different avenues. The first objective—the synthesis of the tetracyclic analogue **30** of the model tricyclic enone **2**—was accomplished by the same reductive methylation[8] and then aldol-type condensation sequence used before. Again the methylation reaction produced the α-methylated ketone and the methyl enol ether as well as the desired ketone **28** as the major product. While the enone **30** lacked the necessary oxygen function at C-11 for fusidic acid, this material can serve as an intermediate in a fusidane[4] or helvolic acid[7] synthesis after formation of an A/B-trans fusion by the method developed above.

Efforts to introduce a C-11 oxygen function at this stage were not nearly as successful. Through peracid oxidation of

Chart IV. Transformations of Enone 13[a]



[a] a, Li, NH_3, THF, H_2O; CH_3I; H_3O^+; b, 0.18 N KOH, H_2O–CH_3OH; c, NaH, THF, Ac_2O; *m*-$ClC_6H_4CO_3H$, dioxane/H_2O; d, LDA; Li, NH_3; NaOBz, then CH_3I or NH_4Cl; e, LDA, THF; C_6H_5SeBr; H_2O, Py; f, KO-*t*-Bu or LDA, *t*-BuOH or THF, CH_3I.

the enol acetate[15] derived from the enone **13** the hydroxy enone **29** became available. As expected,[16] direct lithium–ammonia reduction of this hydroxy enone **29** led only to products of hydrogenolysis of the hard-won alcohol grouping. Relative success in the retention of this alcohol function during lithium–ammonia reduction was found by initial conversion of the alcohol to the lithium alcoholate with lithium diisopropylamide. In this manner the saturated hydroxy ketone **32** was available, but again the problems associated with the previous direct reductive methylation reactions attended the attempts to form the ketone **31**. While it appeared probable that the desired ketone **31** was formed in approximately 15–25% yield by such a sequence, preparative isolation of the material from the complex product mixture was not possible. In addition to the methylation products observed before in similar reductive methylations, there appeared to be products from O-methylation of the C-11 alcohol function as well as those of α'-methylation of both starting hydroxy enone **29** and the expected saturated ketones **31** and **32**. The latter products must arise from enolization reactions promoted by the lithium C-11 alcoholate, the presence of which is necessary to prevent hydrogenolysis of this group.

Although at this stage in this phase of the synthesis the overall yield of the hydroxy ketone **32** was unsatisfactorily low, a final attempt was made to effect C-10 methylation through the isomeric enone **34**. Available from the saturated hydroxy ketone **32** by the procedures[17] of Sharpless and Reich, this enone **34** can only enolize toward the desired C-10 position. Unfortunately, the only methylation product identifiable by spectral examination of the crude product from several different methylation procedures was the O-methyl ether **33**. The presence of a similar product was noted earlier in the direct

reductive methylation reaction, and its reoccurrence here attests to the problems that attend the formation of the syn backbone in these systems by these means.

With a relatively efficient scheme available for the formation of the C-11-deoxygenone **30**, further work on the synthesis of tetracyclic derivatives in the trans-syn-trans-anti-trans series used this enone **30** as the substrate.

Experimental Section[18]

1,1,7,7-Bisethylenedioxy-4bβ,10aα-dimethyl-1,2,3,4aβ,4b,-5,6,7,8,10,10a-dodecahydrophenanthrene. A solution of 618 mg (2.50 mmol) of the enedione **2** (mp 134–137 °C, prepared in 23% overall yield as outlined in ref 5), 1.34 g (21.6 mmol) of ethylene glycol, and 10 mg of *p*-toluenesulfonic acid monohydrate in 30 mL of benzene was heated at reflux for 2 h under a Dean-Stark water separator in a nitrogen atmosphere. After cooling, the reaction mixture was diluted with 50 ml of ether, and the ethereal layer was washed with saturated $NaHCO_3$ solution (30 mL), water (30 mL), and brine (30 mL) and then dried ($MgSO_4$). Evaporation of the solvent at reduced pressure afforded 829 mg of a crystalline residue, which on purification by chromatography on 75 g of silica gel with petroleum ether–ether (1:1) gave 781 mg (93%) of the crystalline bisketal **4**, mp 157.5–159 °C. The analytical sample obtained by one crystallation from ether–*n*-pentane melted at 158–159 °C: IR ($CHCl_3$) 1675 cm^{-1} (C=C, weak); NMR ($CDCl_3$) δ 1.10 (s, 6, 2 CH_3), 3.94 (br s, 8, 2 OCH_2CH_2O), 5.40 (m, 1, C-9 H). Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.80; H, 9.12.

Ketal Enone 3. To a solution of 286 mg (1.16 mmol) of the enedione **2** in 3 mL of CH_2Cl_2 and 20 mL of *n*-pentane containing 5 mg of *p*-toluenesulfonic acid was added under a nitrogen atmosphere 335 mg (5.54 mmol) of ethylene glycol, and the mixture was stirred and heated under reflux for 3.5 h. After cooling, the mixture was diluted with 75 mL of ether, and the product was isolated by ether extraction including a base wash.[19] Purification of the crude, oily product by chromatography on 40 g of silica gel with 1:2 petroleum ether–ether afforded 23 mg of the diketal **4** in the first 160 mL of eluent and then 301 mg (89%) of the ketal enone **3** as a colorless oil in the next 160 mL of eluent. The analytical sample was obtained by evaporative distillation of a portion of this material at 165 °C (0.05 mm): NMR ($CDCl_3$) δ 1.06 (s, 3, CH_3), 1.23 (s, 3, CH_3), 3.98 (s, 4, OCH_2CH_2O), and 5.83 (s, 1, C=CH); IR ($CHCl_3$) 1660 (C=O) and 1625 cm^{-1} (C=C).

Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02. Found: C, 74.52; H, 9.05.

Cis-Syn-Trans Diketone 6. A. From Ketal Enone 3 by Hydrogenation. A mixture of 45.4 mg (0.16 mmol) of the ketal enone **3** and 42 mg of 10% palladium on carbon in 5 mL of absolute EtOH was stirred at room temperature in a hydrogen atmosphere for 45 min. After filtration, evaporation of the solvents from the filtrate at reduced pressure afforded 45.4 mg (99%) of the crystalline, saturated ketone ketal, mp 152–153 °C. Further purification of the product by chromatography on 8 g of silica gel with 1:2 petroleum ether–ether gave 43.1 mg (94%) of the saturated ketone ketal, mp 154–155 °C. The analytical sample, obtained after one crystallization from benzene–*n*-hexane and sublimation at 125 °C (0.03 mm), melted at 154.5–155.5 °C: NMR ($CDCl_3$) δ 1.07 (s, 3, CH_3), 1.27 (s, 3, CH_3), and 3.94 (m, 4, OCH_2CH_2O); IR ($CHCl_3$) 1705 cm^{-1} (C=O).

Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.83; H, 9.72.

Hydrolysis of the ketal was accomplished when a solution of 40 mg (0.14 mmol) of the ketone ketal was stirred at room temperature in 5 mL of acetone and 1.2 mL of 10% aqueous HCl. Isolation of the product by ether extraction including a base wash[19] afforded 34.7 mg (100%) of the diketone **6**, mp 141–142 °C. The analytical sample, obtained after one crystallization from acetone–*n* hexane, melted at 142–143.5 °C: TLC (CH_2Cl_2–Et_2O) R_f 0.49; NMR ($CDCl_3$) δ 1.18 (s, 3, CH_3) and 1.31 (s, 3, CH_3); IR ($CHCl_3$) 1705 cm^{-1} (C=O); VPC (4% SE-30, 192 °C) t_R 3.00 min.

Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.47; H, 9.60.

The melting range of a mixture of this diketone **6**, mp 142–143 °C, and the isomeric trans-syn-trans diketone **9**, mp 134–135 °C, was 123–130 °C. Mixtures of samples of the two diketones **6** and **9** were resolved on TLC and VPC.

B. From the Ketal Enone 3 by Metal–Ammonia Reduction. To a solution of 50 mg (1.3 mg-atoms) of potassium in 10 mL of dry ammonia under a nitrogen atmosphere was added a solution of 67 mg (0.23 mmol) of the ketal enone **3** in 2 mL of dry THF. After stirring for 5 min, the blue reaction mixture was quenched with 0.5 ml of absolute EtOH, and after evaporation of the ammonia, the product was isolated by ether extraction.[19] A solution of the crude, crystalline product (69.5 mg) dipyridine complex[20] in 8 ml of dry CH_2Cl_2 was stirred for 15 min at room temperature, and then the mixture was filtered through 1 g of alumina with the aid of 10 mL of CH_2Cl_2. Evaporation of the solvent from the eluent afforded 65 mg of crystalline product which on chromatography on 15 g of silica gel with 80 mL of 1:2 petroleum ether–ether afforded 55.3 mg (82%) of the saturated ketone ketal, mp 154–155 °C. Further elution with 45 mL of the same eluent afforded 4.5 mg (7%) of the starting ketal enone **3**. There was no evidence in the product from this reduction, or that with lithium, of the corresponding trans-syn-trans ketone ketal, and the NMR, IR, TLC, and VPC spectra of this saturated ketone ketal were identical with those of the material obtained above from hydrogenation of the ketal enone **3**. Hydrolysis of a sample of this material in acetone–10% aqueous HCl afforded a quantitative yield of the diketone **6**.

C. From the Diketal 4. A mixture of 47.5 mg (0.142 mmol) of the diketal **4** and 12 mg of 10% palladium on carbon in 6 mL of absolute EtOH was stirred in a hydrogen atmosphere for 2 h. After filtration, removal of the solvent from the filtrate left 49.0 mg of the saturated diketal as a colorless gum [IR ($CHCl_3$) no > C=O absorption; NMR ($CDCl_3$) δ 1.06 (s, 3 H, CH_3), 1.13 (s, 3, CH_3), and 3.92 (m, 8, 2 OCH_2CH_2O)] which was hydrolyzed by treatment of an acetone (6 mL) solution with 1.5 mL of 10% aqueous HCl at room temperature for 1 h. Isolation of the product by ether extraction including a base wash[19] afforded 32.7 mg (93%) of the diketone **6** as colorless crystals, mp 141.5–142.5 °C. The NMR, IR, TLC, and VPC spectra of this material were identical with those of the diketone **6** prepared above.

D. From the Ketone Diketal 7. To a solution of 19 mg (2.7 mg-atoms) of lithium in 12 mL of dry NH_3 under a nitrogen atmosphere was added a solution of 76 mg (0.216 mmol) of the ketone diketal **7** (judged to be 91% cis-syn-trans and 9% trans-syn-trans by NMR) in 4 mL of dry THF, and the mixture was stirred for 30 min. The blue reaction mixture was quenched with 2 mL of absolute EtOH, and after evaporation of the NH_3, the product was isolated by ether extraction.[19] Purification of the crude product by chromatography on 42 g of silica gel, 230 mL of ether, and then 550 mL of 5% acetone–ether afforded first 11 mg (14%) of starting cis-syn-trans ketone ketal **7** and then 63 mg (81%) of the diketal alcohol as a colorless gum. The IR, NMR, TLC, and VPC spectra of this material were identical with those of the β alcohol obtained from hydroboration of the diketal **4**.

In a manner similar to that described below for the reductive removal of the hydroxyl group from the trans-syn-trans diketal alcohol from the diketal ketone **8**, 26 mg (0.073 mmol) of the cis-syn-trans diketal alcohol above was phosphorylated with 70 μl of a 2.66 M *n*-C_4H_9Li–hexane solution (0.19 mmol), 0.15 mL of NEt_3, 0.3 mL of dry HMPA, and 0.1 mL of $ClPO[N(CH_3)_2]_2$ in 2 mL of dry DME.

The crude phosphorodiamidate formed in this manner was reduced with 22 mg (3 mg-atoms) of lithium and 10 mg of *t*-BuOH in 8 mL of dry $EtNH_2$. Finally, the crude diketal obtained from this reduction was hydrolyzed in 4 mL of acetone with 0.8 mL of 10% aqueous HCl at room temperature for 1 h. Purification of the crude gum obtained from this sequence by chromatography on 2 g of silica gel with 10:1 CH_2Cl_2–Et_2O afforded 11 mg (58%) of the diketone **6**, mp 141–142 °C. The IR, NMR, TLC, and VPC spectra of this material were identical with those of the diketone **6** prepared above.

Hydroboration of Diketal 4. To a solution of 653 mg (1.95 mmol) of the diketal **4** in 100 mL of dry THF was added 10.0 mL of a 0.9 M borane–THF solution, and the clear solution was stirred at room temperature for 3 h. The reaction mixture was cooled in an ice bath, and then treated sequentially with 2 mL of H_2O, 10 mL of 3 N aqueous NaOH, and 10 mL of 30% H_2O_2. After the mixture had stirred at room temperature for 3 h, the product was isolated by benzene extraction.[19] Purification of the crude product by chromatography on 130 g of silica gel with 150 mL of benzene–EtOAc–acetone (10:5:3) and then 400 mL of the same solvents in the ratio 10:5:5 afforded 85 mg (12%) of the *tertiary* diketal alcohol, mp 175–178 °C, and 579 mg (84%) of the desired *secondary* diketal alcohol as a colorless oil.

The analytical sample of the *tertiary* diketal alcohol, obtained after two crystallizations from acetone–*n*-hexane, melted at 179–180 °C: NMR ($CDCl_3$) δ 1.04 (s, 3, CH_3), 1.13 (s, 3, CH_3), and 3.91, 3.93 (2 s, 8, 2 OCH_2CH_2O); IR ($CHCl_3$) 3605 cm^{-1} (OH); TLC (benzene–EtOAc–acetone, 10:5:2) R_f 0.37.

Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 68.29; H, 9.24.

Attempted oxidation of 17 mg (0.048 mmol) of this alcohol with 1.5 mL of a 0.24 M solution of Collins reagent[20] in CH_2Cl_2 led to a

quantitative recovery of the starting alcohol (IR, NMR, TLC). Hydrolysis of 18.5 mg (0.05 mmol) of this diketal alcohol in 1 mL of acetone with 0.25 mL of 10% aqueous HCl at room temperature for 2 h led to the formation of 11 mg (90%) of the enedione **2**, mp 131–133 °C, as shown by identical IR, NMR, and VPC.

The analytical sample of the *secondary* diketal alcohol was obtained as a colorless oil by evaporative distillation at 195 °C (0.05 mm): TLC (benzene–EtOAc–acetone, 10:5:2) R_f 0.28; NMR ($CDCl_3$) δ 1.10 (s, 3, CH_3), 1.17 (s, 3, CH_3), 3.92 (s, 8, 2 OCH_2CH_2O), and 4.3 (m, 1, CHOH); IR ($CHCl_3$) 3620 cm^{-1} (OH).

Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 68.16; H, 9.04.

Diketal Ketone 7. To 24 mL (5.76 mmol) of 0.24 M Collins reagent[20] in CH_2Cl_2 was added a solution of 328 mg (0.93 mmol) if the cis-syn-trans diketal alcohol in 8 mL of dry CH_2Cl_2, and the mixture was stirred at room temperature for 20 min. Filtration of the mixture through 10 g of alumina (activity III) with the aid of 60 mL of CH_2Cl_2 and then evaporation of the solvents at reduced pressure afforded 313 mg (96%) of the diketal ketone **7**, mp 147.5–149 °C. The analytical sample, obtained after two crystallizations of a portion of this material from acetone–*n*-hexane, melted at 150.5–151.5 °C: TLC (ether) R_f 0.37; NMR ($CDCl_3$) δ 1.13 (s, 3, CH_3), 1.28 (s, 3, CH_3), and 3.8–4.3 (m, 8, 2 OCH_2CH_2O); IR ($CHCl_3$) 1705 cm^{-1} (C=O).

Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.58 H, 8.67.

Equilibration Studies on Diketal Ketones 7 and 8. A. From Diketal Ketone 7. A solution of 53 mg (0.15 mmol) of the diketal ketone **7** in 20 mL of EtOH and 0.4 mL of 2 N aqueous NaOH was heated under reflux in a nitrogen atmosphere for 2 h. After dilution with 20 mL of H_2O, isolation of the product by ether extraction[19] afforded 52 mg of crystalline material, mp 142–144 °C. The TLC, VPC, and IR of this material were identical with those of the starting diketal ketone **7**, but the NMR ($CDCl_3$) showed the appearance of two new singlets at δ 0.89 and 1.38, integration of which indicated 8–10% of the diketal ketone **8**.

B. From Diketal Ketone 8. A solution of 35 mg (0.1 mmol) of the diketal ketone **8**, mp 169.5–171.5 °C, in 6 mL of EtOH and 1.4 mL of 10% aqueous NaOH was heated under reflux for 2 h. The progress of the reaction was followed by VPC (4% SE-30, 190 °C) and after the reflux period the peak due to diketal ketone **8** at 23.4 min had diminished to ~8% of the volatile material while that due to the diketal ketone **7** at 21.6 min had increased to ~92%.

Dilution of the reaction mixture with 60 mL of H_2O and isolation of the product by ether extraction[19] afforded 35 mg of crystalline material, mp 144.5–146.5 °C. The IR, TLC, and VPC spectra of this material were identical with those of the diketal ketone **7**, but again the NMR ($CDCl_3$) showed the additional two resonances at δ 0.89 and 1.38 due to the presence of ~8–10% of the diketal ketone **8** by integration. Further purification of this material by chromatography on 6 g of silica gel with 3:1 ether–petroleum ether and then crystallization of the recovered solid from acetone–*n*-hexane gave 32 mg (92%) of the purer diketal ketone **7**, mp 150–152.5 °C, alone or in admixture with authentic material, mp 151.5–152.5 °C, from the hydroboration–oxidation of the diketal olefin **4**.

1,1,7,7-Bisethylenedioxy-4bβ,10aα-dimethyl-8aβ,9β-oxidoperhydrophenanthrene (5). A solution of 470 mg (2.32 mmol) of *m*-chloroperoxybenzoic acid (85%) in 10 mL of CH_2Cl_2 was added dropwise to an ice-cold solution of 672 mg (2.01 mmol) of the diketal **4** in 10 mL of CH_2Cl_2 over a period of 10 min. Stirring was continued at room temperature for 1.5 h, and then the reaction mixture was diluted with 100 mL of ether, washed with 10% aqueous sodium sulfite solution (50 mL), saturated $NaHCO_3$ solution (50 mL), water (50 mL), and brine (50 mL), and finally dried ($MgSO_4$). Evaporation of the solvents at reduced pressure afforded 703 mg of a crystalline residue, which on purification by chromatography on 75 g of silica gel with petroleum ether–ether (2:1) gave 691 mg (98%) of the crystalline epoxide **5**, mp 167–168 °C. The analytical sample, obtained after one crystallization from acetone–*n*-hexane, melted at 167–168 °C: NMR ($CDCl_3$) δ 1.13 and 1.19 (2 s, 6, 2 CH_3), 3.05 (d, J = 6 Hz, 1, C-9 H), 3.94 (s, 8, 2, OCH_2CH_2O).

Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.56; H, 8.57.

1,1,7,7-Bisethylenedioxy-4bβ,10aα-dimethyl-9(8a*H*)-perhydrophenanthrone (8). To a well-stirred solution of 367 mg (1.05 mmol) of the epoxide **5** in 30 mL of dry CH_2Cl_2 under a nitrogen atmosphere at room temperature was added by syringe 0.35 mL of freshly distilled BF_3-Et_2O. The clear solution was stirred for 5 min and then 2 mL of dry Et_3N followed by 25 mL of saturated $NaHCO_3$ solution were added. The heterogeneous mixture was stirred for an additional 5 min and then the organic phase was separated with the aid of 125 mL of ether and washed with water (50 mL) and brine (50 mL). The dried ($MgSO_4$) organic solution was evaporated at reduced pressure, and the semicrystalline residue (358 mg) was chromatographed on 80 g of silica gel with petroleum ether–ether (1:2). The first 415-mL fraction contained 5.5 mg less polar impurities. Further elution with 270 mL of the same solvent mixture gave 230 mg (63%) of the crystalline ketone **8**, mp 170.5–172 °C. There was no evidence for the concomitant formation of the cis-syn-trans diketal ketone **7** or the rearranged alcohol. An analytical sample, prepared by crystallization from acetone–*n*-hexane, melted at 171.5–172.5 °C: IR ($CHCl_3$) 1705 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.90 (s, 3, CH_3), 1.39 (s, 3, CH_3), 3.94 (br s, 8, 2 OCH_2CH_2O).

Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.53; H, 8.65.

4bβ,10aα-Dimethyl-*trans-syn-trans*-1(2*H*),7(8*H*)-perhydrophenanthrenedione (9). A solution of 99 mg (0.282 mmol) of the diketal ketone **8** in 3 mL of benzene–ether (1:1) was added dropwise to a stirred slurry of 23 mg (0.61 mmol) of $LiAlH_4$ in 5 mL of ether under a nitrogen atmosphere over a period of 5 min. After the mixture has stirred at 25 °C for 1.5 h, excess hydride was decomposed with water and the ethereal solution was dried ($MgSO_4$) overnight. The crude alcohol, obtained as a foam (100.2 mg) after evaporation of the ether at reduced pressure, was dissolved in 4 ml of dry glyme under a nitrogen atmosphere, and then treated with 140 mL of 2.7 M *n*-C_4H_9Li in *n*-hexane. To this solution were added sequentially 0.2 mL of dry Et_3N and 0.17 mL of *N,N,N,N*-tetramethyldiamidophosphorochloridate [$ClPO(NMe_2)_2$]. The clear solution was stirred for 75 min and then added dropwise to a stirred solution of 45 mg of lithium in 20 mL of dry $EtNH_2$ under an argon atmosphere at 5 °C over a 2-min period. The blue mixture was stirred for an additional 15 min at 5 °C, and then quenched with 4 mL of 10% aqueous NH_4Cl solution after most of the $EtNH_2$ was evaporated at room temperature in a jet of argon; the residue was partitioned between water (100 mL) and 1:1 ether–*n*-pentane (120 mL). The organic extract was washed with water and brine and dried ($MgSO_4$). Evaporation of the solvents at reduced pressure gave 92.5 mg of the crude bisketal as a gum. A solution of the crude bisketal in 12 mL of acetone and 3 mL of 10% hydrochloric acid was stirred at room temperature for 2 h and then poured into 100 mL of water. After extraction of this solution with ether (3 × 50 mL), the combined extracts were washed with saturated $NaHCO_3$ solution (50 mL), water (50 mL), and brine (50 mL), and dried ($MgSO_4$). Purification of the crystalline residue, obtained by evaporation of the solvent at reduced pressure by chromatography on 20 g of silica gel with methylene chloride–ether ((8:1), gave 48.2 mg (69% overall) of the diketone **9**, mp 133–134 °C. The analytical sample, obtained by crystallization from acetone–*n*-hexane, melted at 134–135 °C: IR ($CHCl_3$) 1705 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.03 (s, 3, CH_3), 1.31 (s, 3, CH_3); TLC (CH_2Cl_2–Et_2O) R_f 0.52; VPC (4% SE-30, 1920) t_R 3.05 min.

Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.47, H. 9.76.

Bisketal 11. To a solution of 3.61 g (8.7 mmol) of the aromatic bisketal (prepared in 52% yield from the ketal ketone **10**[9] with ethylene glycol, *p*-toluenesulfonic acid catalyst in benzene under the standard conditions) in 300 mL of dry THF, 25 mL of dry *tert*-butyl alcohol, and ca. 750 mL of distilled ammonia was added 1.20 g (174 mmol) of lithium, and the deep blue solution was stirred for 8 h. After 25 mL of methanol was added, the ammonia was allowed to evaporate and brine was added to the residue. The crude product, isolated by ether extraction,[19] in 100 mL of dry THF was heated with 25 mL of 5% aqueous oxalic acid at 45–50 °C for 4 h, at which point TLC analysis (2:1 petroleum ether–ether) showed that none of the starting dihydroaromatic bisketal remained. After the solution was cooled and poured into 200 mL of saturated aqueous $NaHCO_3$ solution, the crude product was isolated by ether extraction.[19] This material was purified by medium-pressure liquid chromatography[18] on 410 g of silica gel in 1:2 petroleum ether–ether. Elution with 2100 mL of solvent afforded 1.2 g (35%) of the β,γ-unsaturated ketone bisketal: NMR δ 1.01 (s, 3, CH_3), 1.12 (s, 3, CH_3), 2.42 (br s, allylic H), 2.80 (br s, bisallylic H), 3.93 (s, 8, ketals), 5.59 (m, 1, vinyl); IR 1710 cm^{-1}; TLC (ether) R_f 0.54. An analytical sample was prepared by crystallization from ether, mp 144–146 °C.

Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.29; H, 8.98.

The β,γ-unsaturated ketone was converted to the α,β isomer **11** by rechromatography on basic Al_2O_3 (II) in 95% yield.

Continued elution with 3200 mL of solvent afforded 1.36 g (39%) of the α,β-unsaturated ketone bisketal **11**: NMR δ 1.02 (s, 3, CH_3), 1.15 (s, 3, CH_3), 3.92 (s, 8, ketals), 5.85 (m, 1, enone H); IR 1660 cm^{-1} (unsaturated carbonyl); TLC (ether) R_f 0.38. An analytical sample

was prepared by crystallization from ether, mp 161.5–163 °C.

Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.11; H, 8.94.

Acetylenic Triketone 12. A. Oxide Formation. To a solution of 0.82 g (2.03 mmol) of the α,β-unsaturated ketone **11** in 40 mL of CH_3OH and 5 mL of CH_2Cl_2 cooled in an ice bath were successively added 90 mg of KOH in 1 mL of MeOH and 2.0 mL (23 mmol) of 30% H_2O_2. After 1 h at 0 °C, another 90 mg of KOH in 1 mL of MeOH and 2.0 mL of 30% H_2O_2 were added, and the mixture was stirred for 1 h at 0 °C. The solution was then poured into cold, aqueous $Na_2S_2O_3$ solution, and the product was isolated by ether extraction.[19] The keto epoxide was isolated as a white solid (0.81 g), pure by TLC analysis: NMR δ 1.00 (s, 3, CH_3), 1.07 (s, 3, CH_3), 3.03 (s, 1, epoxide protons), 3.91 (s, 8, ketals); IR 1700 cm^{-1}; TLC (ether) R_f 0.59. An analytical sample was prepared by crystallization from ether, mp 176–178 °C.

Anal. Calcd for $C_{24}H_{36}O_6$: C, 68.54; H, 8.63. Found: C, 68.50; H, 8.75.

B. Eschenmoser Cleavage. A solution of 738 mg (1.76 mmol) of the above keto epoxide and 393 mg (1.80 mmol) of 2,3-*trans*-diphenyl-1-aminoaziridine[11] in 20 mL of dry benzene was stirred at 25 °C for 2 h. The benzene was evaporated at reduced pressure, and the resulting crude hydrozone (1.050 g) dissolved in 18.5 mL of dry DMF. This solution was then heated with stirring at 150–160 °C under an argon atmosphere for 2 h. After cooling, the solution was poured into saturated NaCl solution, and the product was isolated by ether extraction.[19] A solution of the crude product (1.350 g) in 15 mL of acetone containing 2 mL of 10% aqueous HCl was stirred at 25 °C for 4 h to effect ketal cleavage. Subsequent isolation of the product by ether extraction including a base wash[19] gave 1.010 g of a mixture of *trans*-stilbene and the acetylenic triketone **12**. Purification of this mixture by chromatography on 100 g of silica gel with ether afforded 419 mg (75%) of the acetylenic triketone **12**: mp 72–75 °C; NMR δ 1.00 (s, 3, CH_3), 1.16 (s, 3, CH_3); IR 3310 (C≡CH), 2130 (C≡C), 1705 cm^{-1} (carbonyl); TLC (ether) R_f 0.34; VPC t_R 2.4 min (280). An analytical sample was prepared by preparative TLC (1:1 petroleum ether–ether) and bulb-to-bulb distillation at 160 °C (0.03 mm).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 76.01; H, 9.23.

Enone 13. A solution of 308 mg (0.975 mmol) of the acetylenic triketone **12** in 100 ml of 1% aqueous KOH in 75% aqueous methanol was heated under reflux in an argon atmosphere for 15 h. After the mixture was cooled and then neutralized with 1 mL of acetic acid, the product was isolated by ether extraction including a base wash.[19] The resulting crude, solid acetylenic diketone amounted to 288 mg (99%), mp 148–150 °C, TLC (ether) R_f 0.40, UV active. The analytical sample was prepared after crystallization from ether and melted at 150–151 °C: NMR ($CDCl_3$) δ 1.09 (s, 3, CH_3), 1.33 (s, 3, CH_3); IR ($CDCl_3$) 3300 (C≡CH), 2120 (C≡C), 1710 (saturated C=O), and 1660 cm^{-1} (unsaturated C=O).

Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.60; H, 8.78.

This acetylenic diketone, together with similar material from another run (746 mg, 2.50 mmol) in 36 mL of CH_3OH was treated with 3.62 mL of saturated mericuric sulfate in 1% sulfuric acid solution, and the mixture stirred at 25 °C for 2 h. The crude product, isolated by CH_2Cl_2 extraction including a base wash,[19] amounted to 758 mg of a solid that showed no absorption due to –C≡CH in the infrared and only saturated and unsaturated carbonyl bands.

A solution of the above crude triketone (758 mg) in 125 mL of benzene and 20 mL of ethylene glycol containing 250 mg of *p*-toluenesulfonic acid was heated at reflux under a Dean-Stark water separator for 2.5 h. After cooling, the mixture was poured in 100 mL of saturated aqueous $NaHCO_3$, and the crude product was isolated by ether extraction.[19] Chromatography of the crude product (762 mg) over 50 g of silica gel with ether afforded 529 mg (52%) of the bisketal **13**, mp 113–116 °C: NMR ($CDCl_3$) δ 0.82 (s, 3, CH_3), 1.13 (s, 3, CH_3), 1.35 (s, 3, CH_3), 3.94 (s, 4, OCH_2CH_2O); IR ($CHCl_3$) 1670 cm^{-1} (unsaturated C=O); TLC (ether) R_f 0.43. The analytical sample, obtained after several crystallizations of a portion of this material from ether, melted at 115.5–116 °C.

Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.30; H, 8.85.

Methyl 6,6-Ethylenedioxy-2-methyleneheptanoate (17). To a solution of 12 g (0.55 g-atom) of sodium in 220 mL of dry CH_3OH under an argon atmosphere was added 62.5 mL (72 g, 0.55 mol) of dimethyl malonate, and the mixture was heated to 75 °C to avoid precipitation of the sodiomalonate. To this mixture was added 140 g (0.545 mol) of 4,4-ethylenedioxy-1-iodopentane,[21] and the solution was heated at 75 °C for 3 h. The flask was cooled to room temperature and 30.6 g (0.55 mol) of KOH in 85 mL of CH_3OH was added in 2 min with vigorous stirring. After the reaction mixture had stirred for 15 h at room temperature, approximately 200 mL of CH_3OH was removed at reduced pressure and then replaced with 200 mL of ether. The ethereal slurry was cooled to 0 °C and acidified with 400 mL of precooled 1 N aqueous H_2SO_4. Isolation of the product by ether extraction[19] afforded 113 g of the crude monoacid.

Following the procedure of Mannich[22] this crude monoacid was neutralized at 0 °C with 51.5 mL (37.6 g, 0.5 mol) of $(C_2H_5)_2NH$ (no solvent) and the resulting salt was treated with 37 mL (40.5 g, 0.5 mol) of 37% aqueous HCHO solution. This mixture was stirred at room temperature for 1 h and then at 60 ° for 2 h. After the mixture was cooled, the product was isolated by ether extraction including both an acid and base wash.[19] Purification of the crude acrylate combined from two such runs (73 and 78 g) by distillation afforded 87.3 g (38%) of the acrylate **17**, bp 78–83 °C (0.5 mm). The analytical sample, obtained after redistillation of a portion of this material, boiled at 79–81 °C (0.5 mm): NMR ($CDCl_3$) δ 1.32 (s, 3, CH_3), 3.76 (s, 3, OCH_3), 3.96 (s, 4, OCH_2CH_2O), 5.60 (d, J = 1 Hz, 1, C=CH_2); IR ($CHCl_3$) 1725 (C=O) and 1630 cm^{-1} (C=C).

Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.62; H, 8.47.

Diels–Alder Reactions with Methylene Ketone 14. General Procedure. A mixture of five- to tenfold molar excess of the appropriate methyl acrylate **15**, **16**, or **17** and the α-methylene ketone **14**[9] was sealed under vacuum in an ampulla, and the tube was heated for 22–24 h in an oil bath at 180–185 °C. The products from the acrylates **15** and **16** were isolated by chromatography with 1:1 ether–petroleum ether on silica gel after first removing the excess acrylate on the rotary evaporator at reduced pressure.

In this manner 1.530 g (90%) of a 1:1 mixture of stereoisomeric adducts **18** was obtained from 1.200 g (5.08 mmol) of the α-methylene ketone **14** and a tenfold molar excess of methyl methacrylate (**15**, 5.10 g, 50.9 mmol). For identification purposes the stereoisomers were separated by rechromatography of a sample of this mixture on silica gel with 2:1 petroleum ether–ether, and both crystalline isomers were obtained pure for analytical purposes after two crystallizations from acetone–*n*-hexane. Isomer **18-I**: mp 96.5–98 °C; NMR ($CDCl_3$) δ 0.90 (s, 3, CH_3), 1.40 [s, 3, O=C–C(CH_3)O–], 3.75 (s, 3, OCH_3), and 3.96 (s, 4, OCH_2CH_2O–); IR ($CHCl_3$) 1730 (C=O) and 1675 cm^{-1} (enol ether C=C).

Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 68.03; H, 8.45.

Isomer 18-II mp 98–99 °C; NMR ($CDCl_3$) δ 0.91 (s, 3, CH_3), 1.46 [s, 3, O=C–]C(CH_3)O–, 3.71 (s, 3, OCH_3), and 3.94 (s, 4, $-OCH_2CH_2O$–); IR ($CHCl_3$) 1730 (C=O) and 1675 cm^{-1} (enol ether C=C).

Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.99; H, 8.46.

Similarly, 663 mg (90%) of a mixture of the stereoisomeric adducts **19** was obtained from 500 mg (2.11 mmol) of the α-methylene ketone **14**[9] and a tenfold excess of the acrylate **16**.[22] This mixture was usually not further purified but used directly in the next experiments. For identification the two stereoisomers were separated by rechromatography on 60 g of silica gel with 1:1 ether–petroleum ether. The crystalline isomer was crystallized twice from 1:1 ether–petroleum ether for analysis, while the oily isomer was rechromatographed and dried at high vacuum.

Isomer 19-I: oil; TLC (Et_2O–petroleum ether) R_f 0.48; NMR ($CDCl_3$) δ 0.85 [t, J = 7 Hz, 3, CH_3(ethyl)], 0.88 (s, 3, CH_3), 3.72 (s, 3, OCH_3), and 3.92 (s, 4, OCH_2CH_2O); IR ($CHCl_3$) 1730 (ester C=O) and 1675 cm^{-1} (enol ether C=C).

Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.37; H, 8.49.

Isomer 19-II: mp 95–96.5 °C; TLC (Et_2O–petroleum ether) R_f 0.42; NMR ($CDCl_3$) δ 0.90 (t, J = 8 Hz, 3, ethyl CH_3), 0.91 (s, 3, CH_3), 3.70 (s, 3, OCH_3), and 3.94 (s, 4, OCH_2CH_2O); IR ($CHCl_3$) 1730 (ester C=O) and 1675 cm^{-1} (enol ether C=C).

Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63. Found: C, 68.67; H, 8.66.

In the case of the acrylate **17** the reaction mixture from 1.50 g (6.36 mmol) of α-methylene ketone **14**[9] and 6.50 g (30.4 mmol) of acrylate **17** was cooled and then dissolved in 25 mL of ether. After the resulting ethereal solution was treated with 25 mL of petroleum ether the mixture was cooled at 5 °C in the refrigerator for 2 days. Collection of the crystalline product afforded 2.22 g (77%) of an approximately (NMR) 1:1 mixture of the stereoisomeric adducts **20**. Chromatography of the mother liquors (6 g) on 200 g of silica gel with 1:1 ether–petroleum ether afforded the following fractions.

Fraction I: 4.37 g (85% recovery) of unreacted acrylate **17** (NMR, IR) with 250 mL of eluent.

Fraction II: 0.535 g (19%) of a stereoisomeric mixture of the adduct **20** with 900 mL of eluent. The total combined yield of adduct **20** isolated was 2.755 g (96%). For further experimentation it was not necessary to separate these stereoisomers, but for analytical purposes, a sample was rechromatographed on silica gel with 1:1 ether–petroleum ether, and the individual crystalline isomers crystallized from chloroform–petroleum ether.

Isomer 20-I: mp 125.5–126.5 °C; TLC (Et_2O–petroleum ether) R_f 0.18; NMR ($CDCl_3$) δ 0.88 (s, 3, CH_3), 1.28 (s, 3, side-chain CH_3), 3.72 (s, 3, OCH_3) and 3.92 (s, 8, 2 OCH_2CH_2O); IR ($CHCl_3$) 1725 (ester C=O) and 1675 cm^{-1} (enol ether C=C).

Anal. Calcd for $C_{25}H_{38}O_7$: C, 66.64; H, 8.50. Found: C, 66.70; H, 8.53.

Isomer 20-II: mp 158–159 °C; TLC (Et_2O–petroleum ether) R_f 0.13; NMR ($CDCl_3$) δ 0.90 (s, 3, CH_3), 1.28 (s, 3, side-chain CH_3), 3.68 (s, 3, OCH_3), and 3.94 (s, 8, 2 OCH_2CH_2O); IR ($CHCl_3$) 1725 (ester C=O) and 1675 cm^{-1} (enol ether C=C).

Anal. Calcd for $C_{25}H_{38}O_7$: C, 66.64; H, 8.50. Found: C, 66.56; H, 8.66.

Ketone Ketal 24. A solution of 2.546 g (7.57 mmol) of the Diels–Alder adducts **18** (1:1) in 20 mL of dry ether was added to a well-stirred slurry of 435 mg (11.5 mmol) of $LiAlH_4$ in 80 mL of dry ether under an argon atmosphere at room temperature over a period of 15 min. After stirring for 1 h, the mixture was treated with 3 mL of pyridine, and then 1.00 mL of water and 10 g of anhydrous $MgSO_4$ were added. Stirring was continued for 90 min, and the mixture was then filtered. After removal of the ether at reduced pressure, the viscous residue was dissolved in 60 mL of dry THF and 10 mL of TMEDA under an argon atmosphere and then a few crystals of 1,10-phenanthroline were added. This solution was titrated with 2.2 M n-C_4H_9Li in hexane solution (4.2 mL, 9.2 mmol) to the phenanthroline color change The reaction flask was then immersed in an ice bath and 4.8 mL of $ClPO[N(CH_3)_2]_2$ was added in one lot. After the ice bath was removed, the clear, again yellow solution was stirred for 1 h. The reaction mixture was then poured into 500 mL of 1 N aqueous NaOH solution, and the product was isolated by ether extraction.[19] Purification of the residual gum by chromatography on 250 g of silica gel with 1:1 CH_2Cl_2–acetone afforded 3.070 g (92%) of the two epimeric phosphorodiamidates **21** as a semicrystalline solid: NMR ($CDCl_3$) δ 0.93 (s, 3, CH_3), 1.13 and 1.26 [2 s, 3, CH_2=C(CH_3)O], 2.67 (d, J = 10 Hz, 12, NCH_3), 3.78 (m, 2, $-CH_2O$), 3.94 (s, 4, OCH_2CH_2O–); IR ($CHCl_3$) 1675 cm^{-1} (enol ether C=C). This material was not further purified but used directly for the following type of experiment.

A solution of 104.0 mg (0.235 mmol) of the above phosphorodiamidate mixture **21** in 1.5 mL of dry THF was added in one lot to a well-stirred solution of 7.0 mg (1 mmol) of lithium in 8 mL of dry CH_3NH_2 (freshly distilled from lithium) under an argon atmosphere at reflux temperature. The blue mixture was stirred for 5 min and then quenched with 50 mg of $NaO_2CC_6H_5$, followed by 0.5 mL of water. The CH_3NH_2 was allowed to evaporate, and the residue was partitioned between 70 mL of dilute brine and 30 mL of ether. The aqueous phase was extracted with a second 30-mL portion of ether, and the combined ethereal phases were washed with water (30 mL) and brine (30 mL) and then dried ($MgSO_4$). Evaporation of the solvent at reduced pressure and purification of the residue by chromatography on 25 g of silica gel with 2:1 petroleum ether–ether gave 61.3 mg (89%) of the crystalline ketone ketal **24**, mp 78.5–80 °C. The analytical sample, obtained after crystallization from acetone–n-hexane, melted at 79–80.5 °C: NMR ($CDCl_3$) δ 0.67 (s, 3, CH_3), 3.95 (s, 4, OCH_2CH_2O), and 4.65 (br m, 2, CH_2); IR ($CHCl_3$) 1705 (C=O) and 1650 cm^{-1} (C=C).

Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.93; H, 9.58.

Methylated Ketone Ketals 25 and 26. General Procedure. A. A solution of the stereoisomeric mixture of the esters **19** or **20** in ether was reduced with excess $LiAlH_4$ at room temperature for 1 h. After the addition of a twofold excess (volume/weight of esters) used of pyridine, the mixture was worked up with water and anhydrous $MgSO_4$. After removal of most of the solvents (leaving traces of pyridine to maintain a basic residue), the quantitative recovery of crude alcohols was not further purified but used directly in the following experiment.

B. A solution of the above crude alcohols in 5:1 THF–TMEDA containing a trace of 1,10-phenanthroline as indicator was titrated with an n-C_4H_9Li in hexane solution to the expected color change of the indicator. To this solution was added the calculated quantity of $ClPO[N(CH_3)_2]_2$, and the reaction mixture was stirred at room temperature for 1 h. The crude products **22** or **23**, quantitatively isolated by ether extraction including a base wash,[19] were spectrographically characterized (NMR, IR), but no further purified.

C. A solution of the above phosphorodiamates **22** or **23** in THF was added to a previously prepared blue solution of excess lithium and biphenyl in THF under an argon atmosphere at room temperature, and the mixture was stirred for 2–3 h. This blue-green mixture was cooled to −15 °C and then an eight- to tenfold excess (over phosphorodiamidate) of CH_3I was added. After this muddy brown mixture was stirred for 1.5 h at −10 °C, the suspension was poured into a tenfold volume excess of saturated aqueous $NaHCO_3$ solution, and the products were isolated by ether extraction.[19] After removal of the solvents at reduced pressure, the crude product, which showed the presence of three major components in addition to biphenyl on TLC (Et_2O–petroleum ether), was chromatographed on silica gel with 1:1 ether–petroleum ether. The following products were isolated by this procedure.

Ester 19. A. A solution of 1.67 g (4.77 mmol) of the ester **19** was reduced with 380 mg (10 mmol) of $LiAlH_4$ in 75 mL of ether, and worked up after the addition of 3 mL of pyridine: TLC (Et_2O–petroleum ether) R_f 0.21 and 0.13; NMR ($CDCl_3$) δ 0.87 (t, J = 7 Hz, 3, ethyl CH_3), 0.93 (s, 3, CH_3), 3.50 (m, 2, CH_2OH), and 3.94 (s, 4, OCH_2CH_2O); IR ($CHCl_3$) 3580 (OH) and 1680 cm^{-1} (enol ether C=C).

B. The crude alcohol mixture (1.62 g) in 54 ml of 5:1 THF–TMEDA containing a trace of 1,10-phenanthroline was titrated with 2.5 mL of 2.13 N n-C_4H_9Li solution and quenched with 3.1 mL of $ClPO[N(CH_3)_2]_2$: TLC (Et_2O) R_f ca. 0; NMR ($CDCl_3$) δ 0.98 (t, J = 6 Hz), B, ethyl CH_3), 0.92 (s, 3, CH_3), 2.65 (d, J = 10 Hz, 12, NCH_3), 3.80 (m, 2, CH_2O), and 3.92 (s, 4, OCH_2CH_2O); IR ($CHCl_3$) 1675 cm^{-1} (enol ether C=C).

C. A solution of the above crude phosphorodiamidate (402 mg, 0.88 mmol) in 4 mL of THF was reduced in a solution of 35 mg (1 cm, 5 mmol) of lithium and 300 mg (1.95 mmol) of biphenyl in 10 mL of THF. Methylation was accomplished by the addition of 1.0 mL (16 mmol) of CH_3I in 1 mL of THF. Chromatography of the product mixture afforded the following fractions.

Fraction I: oil, 39 mg (14%) of the O-methylated olefin ketal; TLC (Et_2O–petroleum ether) R_f 0.41; NMR ($CDCl_3$) δ 0.92 (s, 3, CH_3), 1.03 (t, J = 7 Hz, ethyl CH_3), 3.47 (s, 3, OCH_3), 3.94 (s, 4, OCH_2CH_2O), and 4.70 (br s, 2, C=CH_2); IR ($CHCl_3$) 1675 (enol ether C=C) and 1645 cm^{-1} (C=C). This sample was too hydrolytically labile for combustion analysis.

Fraction II: oil, 14 mg (5%) of the C-1 epimeric methylated olefin ketone ketal; TLC (Et_2O–petroleum ether) R_f 0.27; NMR ($CDCl_3$) δ 0.82 (s, 3, C-9 CH_3), 1.16 (t, J = 7 Hz, 3, ethyl CH_3), 1.18 (s, 3, $ClCH_3$), 3.94 (s, 4, OCH_2CH_2O), and 4.70 (br s, 2, C=CH_2); IR ($CHCl_3$) 1690 (C=O) and 1645 cm^{-1} (C=C).

Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 74.79; H, 10.07.

Fraction III: oil, 168 mg (59%) of the ketone ketal **25**; TLC (Et_2O–petroleum ether) R_f 0.19; NMR ($CDCl_3$) δ 0.76 (s, 3, C-9 CH_3), 1.03 (t, J = 7 Hz, 3, ethyl CH_3), 1.20 (s, 3, $ClCH_3$), 3.94 (s, 4, OCH_2CH_2O), and 4.70 (br s, 2, C=CH_2); IR ($CHCl_3$) 1705 (C=O) and 1645 cm^{-1} (C=C).

Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 75.00; H, 10.11.

Ester 20. A. A solution of 5.64 (12.5 mmol) of the ester **20** in 290 mL of THF was reduced with 950 mg (25 mmol) of $LiAlH_4$ and worked up after the addition of 10 mL of pyridine: TLC (Et_2O) R_f 0.31 and 0.25; NMR ($CDCl_3$) δ 0.92 (s, 3, CH_3), 1.30 (s, 3, side-chain CH_3), 3.52 (m, 2, CH_2OH), and 3.94 (s, 8, 2 OCH_2CH_2O); IR ($CHCl_3$) 3580, 3480 (OH), and 1675 cm^{-1} (enol ether C=C).

B. A solution of the above crude alcohol (6.0 g) in 120 ml of 5:1 THF–TMEDA containing a trace of 1,10-phenanthroline was titrated with 5.6 mL of 2.37 N n-C_4H_9Li and then quenched with 9.0 mL of $ClPO[N(CH_3)_2]_2$: TLC (CH_2Cl_2–acetone, 1:1) R_f 0.31; NMR ($CDCl_3$) δ 0.92 (s, 3, CH_3), 1.30 (s, 3, side-chain CH_3), 2.65 (d, J = 10 Hz, 12, NCH_3), 3.80 (m, 2, $-CH_2O$), and 3.94 (s, 8, 2 OCH_2CH_2O); IR ($CHCl_3$) 1675 cm^{-1} (enol ether C=C).

C. A solution of the above crude phosphorodiamidate (2.03 g, 3.65 mmol) in 18 mL of THF was reduced in a solution of 175 mg (5 cm, 25 mmol) of lithium and 1.5 g (9.75 mmol) of biphenyl in 40 mL of THF. Methylation was accomplished by the addition of 5.0 mL (80 mmol) of CH_3I in 5 mL of THF. Chromatography of the product mixture afforded the following fractions.

Fraction I: oil, 184 mg (12%) of the O-methylated olefin ketal; TLC (C_6H_6–EtOAc, 3:1) R_f 0.43; NMR ($CDCl_3$) δ 0.92 (s, 3, CH_3), 1.31 (s, 3, side-chain CH_3), 3.47 (s, 3, OCH_3), 3.94 (s, 8, 2 OCH_2CH_2O), and 4.72 (br s, 2, C=CH_2); IR ($CHCl_3$) 1665 (enol ether C=C) and 1645 cm^{-1} (C=C)

Anal. Calcd for $C_{25}H_{40}O_5$: C, 71.39; H, 9.59. Found: C, 71.11; H, 9.57.

Fraction II: oil, 213 mg (14%) of the C-1 epimeric methylated olefin ketone ketal; TLC (C_6H_6–EtOAc, 3:1) R_f 0.35; NMR ($CDCl_3$) δ 0.82 (s, 3, C-9 CH_3), 1.17 (s, 3, $ClCH_3$), 1.31 (s, 3, side-chain CH_3), 3.92, 3.97 (2 s, 8, 2 OCH_2CH_2O), and 4.72 (br s, 2, $C=CH_2$); IR ($CHCl_3$) 1690 (C=O) and 1645 cm^{-1} (C=C).

Anal. Calcd for $C_{25}H_{40}O_5$: C, 71.39; H, 9.59. Found: C, 71.31; H, 9.59.

Fraction III: oil, 796 mg (52%) of the ketone ketal **26**;TLC (C_6H_6–EtOAc, 3:1) R_f 0.27; NMR ($CDCl_3$) δ 0.77 (s, 3, C-9 CH_3), 1.20 (s, 3, C-1 CH_3), 1.31 (s, 3, side-chain CH_3), 3.94, 3.97 (2 s, 8, 2 OCH_2CH_2O), and 4.72 (br s, 2, $C=CH_2$); IR ($CHCl_3$) 1700 (C=O) and 1645 cm^{-1} (C=C).

Anal. Calcd for $C_{25}H_{40}O_5$: C, 71.39; H, 9.59. Found: C, 71.36; H, 9.50.

Ozonization of Olefinic Ketone Ketals 25 and 26. General Procedure. A stream of ozonized oxygen was passed through a methanolic solution of the respective olefins **25** and **26** for the indicated time at −40 °C. After cooling to −60 °C, the reaction mixture was treated with CH_3SCH_3 and then stirred at −10 °C (1 h), 0 °C (1 H), and room temperature (4 h). Evaporation of the solvents at reduced pressure and isolation of the product from the residue by ether extraction[19] afforded the crude ketones, which were then purified by chromatography on silica gels indicated.

Olefinic Ketone Ketal 25. Ozonization of 137 mg (0.428 mmol) of the olefin **25** in 25 mL of CH_3OH for 7 min, workup with 2.0 mL of CH_3SCH_3, and chromatography of the crude product on 20 g of silica gel with 3:1 C_6H_6–EtOAc afforded 118 mg (85%) of the corresponding diketone ketal as an oil which crystallized on standing. The analytical sample, obtained after two crystallizations of this material from EtOAc–hexane, melted at 64–65 °C; TLC (C_6H_6–EtOAc) R_f 0.25; NMR ($CDCl_3$) δ 0.77 (s, 3, C-9 CH_3), 1.05 (t, J = 7 Hz, side-chain CH_3), 1.16 (s, 3, C-1 CH_3), and 3.94 (s, 4, OCH_2CH_2O); IR ($CHCl_3$) 1700 cm^{-1} (C=O).

Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.73; H, 9.33.

Olefinic Ketone Ketal 26. Ozonization was carried out on three equal batches of 6.0 g (14.25 mmol) of the olefin **26** in 600 mL of CH_3OH at −40 °C for 40 min, and each batch was worked up with 45 mL of CH_3SCH_3. The combined crude products were first filtered through 50 g of silica gl with EtOAc and then the residue from the eluent was rechromatographed on 410 g of silica gel in a medium-pressure chromatography apparatus[18] with gradient solvent elution. Solvents used in sequence were 1.2 L of C_6H_6, followed by adding the following amounts to a stirred reservoir: 1.2 L of 3:1 C_6H_6–EtOAc, 4 L of 2:1 C_6H_6–EtOAc, and 3 L of 1:1 C_6H_6–EtOAc. In this manner 13.0 g (72%) of the diketone diketal was obtained from the latter two eluent fractions as an oil. The analytical sample, obtained after another chromatogram with 2:1 C_6H_6–EtOAc, was also an oil: TLC (3:1 C_6H_6–EtOAc) R_f 0.11; NMR ($CDCl_3$) δ 0.78 (s, 3, C-9 CH_3), 1.15 (s, 3, C-1 CH_3), 1.31 (s, 3, side-chain CH_3), and 3.95, 3.98 (2 s, 8, 2 OCH_2CH_2O); IR ($CHCl_3$) 1700 cm^{-1} (C=O).

Anal. Calcd for $C_{24}H_{38}O_6$: C, 68.22; H, 9.06. Found: C, 68.29; H, 9.10.

Enone 27. In a manner similar to that described above for the formation of the enone **13** a solution of 115 mg (0.355 mmol) of the diketone in 35 ml of degassed 0.18 N 75% aqueous methanolic KOH was heated under reflux under an argon atmosphere for 14 h. The solution was neutralized with 0.36 mL of HOAc, cooled, and diluted with water, and the product was isolated by ether extraction.[19] The product obtained after removal of the solvent at reducd pressure amounted to 108 mg (98%) of the enone **27**. mp 126–127 °C. The analytical sample, obtained after one crystallization of a sample of this material from ether, melted at 127–128 °C: TLC (1:1 Et_2O–petroleum ether) R_f 0.17; NMR ($CDCl_3$) δ 0.82 (s, 3, C-9b CH_3), 1.30 (s, 3, C-4a CH_3), 1.78 (s, 3, C-1 CH_3), and 3.95 (s, 4, OCH_2CH_2O); IR ($CHCl_3$) 1655, 1605 cm^{-1} (C=C–C=O).

Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.97: H. 9.24.

In the same manner of the above diketone diketal (12.4 g, 29.4 mmol) afforded 10.1 g (85%) of the enone **13** which was identical with that prepared above.

Triketone 28. To an argon-protected solution of 3.7 mg (1 mm, 0.53 mmol) of lithium in 6 mL of dry NH_3 and 1 mL of dry THF was added a solution of 80.8 mg (0.2 mmol) of the enone **13** in 1 mL of dry THF and 3.7 μL (0.2 mmol) of H_2O. After the blue mixture had stirred for 15 min a solution of 0.15 mL of CH_3I in 0.5 mL of dry THF was added, and the resulting mxiture was stirred for 45 min. After evaporation of the ammonia in an argon jet, the product was isolated by ether extraction.[19] Evaporation of the solvent at reduced pressure afforded 104 mg of crude solid product which was combined with 414 mg of similar material from the reductive methylation of 344.1 mg (0.85 mmol) of the enone **13** with 16.6 mg (4.5 mm, 2.37 mmol) of lithium and 0.52 mL of CH_3I in 26 mL of dry NH_3 and 10 mL of dry THF containing 15.8 μL (0.86 mmol) of H_2O.

A solution of these combined crude products (518 mg) in 35 mL of acetone and 6 mL of 10% aqueous hydrochloric acid was stirred at room temperature for 1 h. The reaction mixture was then poured into 100 mL of saturated aqueous $NaHCO_3$, and the product was isolated by ether extraction.[19] Purification of the crude product (414 mg) by chromatography on 100 g of silica gel with 3:1 benzene–ethyl acetate afforded 230 mg (64%) of the triketone **28**, mp 158–161 °C. The analytical sample obtained after crystallization of a portion of this material from ether, melted at 161–162.5 °C: TLC (ether) R_f 0.28; NMR ($CDCl_3$) δ 1.06 (s, 3, CH_3), 1.10 (s, 3, CH_3), 1.34 (s, 3, CH_3), and 2.06 (s, 3, $COCH_3$); IR ($CHCl$) 1700 cm^{-1} (C=O).

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.86; H, 9.63.

Enedione 30. A solution of 245 mg (0.74 mmol) of the triketone 28 in 74 mL of 1% aqueous methanolic (3:1) KOH was heated at reflux in an argon atmosphere for 1.5 h. After cooling, the reaction mixture was neutralized with 0.74 mL of glacial HOAc, and the product was isolated by ether extraction.[19] Purification of the crude solid product by chromatography on 100 g of silica gel with 2:1 benzene–ethyl acetate gave 195 mg (84%) of the crystalline enedione **30**, mp 250–252 °C. The analytical sample, obtained after crystallization of a portion of this material from CH_2Cl_2–C_2H_5OH, melted at 252–253 °C: TLC (1:1 benzene–ethyl acetate) R_f 0.38; NMR ($CDCl_3$) δ 0.97 (s, 3, CH_3), 1.15 (s, 3, CH_3), 1.27 (s, 3, CH_3), 5.82 (s, 1, C-4 H); IR ($CHCl_3$) 1705 (C=O), 1660 α,β-unsaturated C=O), and 1640 cm^{-1} (C=C).

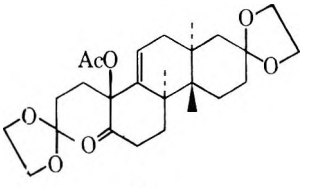
Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.08; H, 9.75.

Hydroxy Enone 29. A. Preparation of Dienol Acetate. A solution of 1.205 g (2.98 mmol) of the enone **13** in 120 mL of dry THF containing 5 drops of dry t-BuOH was stirred and heated under reflux in an argon atmosphere for 20 h with 145 mg (82.5 mg of NaH, 3.44 mmol) of a 57% mineral oil dispersion of NaH. After the mixture was cooled to −15 °C, 2.5 mL (26.5 mmol) of acetic anhydride was added, and stirring was continued for 18 min as the mixture was warmed to 10 °C. The mixture was then poured into 600 mL of ice-cooled, saturated $NaHCO_3$, and the product was isolated by ether extraction.[19] Purification of the crude product (1.378 g) on 150 g of silica gel with ether afforded 1.119 mg (84%) of the dienol acetate as an oil. Rechromatography of a portion of this material on silica gel with 1:1 ether–petroleum ether afforded the analytical sample as an oil: TLC (ether) R_f 0.48; NMR ($CDCl_3$) δ 0.82 (s, 3, CH_3), 1.05 (s, 3, CH_3), 1.30 (s, 3, CH_3), 2.15 (s, 3, $COCH_3$), 3.92 (s, 8, 2 OCH_2CH_2O), and 5.67 (t, $J \simeq 3$ Hz, 1, C=CH); IR ($CHCl_3$) 1745 (C=O) and 1655, 1630 cm^{-1} (C=C).

Anal. Calcd for $C_{26}H_{38}O_6$: C, 69.93; H, 8.58. Found: C, 69.96; H, 8.59.

B. Oxidation of Dienol Acetate. At nine 15-min intervals 0.1 mL of a 1.54 M solution of peracid (prepared from 1.25 g of 85% m-chloroperbenzoic acid and 12.5 mg of 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide in 4 mL of pure dioxane) was added with stirring at room temperature to a solution of 1.100 g (2.46 mmol) of the dienol acetate above in 45 mL of dioxane and 17 mL of H_2O. A total of 2.25 equiv of peracid was added over the initial 2-h period, and then the mixture was stirred for an additional 4 h. After the reaction was quenched by the addition of 3 mL of 10% aqueous $NaHSO_3$ solution, the product was isolated by 4:6 CH_2Cl_2–ether extraction including a base wash.[19] Purification of the crude oily residue (1.299 g) was accomplished by chromatography on 150 g of silica gel. Fractions of 20 mL were collected in the following sequence: 1:1 benzene–ethyl acetate (fractions 1–25), 4:6 benzene–ethyl acetate (fractions 26–80), and 3:7 benzene–ethyl acetate (fractions 81–130).

I. Fractions 16–27 contained 399 mg (35%) of the acetoxy ketone **35**.



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This material crystallized, and the analytical sample, prepared by crystallization of a portion from ether and then CH_2Cl_2–petroleum ether, melted at 137–138 °C: TLC (ether) R_f 0.33; NMR ($CDCl_3$) δ 0.89 (s, 3, CH_3), 1.23 (s, 3, CH_3), 1.28 (s, 3, CH_3), 2.05 (s, 3, CH_3CO), 3.92

(s, 8, 2 OCH_2CH_2O), and 5.57 (m, 1, C=CH); IR ($CHCl_3$) 1745 (CH_3C=O), 1720 (C=O), and 1655 cm^{-1} (C=C).

Anal. Calcd for $C_{26}H_{38}O_7$: C, 67.51; H, 8.28. Found: C, 67.59; H, 8.23.

II. Fractions 56–130 contained 647 mg (59%) of the desired hydroxy enone **29** which crystallized on trituration with ether. The analytical sample, obtained after two crystallizations of a portion of this material from CH_2Cl_2–petroleum ether, melted at 182–183 °C: TLC (ether) R_f 0.125; NMR ($CDCl_3$) δ 0.80 (s, 3, CH_3), 1.34 (s, 3, CH_3), 1.49 (s, 3 CH_3), 3.92, 3.93 (2 s, 8, 2 OCH_2CH_2O), and 4.90 (m, 1, CHOH); IR ($CHCl_3$) 3590, 3450 (OH), 1650 (C=O), and 1575 cm^{-1} (C=C).

Anal. Calcd for $C_{24}H_{36}O_6$: C, 68.55; H, 8.63. Found: C, 68.39; H, 8.57.

Hydroxy Ketone 32. To an argon-protected solution of 8.3 mL (1.92 mmol) of 0.232 M lithium diisopropylamide in THF in 8.3 mL of dry THF cooled to −78 °C was added in 2 min a solution of 647 mg (1.54 mmol) of the hydroxy enone **29** in 4 mL of dry THF and stirring was continued at −78 °C for an additional 2 min. This "alkoxide" solution was then transferred via fine Teflon tubing under argon pressure to an argon-protected, cold (−78 °C) solution of 35 mg (1 cm, 5 mmol) of lithium in 70 mL of dry NH_3 and 20 mL of dry THF. The flask and tubing were rinsed with 1.0 mL of dry THF. After the reaction mixture had stirred at −78 °C for 45 min, $NaO_2CC_6H_5$ was added to discharge the blue color, and then 270 mg (5 mmol) of NH_4Cl was added. The ammonia was evaporated; water was added, and the products were isolated by extraction with 4:6 CH_2Cl_2–ether.[19] Purification of the crude product (590 mg) by one chromatogram on 150 g of silica gel with ether and then rechromatography of the mixed center fractions on 50 g of silica gel with ether afforded 240 mg (37%, 54% based on recovered hydroxy enone **29**) of the hydroxy ketone **32**, as a glass which crystallized on trituration with ether, and 302 mg (31%) of recovered hydroxy enone **29**.

The analytical sample of the hydroxy ketone **32**, obtained after two crystallizations of a portion of this material from ether, melted at 121–122 °C; TLC (ether) R_f 0.15; NMR ($CDCl_3$) δ 0.87 (s, 3, CH_3), 1.32 (s, 3, CH_3), 1.37 (s, 3, CH_3), 3.95 (s, 8, 2 OCH_2CH_2O), and 4.05 (m, 1, CHOH); IR ($CHCl_3$) 3610, 3475 (OH), and 1700 cm^{-1} (C=O).

Anal. Calcd for $C_{24}H_{38}O_6$: C, 68.22; H, 9.06. Found: C, 68.16; H, 9.13.

Reductive methylation of the hydroxy enone **29** by a similar process but with the substitution of CH_3I addition for the $NaO_2CC_6H_5$ quench led to a crude product with at least seven components as judged by TLC (ether). No pure products were obtained after extensive chromatography.

Enone 34. The hydroxy ketone **32** (74 mg) was converted in quantitative crude yield (yellow foam) to the α,β-unsaturated hydroxy ketone **34** with 2.16 equiv of lithium diisopropylamide and 1.18 equiv of phenylselenium bromide in 10 mL of dry THF at −78 °C and then 0.05 mL of 30% H_2O_2 in 10 mL of dry THF and 0.025 mL of pyridine. After chromatography of this material on 5 g of alumina (Woelm III) with 20:10:1 benzene–EtOAc–CH_3OH, a white foam was obtained with resisted crystallization: TLC (1:1 ethyl acetate–benzene) R_f 0.17; NMR ($CDCl_3$) δ 0.88 (s, 3, CH_3) 1.30 (s, 3, CH_3), 1.34 (s, 3, CH_3), 3.96 (s, 8, 2 OCH_2CH_2O), 4.05 (m, 1, CHOH), 5.86 (d, J = 10 Hz, 1, O=CCH=C), and 6.93 (d, J = 10 Hz, 1, O=CC=CH); IR ($CHCl_3$) 3600 (OH) and 1665 cm^{-1} (C=O); MS molecular ion peak at 420.253 (calcd, 420.251). No material was used in combustion analysis.

Attempted methylation of this enone **34** in *t*-BuOH or THF with KO-*t*-Bu and CH_3I led to no isolable C-methylated product. The NMR spectrum of the crude methylation mixture instead showed a major resonance at δ 3.72 ($CDCl_3$), probably due to O-methylation of the hydroxyl group, as, for example, **33**. No further experimentation on this process was conducted.

Registry No.—**2,** 38255-71-9; **3,** 38255-75-3; *cis*-**3** dihydro derivative, 61570-10-3; **4,** 38255-76-4; *cis*-**4** dihydro derivative, 61616-08-8; **4** tertiary alcohol derivative, 61570-11-4; **4** secondary alcohol derivative, 61570-12-5; **5,** 38255-78-6; **6,** 38255-77-5; **7,** 38255-80-0; **7** β-ol phosphorodiamidate, 61570-13-6; **8,** 38255-81-1; **8** deoxo derivative, 38255-79-7; **9,** 38255-84-4; **10,** 35890-75-6; **10** bisketal, 61570-14-7; **11,** 61570-15-8; **11** β,γ-unsaturated derivative, 61570-16-9; **11** epoxide, 61570-17-0; 11 epoxide hydrazone, 61570-18-1; **12,** 61570-19-2; **12** acetylenic diketone derivative, 61570-20-5; **12** triketone derivative, 61570-21-6; **13,** 61570-22-7; **13** dienol acetate, 61570-23-8; **14,** 35890-72-3; **15,** 80-62-6; **16,** 10500-08-0; **17,** 61570-24-9; **18**-I α-Me, 61570-25-0; **18**-II β-Me, 61616-09-9; **19**-I α-Et, 61570-26-1; **19**-II β-Et, 61616-10-2; **20**-I α-$(CH_2)_3$–C(CH_3)–O–O, 61570-27-2; **20**-II β-$(CH_2)_3$–C(CH_3)–O–O, 61616-11-3; **21** α-Me, 61570-28-3; **21** β-Me, 61616-12-4; **22,** 61570-29-4; **23,** 61617-67-2; **24,** 61570-30-7; **25,** 61570-31-8; **25** fraction I, 61570-32-9; **25** fraction II, 61616-13-5; **25** diketone ketal, 61618-15-3; **26,** 61665-00-7; **26** fraction I, 61570-33-0; **26** fraction II, 61570-34-1; **26** diketone diketal, 61618-16-4; **27,** 61570-35-2; **28,** 61570-36-3; **29,** 61570-37-4; **30,** 61616-14-6; **32,** 61570-38-5; **34,** 61570-39-6; **35,** 61570-40-9; ethylene glycol, 107-21-1; dimethyl malonate, 108-59-8; 4,4-ethylenedioxy-1-iodopentane, 369-28-1; $ClPO[N(CH_3)_2]_2$, 1605-65-8.

References and Notes

(1) The authors are grateful for the support of this investigation by Public Health Service Research Grant AM 14160 from the National Institute of Arthritis and Metabolic Diseases and the Hoffmann-La Roche Foundation.
(2) On study leave from the Centre National de la Recherche Scientifique, France.
(3) Fellow of Stiftung für Stipenden auf dem Gebiete der Chemie, Switzerland.
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(18) Boiling points are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 237B grating infrared spectrometer and nuclear magnetic resonance (NMR) spectra were recorded using a Varian T-70 spectrometer. Chemical shifts are reported as δ values in parts per million relative to Me_4Si (δ 0.0 ppm) as an internal standard. Deuteriochloroform for NMR and chloroform for IR spectra were filtered through neutral alumina before use.

Vapor phase chromatographic (VPC) analyses were determined on either a Hewlett-Packard 5750 equipped with a flame ionization detector of a Varian 920 equipped with a thermal conductivity detector using helium as the carrier gas under the indicated conditions. The indicated liquid phase was absorbed on 60–80 mesh Chromosorb W AW DMCS.

Silica gel columns used the 0.05–0.2 mm silica gel manufactured by E. Merck and Co., Darmstadt, Germany. Acidic silica gel refers to Silicar CC-4 Special "for column chromatography", sold by Mallinckrodt Chemical Works, St. Louis, Mo. Preparative medium-pressure chromatography was performed using glass columns of the indicated length and diameter with fittings supplied by Laboratory Data Control, Riviera Beach, Fla., and an instrument minipump supplied by Milton Roy Co., St. Petersburg, Fla. (Instrumentation designed by R. H. Mueller, those laboratories, and copies are available on request). The columns were packed with silica gel H "for TLC acc. to Stahl" (10–40 μ) manufactured by E. Merck and Co., Darmstadt, Germany. Solvents were degassed under water aspirator vacuum prior to use.

Analytical thin layer chromatography was conducted on 2.5 × 10 cm precoated TLC plates, silica gel 60 F-254, layer thickness 0.25 mm, manufactured by E. Merck and Co., Darmstadt, Germany.

"Dry" solvents were dried immediately prior to use. Ether and tetrahydrofuran (THF) were distilled from lithium aluminum hydride; pyridine, triethylamine, diisopropylamine, *N*-isopropylcyclohexylamine, trimethylchlorosilane (Me_3SiCl), hexamethylphosphoramide (HMPA), and benzene were distilled from calcium hydride; dichloromethane, methyl iodide, and hexane were distilled from phosphorus pentoxide. "Petroleum ether" refers to the "analyzed reagent" grade hydrocarbon fraction, bp 30–60 °C, which is supplied by J. T. Baker Co., Phillipsburg, N.J., and was not further purified.

Standard solutions of *tert*-butyldimethylchlorosilane (*t*-$BuMe_2SiCl$) in hexane (ca. 3.3 M) or HMPA (ca. 1.5 M) were employed.

Reactions were run under an argon atmosphere arranged with a mercury bubbler so that the system could be alternately evacuated and filled with argon and left under a positive pressure.

Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.
(19) In cases where the products were isolated "by solvent extraction", the procedure generally followed was to dilute the reaction mixture with the indicated solvent or to extract the aqueous solution with several portions of the indicated solvent; then the combined organic layers were washed with several portions of water followed by saturated brine. The organic layer was dried over anhydrous sodium or magnesium sulfate, then filtered, and the solvent was evaporated from the filtrate under reduced pressure (water aspirator) using a rotary evaporator. The use of the terms "base wash" or "acid wash" indicate washing the organic solution with saturated

aqueous sodium bicarbonate solution or with dilute aqueous hydrochloric acid, respectively, prior to the aforementioned wash with water.

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Studies on the Total Synthesis of Steroidal Antibiotics. 3. Generation and Correlation of Tetracyclic Derivatives from the Degradation of Fusidic Acid and Total Synthesis[1]

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Received October 1, 1976

idic acid (1) to the tetracyclic enone 11 is described. The principle phases of this conver-
side chain and then expansion of the five-membered D ring. The racemic form of the
e synthetic enedione 12. The central feature of this transformation entails the boron
rrangement of the epoxide 14 and then removal of the C-6 ketone through reduc-
date. The identity of the racemic and naturally derived enones 11 establishes
thetic plan employed.

Robert E. Ireland
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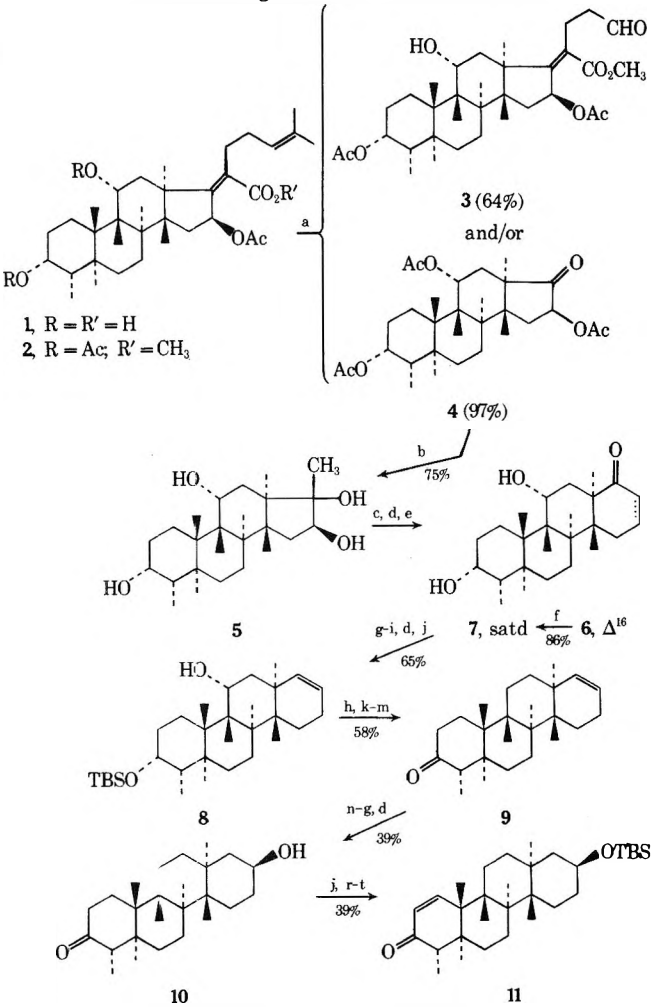
Rudolf Giger, and Susumu Kamata:
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Synthesis
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In the preceding pape ent ap-
proaches to the synthesis etra-
cyclic intermediates, such as t ed.
In addition to the necessary dev
the construction of such intermedi
of these and subsequent substances
portance. The availability of fusidic acid
sources through the kind auspices of Dr. W
(Leo Pharmaceuticals) and Hoffmann-La Co.
made possible a project aimed at not only the p ion of
comparison samples of tetracyclic derivatives known
stereochemistry through the selective degradation of the
natural product, but also the generation of larger quantities
of these materials suitable for use as relay substances for the
synthetic effort. The latter consideration becomes of impor-
tance as a result of the low yields experienced in the synthetic
phase of the work that is associated with the introduction of
the C-11α OH and the formation of the trans A/B ring system.
To these ends the degradation of fusidic acid (1) outlined in
Chart I was undertaken and together with the further syn-
thetic transformations of the diketone 12 (Chart II) forms the
subject of this report.

In view of the previously reported[2] difficulties involved in attempts to introduce the C-11α OH function into tricyclic synthetic intermediates, this problem was shelved and efforts continued to develop a synthetic scheme for the C-11 deoxy series. In this series a logical junction between the synthetic and degradation sequences was at the enone **11**. This intermediate that had the required fusidic acid nuclear stereochemistry and was as well prestaged for the completion of the synthesis of C-11 deoxyfusidic acid through contraction of ring D and addition of the side chain. The ring A enone functionality in the intermediate **11** was necessary in the synthetic sequence (Chart II) in order to append the C-4 CH_3, but was also envisaged as possibly providing access through C-1 to C-11, and hence the ultimate introduction of a C-11α OH grouping.

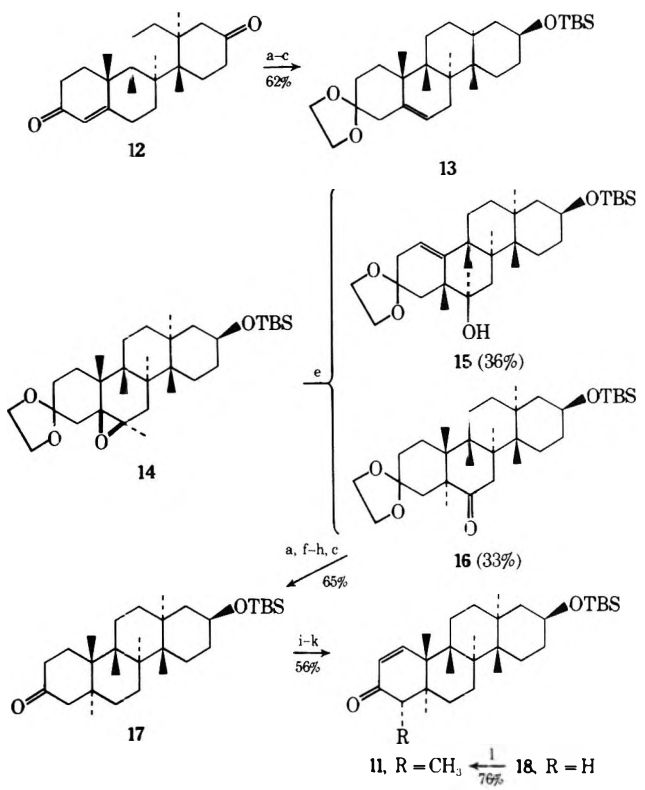
In the fusidic acid (1) degradation[3,4] removal of the side chain could be accomplished by stages whereby the isopropylidene grouping was cleaved first by brief treatment with ozone (aldehyde **3**) or completely in one more prolonged ozonization to the keto triacetate **4**. Expansion of the D ring to the enone **6** was accomplished through aldol-type cyclization of the *D*-secoketo aldehyde obtained by periodate

Chart I. Degradation of Fusidic Acid[a]



[a] a, O_3, CH_3OH, CH_3SCH_3; b, CH_3Li, THF; c, H_5IO_6, CH_3OH–H_2O; d, H_3O^+; e, KOH, CH_3OH–H_2O; f, 10% Pd/C, H_2, HOAc; g, DHP, H^+, C_6H_6; h, LDA, THF; $ClPO(NMe_2)_2$, HMPA–THF; i, Li, *t*-BuOH, $NH_3(l)$; j, *t*-$BuMe_2SiCl$, imidazole, DMF; k, Li, *t*-BuOH, $EtNH_2$; l, $(n\text{-}Bu)_4NF$, THF; m, CrO_3, HOAc; n, $(HOCH_2)_2$, H^+, C_6H_6; o, Sia_2BH, H_2O_2, OH–THF; p, $CrO_3 \cdot 2Py$, CH_2Cl_2; q, $Li(t\text{-}BuO)_3AlH$, THF; r, NaH, HCO_2Et, C_6H_6; s, DDQ, C_6H_6; t, $[(C_6H_5)_3P]_3RhCl$, C_6H_6.

Chart II. Synthesis of Tetracyclic Relay[a]



[a] a, Li(*t*-BuO)$_3$AlH, THF; b, $(CH_2OH)_2$, H^+, C_6H_6; c, *t*-BuMe$_2$SiCl, imidazole, DMF; d, MCPBA, CH_2Cl_2; e, $BF_3 \cdot Et_2O$, CH_2Cl_2; f, LDA, THF; $ClPO(NMe_2)_2$, THF–HMPA; g, Li, *t*-BuOH, THF, $EtNH_2$; h, H_3O^+; i, NaH, HCO_2Et, C_6H_6; j, DDQ, C_6H_6; k, $[(C_6H_5)_3P]_3RhCl$, C_6H_6; l, LDA, THF; CH_3I.

cleavage of the tetrol **5**. Conversion of the dihydroxy ketone **7** to the olefinic ketone **9** utilized a sequence of phosphorodiamidate reductions.[5] First the 17(17a) olefin was generated through reduction of the enol phosphorodiamidate of the C-17a carbonyl and then C-11α OH was reductively removed through the phosphorodiamidate of the C-3 silyl ether **8**. Hydroboration of the ketal of the ketone **9** served to introduce the C-17 OH and then introduction of the C-1(2) unsaturation by the method of Caspi[6] led to the desired enone **11**. While the unimpressive overall yield of this multistage process (2–4% depending on the variations in the yields observed in the periodate cleavage step) leaves a lot to be developed before the enone **11** is a viable relay substance, sufficient naturally derived material was obtained for comparison with the enone **11** from the synthetic sequence (Chart II).

The key to the synthetic effort was the plan developed in the earlier tricyclic model series[7] for the introduction of the C-5α H. This process entailed the boron trifluoride etherate rearrangement of the initially formed C-5β,C-6β epoxide **14**, a substance that was efficiently formed from the enedione **12** as shown (Chart II). In contrast to the tricyclic model series, however, the yield of this rearrangement was not high. In the tricyclic model series an adequate 63% yield of the desired trans-syn-trans C-6 ketone resulted and no other skeletally rearranged by-products could be found. In the present tetracyclic series, the yield of the desired ketone **16** was only 33% and in this case skeletally rearranged alcohols such as **15** were equally as available. In spite of much variation of reaction conditions and substrate functionality, the best yield of the desired ketone **6** was obtained under the initial conditions. In view of this setback in the yield of this crucial rearrangement, it became particularly important to be certain of the stereochemistry of the ketone **16**. Since the results in this tetracyclic series differed so much from those of the tricyclic model series, doubt was even cast on the expected stereochemical outcome of the desired product. In order to assuage this doubt as well as investigate the subsequently planned transformations, the ketone **16** was converted into the enone **11**.

In the same manner as described for the tricyclic model series, the C-6 ketone was removed through the phosphorodiamidate reduction and the trans-syn-trans-anti-trans ketone **17** became available. In order to correlate this synthetic series with the derivatives from fusidic acid (**1**) itself it was necessary to introduce the C-4 CH_3. This process required the blocking of the C-2 position of the ketone **17** and the C-1(2) unsaturation was chosen for this purpose. Again the procedure developed by Caspi[6] proved satisfactory, and the ketone **11** was prepared through the unsaturated ketone **18**. It was gratifying to find that the spectral (NMR, IR, TLC, and MS) properties of this racemic sample of the ketone **11** and those of the naturally derived material above were indeed identical. It is thus possible to utilize this synthetic scheme for the further contraction of the D ring and the addition of the fusidic acid side chain with the aim toward completion of the total synthesis. As well, the naturally derived material may provide a useful relay substance for the synthesis after resolution of the synthetic sample and refinement of the degradation scheme. Work in these directions is in progress.

Experimental Section[8]

Methyl Diacetylfusidate (2). To a solution of 11.4 g (21.5 mmol) of methyl fusidate[3] [prepared in quantitative yield by the action of ethereal diazomethane on fusidic acid (**1**)[9]] in 100 mL (1.15 mol) of acetic anhydride and 40 mL (0.37 mol) of acetyl chloride was added 1 g (8.2 mmol, 0.38 equiv) of 4-dimethylaminopyridine,[10] and the mixture was stirred in the dark at room temperature for 2 h. After treatment of the reaction mixture with ice (500 g) and 120 mL of pyridine for 2 h, isolation of the product from this aqueous mixture by ether extraction[11] and then azeotropic distillation of toluene (3 × 100 mL) gave 12.2 g (quantitative) of the diacetate **2**, mp 135–137 °C. The analytical sample, obtained after crystallization of a portion of this material from EtOH, melted at 137–138 °C: TLC (1:1 benzene–EtOAc) R_f 0.64; IR ($CHCl_3$) 1710–1725 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.80 (d, J = 7 Hz, 3, C-4 CH_3), 0.94 (s, 3, CH_3), 0.98 (s, 3, CH_3), 1.36 (s, 3, CH_3), 1.56 (s, 3, CH_3C=C), 1.66 (s, 3, CH_3C=C), 1.99 (s, 3, CH_3CO), 2.06 (s, 3, CH_3CO), 3.62 (s, 3, CH_3O), 4.94 (m, 1, C-3β H), 5.02 (m, 1, C-24 H), 5.24 (m, 1, C-11β H), and 5.83 (d, J = 8 Hz, 1, C-16α H).

Anal. Calcd for $C_{36}H_{54}O_8$: C, 70.33; H, 8.85. Found: C, 70.42; H, 8.87.

Ozonolysis of Methyl Diacetylfusidate (2). A. Formation of Trisnoraldehyde 3. A solution of 93 mg (0.15 mmol) of methyl diacetylfusidate (**2**) in 8 mL of CH_3OH was cooled to −40 °C and ozonized oxygen was passed through the solution until the effluent gases liberated iodine (yellow coloration) from a test solution of 10% aqueous KI. After the temperature of the cooling bath was lowered to −60 °C and a stream of nitrogen had been passed through the solution for 5 min, 2 mL of CH_3SCH_3 was added, and the mixture was stirred for 1 h at −10 °C, 1 h at 0 °C, and 2 h at room temperature. Isolation of the products by ether extraction including a base wash[11] afforded 103 mg of a mixture of two products which was separated by preparative TLC (silica gel, 1:1 benzene–EtOAc). The material with R_f 0.51 (23 mg, 34%) was shown to be the keto triacetate **4** by comparison of its spectra (IR, NMR) with those of the material obtained in part B.

The material with R_f 0.41 amounted to 57 mg (64%) of the aldehyde **3**, an analytical sample of which was obtained by crystallization from benzene: mp 81–82 °C; IR ($CHCl_3$) 2820, 2720 (HC=O), and 1720 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.82 (s, 3, CH_3), 0.95 (s, 3, CH_3), 1.00 (s, 3, CH_3), 1.38 (s, 3, CH_3), 3.64 (s, 3, CH_3O), 4.91 (m, 1, C-3β H), 5.27 (m, 1, C-11β H), 5.83 (d, J = 8 Hz, 1, C-16α H), and 9.72 (s, 1, HC=O).

Anal. Calcd for $C_{33}H_{49}O_9$: C, 67.32; H, 8.22. Found: C, 67.36; H, 8.15.

Reduction of a sample (100 mg) of this aldehyde **3** from another experiment with $NaBH_4$ (6.5 mg) in 10 mL of EtOH afforded 83 mg of crude alcohol which was acetylated with acetic anhydride (1 mL) and pyridine at room temperature for 2 h. Isolation of the product by azeotropic removal of 10 mL of toluene by distillation afforded 105 mg (98%) of crystalline tetraacetate, mp 146–150 °C. The analytical

sample, obtained after crystallization of this material from EtOH, melted at 153–154 °C: TLC (1:1 benzene–EtOAc) R_f 0.51; IR ($CHCl_3$) 1720 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.82 (d, J = 6 Hz, 3, C-4 CH_3), 0.94 (s, 3, CH_3), 0.99 (s, 3, CH_3), 1.37 (s, 3, CH_3), 1.98, 2.04, 2.05 (3 s, 4 × 3, 4 CH_3CO), 3.63 (s, 3, CH_3O), 4.04 (t, J = 6 Hz, 2, CH_2OAc), 4.96 (m, 1, C-3β H), 5.29 (m, 1, C-11β H), and 5.88 (d, J = 8 Hz, 1, C-16α H).

Anal. Calcd for $C_{35}H_{52}O_{10}$: C, 66.43; H, 8.28. Found: C, 66.42; H, 8.28.

B. Formation of Keto Triacetate 4. A solution of 10 g (16.3 mmol) of methyl diacetylfusidate (**2**) in 1 L of CH_3OH was treated with ozonized oxygen at −40 °C for 85 min, and after a stream of nitrogen was run through the solution for 10 min, the mixture was treated with 40 mL of CH_3SCH_3. The reaction mixture was then allowed to warm and stand at room temperature for 14 h. Isolation of the product by ether extraction including a base wash[11] afforded 7.5 g (97%) of keto triacetate **4**, mp 158–162 °C, which was sufficiently pure for further experimentation. The analytical sample, obtained after three crystallizations of a portion of this material from EtOH, melted at 164–165 °C: TLC (1:1 benzene–EtOAc) R_f 0.54; IR ($CHCl_3$) 1745, 1720 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.84 (d, J = 6 Hz, 3, C-4 CH_3), 0.94 (s, 3, CH_3), 1.27 (s, 3, CH_3), 1.47 (s, 3, CH_3), 2.00, 2.04, 2.10 (3 s, 3 × 3, 3 CH_3CO), 4.94 (m, 1, C-3β H), 5.30 (m, 1, C-11β H), and 5.35 (m, 1, C-16α H).

Anal. Calcd for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 68.13; H, 8.46.

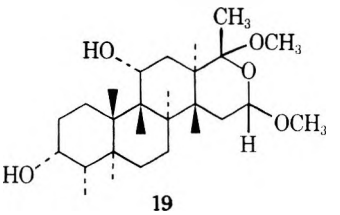
Tetrol 5. To an argon protected solution of 115 mL (180 mmol) of a 1.56 M ethereal CH_3Li solution in 165 mL of dry THF cooled at −70 °C was added dropwise over 1 h a solution of 5 g (10.5 mmol) of the keto triacetate **3** in 90 mL of dry THF. The mixture was then allowed to warm to room temperature, and stirring was continued for 15 h. The mixture was then cooled to 3 °C, quenched with 50 mL of H_2O, and the product isolated by 2:1 Et_2O–CH_2Cl_2 extraction.[11] Purification of the crude product (3.70 g) by chromatography on silica gel with 1:5 benzene–EtOAc afforded 2.86 g (75%) of the tetrol **5** as a white solid: TLC (1:1 benzene–EtOAc) R_f 0.03; IR ($CHCl_3$) 3600 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.88 (d, J = 6 Hz, 3, C-4 CH_3), 0.95 (s, 3, CH_3), 1.11 (s, 3, CH_3), 1.29 (s, 3, CH_3), 1.31 (s, 3, CH_3), 3.70 (m, 1, C-3β H), 3.96 (d, J = 9 Hz, 1, C-16α H), and 4.20 (m, 1, C-11β H).

For analytical purposes this tetrol **5** was characterized as its 3,16-diacetate, which was prepared from a 100-mg (0.27 mmol) sample with 1 mL of acetic anhydride and 1 mL of pyridine in the standard fashion. After crystallization from EtOH, the analytical sample melted at 226–227 °C: TLC (1:1 benzene–EtOAc) R_f 0.26; IR ($CHCl_3$) 3600 (OH) and 1720 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.84 (d, J = Hz, 3, C-4 CH_3), 0.99 (s, 3, CH_3), 1.22 (s, 3, CH_3), 1.30 (s, 3, CH_3), 1.38 (s, 3, CH_3), 2.06, 2.11 (2 s, 2 × 3, 2 CH_3CO), 4.38 (m, 1, C-11β H), 4.88 (d, J = 8 Hz, 1, C-16α H), and 4.98 (m, 1, C-3β H).

Anal. Calcd for $C_{26}H_{42}O_6$: C, 69.30; H, 9.39. Found: C, 69.32; H, 9.41.

Dihydroxy Enone 6. A. Periodate Cleavage of Tetrol 5. To a stirred solution of 3 g (8.22 mmol) of the tetrol **5** in 400 mL of CH_3OH was added dropwise over a period of 20 min 2.625 g (12.38 mmol, 1.50 equiv) of H_5IO_6 in 60 mL of H_2O and 90 mL of CH_3OH, and the mixture was stirred in the dark for 3.5 h. The solution was then treated with 250 mL of saturated brine, and the resulting voluminous white precipitate removed by filtration. The filter cake was washed with 200 mL of ether, and the product was isolated from the combined filtrate by further ether extraction.[11] The crude product (3.3 g) was tentatively assigned the acetal structure **19** on the basis of the IR [($CHCl_3$) 3605 cm^{-1} (OH)] and NMR [($CDCl_3$) δ 0.90 (d, J = 6 Hz, 3, C-4 CH_3), 0.98 (s, 3, CH_3), 1.20 (s, 3, CH_3), 1.40 (s, 2 × 3, 2 CH_3), 3.28, 3.54 (2, 2 × 3, 2 CH_3O), 3.73 (m, 1, C-3β H), 4.34 (m, 1, C-11β H), and 4.66 (q, J = 4 Hz, 1, C-16β H)]. The TLC (1:1 benzene–EtOAc) showed two spots at R_f 0.15 and 0.21 which we have taken to be isomers of the acetal structure **19**. No further purification was attempted with this material, but samples from this and similar experiments were used directly in the following cyclizations.

B. Hydrolysis of Acetal 19. To a solution of 5.0 g (11.9 mmol) of the crude acetal **19** from an experiment similar to that above in 1100 mL of acetone was added with stirring 360 mL of 4% hydrochloric acid,



19

and the mixture was stirred at room temperature for 2 h. After 200 mL of saturated brine was added, the mixture was neutralized with solid K_2CO_3, and the product was isolated by ether extraction.[11] The total crude yield of what appeared to be a mixture of the enone **6** and its hydration product (TLC, IR, NMR) was 4.50 g, but this material was not further purified for the next experiments.

C. Base-Catalyzed Enone Formation. A 1.063-g (2.93 mmol) portion of the above crude hydrolysate in 160 mL of a 1.5% solution of KOH (2.4 g) in 1:1 CH_3OH–H_2O was thoroughly degassed with an argon stream for 30 min, and then the mixture was heated under reflux in an argon atmosphere for 5 h. Isolation of the product from the cooled reaction mixture by ether extraction[11] afforded 863 mg of crude enone **6**. Chromatography of this material combined with 314 mg of similar crude enone **6** from another experiment (1177 mg) on 60 g of silica with 2:3-benzene–EtOAc in a medium-pressure chromatographic apparatus[8] and then crystallization of the solid material eluted in fractions 5–14 (125 mL) from EtOH afforded 990 mg of the enone **6**, mp 210–212 °C. The analytical sample, obtained after two further crystallizations of a portion of this material from EtOH, melted at 213–215 °C: TLC (1:1 benzene–EtOAc) R_f 0.14; IR ($CHCl_3$) 3605 (OH) and 1660 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.84 (d, J = 6 Hz, 3, C-4 CH_3), 0.97 (s, 2 × 3, 2 CH_3), 1.53 (s, 3, CH_3), 3.65 (m, 1, C-3β H), 4.32 (m, 1, C-11β H), 5.88 (d, J = 10 Hz, 1, C-17 H), and 6.80 (m, 1, C-16 H).

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.27; H, 9.95.

In larger scale experiments, chromatographic purification of the enone **6** from this sequence of reactions was not necessary and the crystalline crude product was used directly in further experiments.

The 3-monoacetate of a sample of the 3,11-dihydroxy enone **6** (100 mg) was prepared with 2 mL of acetic anhydride and 2 mL of pyridine for identification purposes. After preparative TLC (silica gel, 1:1 benzene–EtOAc) and crystallization (twice) from ether, the analytical sample melted at 174–175 °C: TLC (1:1 benzene–EtOAc) R_f 0.41; IR ($CHCl_3$) 3640 (sh), 3600 (OH), 1720 (CH_3C=O), and 1665 cm^{-1} (α,β-unsaturated C=O); NMR ($CDCl_3$) δ 0.82 (d, J = 6 Hz, 3, C-4 CH_3), 1.00 (s, 2 × 3, 2 CH_3), 1.54 (s, 3, CH_3), 2.08 (s, 3, CH_3C=O), 3.06 (dd, J = 4, 12 Hz, C-13α H), 4.40 (m, 1, C-11β H), 4.98 (m, 1, C-3β H), 6.00 (dd, J = 3, 5 Hz, 1, C-17 H), and 6.88 (m, 1, C-16 H).

Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.19; H, 9.34.

Dihydroxy Ketone 7. A mixture of 475 mg (1.37 mmol) of the enone **6** and 50 mg of 10% palladium on carbon in 16 mL of HOAc was stirred in a hydrogen atmosphere at room temperature for 3 h. After filtration removed the catalyst and most of the acetic acid was removed at the rotary evaporator at reduced pressure, the product was isolated by ether extraction including a base wash.[11] The crude product obtained after removal of the ether amounted to 413 mg (86%) of the dihydroxy ketone **7**, mp 199–201 °C. The analytical sample, obtained after crystallization of a portion of this material from CH_2Cl_2–EtOH, melted at 204–206 °C: TLC (1:1 benzene–EtOAc) R_f 0.11; IR ($CHCl_3$) 3605 (OH) and 1700 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.83 (s, 3, C-4 CH_3), 0.99 (s, 2 × 3, 2 CH_3), 1.51 (s, 3, CH_3), 2.95 (dd, J = 5, 10.5 Hz, 1, C-13α H), 3.70 (m, 1, C-3β H), and 4.35 (m, 1, C-11β H).

Anal. Calcd for $C_{22}H_{36}O_3$: C, 75.82; H, 10.41. Found: C, 75.88; H, 10.38.

The 3-monoacetate of a sample of the 3,11-dihydroxy ketone **7** (100 mg) was prepared with 2 mL of acetic anhydride and 2 mL of pyridine for identification purposes. The analytical sample, obtained after two crystallizations of this material from CH_2Cl_2–EtOH, melted at 231–231.5 °C: TLC (1:1 benzene–EtOAc) R_f 0.45; IR ($CHCl_3$) 3640 (sh), 3600 (OH), and 1720–1705 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.79 (s, 3, CH_3), 0.90 (d, J = 6 Hz, 3, C-4 CH_3), 1.00 (s, 3, CH_3), 1.51 (s, 3, CH_3), 2.09 (s, 3, CH_3C=O), 2.96 (dd, J = 4, 11 Hz, 1, C-13α H), 4.35 (m, 1, C-11β H), and 4.98 (m, 1, C-3β H).

Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.81; H, 9.81. Found: C, 73.80; H, 9.94.

6α,9α-Dihydroxy-6bβ,10α,12aα,12bβ-tetramethyl-1,2,4aα,5,6,6aβ,6b,7,8,9,10,10aα,11,12,12a,12b-hexadecahydrochrysene. A. To a stirred solution of 172 mg (0.495 mmol) of the dihydroxy ketone **7** in 35 mL of dry benzene was added 12 mg (0.14 mL, 1.5 mmol) of dihydropyran and 5 mg of *p*-toluenesulfonic acid monohydrate, and the mixture was stirred at room temperature for 15 h. After the mixture was treated with 20 mL of saturated aqueous $NaHCO_3$, isolation of the product by ether extraction[11] afforded 262 mg of the crude ditetrahydropyranyl derivative. This was used for next reaction without further purification.

B. To a stirred solution of 150 mg (0.21 mL, 1.5 mmol) of diisopropylamine in THF at −78 °C under an argon atmosphere was added dropwise 0.62 mL (1.5 mmol) of 2.4 M *n*-butyllithium in *n*-hexane

solution, and the mixture was stirred at −78 °C for 80 min and then at room temperature for 30 min. To this solution which was cooled again to −78 °C was added a solution of 262 mg of the ditetrahydropyranyl derivative above in 2.5 mL of THF, and the mixture was allowed to warm up to 0 °C and stir at 0 °C for 30 min. Then 3.5 mL of HMPA and 1.7 g (10 mmol) of $ClPO[N(CH_3)_2]_2$ were added, and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was poured into 50 mL of saturated aqueous $NaHCO_3$, and stirring was continued for 30 min before extraction. The product was isolated by ether extraction,[11] and the oily crude material was dried and used directly for the next reaction without further purification.

C. A solution of the crude enol phosphorodiamidate above and 741 mg (10 mmol) of *t*-BuOH in 10 mL of THF was added to a stirred solution of 77 mg (11 mg-atoms) of lithium in 50 mL of liquid ammonia, and the reaction mixture was stirred under reflux of ammonia for 3 h. Ammonium chloride was added to decompose excess lithium, and the ammonia was evaporated. The product was isolated by ether extraction[11] and was used for the next reaction without further purification.

D. The olefin above was dissolved in 30 mL of acetone and 10 mL of 2 N hydrochloric acid, and the mixture was stirred at room temperature for 2 h. Isolation of the product by ether extraction[11] and purification by preparative TLC (silica gel, 25% *n*-hexane–ether) afforded 116 mg (overall yield 71%) of solid olefinic diol, which proved difficult to purify by crystallization and was directly silylated below.

3α-*tert*-Butyl Dimethylsilyl Ether (8). To a solution of 328 mg (0.99 mmol) of the olefinic diol accumulated from several runs in 3 mL of dry DMF was added 150 mg (2.5 mmol) of imidazole and 186 mg (1.23 mmol) of *t*-$BuMe_2SiCl$ under an argon atmosphere, and the mixture was stirred at room temperature for 2 days. After evaporation of the DMF and treatment of the residue with 10 mL of saturated brine, the product was isolated by ether extraction.[11] Purification of the crude product by chromatography on 30 g of silica gel with 10% EtOAc–*n*-hexane afforded 412 mg (92%, 65% overall) of the crystalline monosilyl ether **8**. Crystallization of a portion of this material from Et_2O–CH_3OH gave the silyl ether **13** as colorless crystals: mp 128–129 °C; IR ($CHCl_3$) 3625 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.0 (s, 6), 0.77 (d, 3, *J* = 6 Hz), 0.79 (s, 3), 0.87 (s, 3), 0.90 (s, 3), 1.32 (s, 3), 3.67 (m, 1, $R_2CHOSiMe_2$-*t*-Bu), 4.25 (m, 1, R_2CHOH), 5.23 and 5.57 (two m, 1 each, CH=CH).

Anal. Calcd for $C_{28}H_{50}O_2Si$: C, 75.27; H, 11.28. Found: C, 75.24; H, 11.17.

Olefinic Ketone 9. A. To a stirred solution of 116 mg (0.16 mL, 1.15 mmol) of diisopropylamine in 1.5 mL of THF at −78 °C under an argon atmosphere was added dropwise 0.48 mL (1.15 mmol) of 2.4 M *n*-butyllithium in *n*-hexane solution, and the mixture was stirred at −78 °C for 30 min and then at room temperature for 30 min. To this solution, which was cooled again to −78 °C, was added a solution of 103 mg (0.25 mmol) of the alcohol **8** in 1.5 mL of THF. The cooling bath was removed, and the mixture was stirred at room temperature for 30 min. Then 1 mL of HMPA and 392 mg (2.3 mmol) of $ClPO[N(CH_3)_2]_2$ were added, and the mixture was stirred at room temperature for 3 h. The mixture was poured into 30 mL of saturated aqueous $NAHCO_3$, and stirring was continued for 1 h before extraction[11] and used directly for the next reaction without further purification.

B. The above crude phosphorodiamidate and 341 mg (4.6 mmol) of *t*-BuOH were dissolved in 1 mL of THF and 15 mL of ethylamine, and to this solution 35.5 mg (5.1 mg-atoms) of lithium was added. The mixture was stirred under reflux of ethylamine and an argon atmosphere for 1 h. The excess lithium was destroyed with NH_4Cl, and most of ethylamine was evaporated. After treatment of the residue with 10 mL of saturated brine, isolation of the product by ether extraction[11] and purification by chromatography on 20 g of silica gel with 5% EtOAc–*n*-hexane afforded 92 mg (93%) of crystalline 11-deoxysilyl ether. Crystallization of a portion of this material from Et_2O–CH_3OH gave colorless crystals: mp 115–116 °C; NMR ($CDCl_3$) δ 0.0 (s, 6), 0.80 (d, 3, *J* = 6 Hz), 0.83 (s, 6), 0.88 (s, 9), 1.13 (s, 3), 3.67 (m, 1, $R_2CHOSiMe_2$-*t*-Bu), 5.22 and 5.50 (two m, 1 each, CH=CH).

Anal. Calcd for $C_{28}H_{50}OSi$: C, 78.06; H, 11.70. Found: C, 77.94; H, 11.53.

C. A solution of 380 mg (0.88 mmol) of the 11-deoxysilyl ether above and 2.3 g of *tert*-butylammonium fluoride in 5 mL of THF was stirred at room temperature for 4 days. Isolation of the product by ether extraction and purification by chromatography on 20 g of silica gel with 5% EtOAc–*n*-hexane afforded 251 mg (94%) of the corresponding alcohol: IR ($CHCl_3$) 3600, 3300–3550 cm^{-1} (OH); NMR ($CDCl_3$) δ 3.75 (m, 1, $R_2CHOSiMe_2$-*t*-Bu), 5.27 and 5.56 (two m, 1 each, CH=CH). This material was not further purified, but used directly in the following experiment.

D. To a solution of 261 mg (0.83 mmol) of the above alcohol in 4 mL of HOAc which was cooled in an ice bath was added a solution of 105 mg (1.05 mmol) of chromium trioxide in 2 mL of 95% HOAc and the mixture was stirred at room temperature for 30 min. After CH_3OH was added to destroy excess oxidant, the solvent was evaporated under reduced pressure, and the product was isolated by $HCCl_3$ extraction.[11] Purification of the crude product by chromatography on 20 g of silica gel with 20% EtOAc–*n*-hexane afforded 187 mg (72%) of crystalline ketone **9**. Crystallization of a portion of this material from CH_2Cl_2–CH_3OH gave colorless crystals: mp 159–161 °C; IR ($CHCl_3$) 1680 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.81 (s, 3), 0.98 (s, 3), 0.99 (d, 3, *J* = 6 Hz), 1.07 (s, 3), 5.28 and 5.57 (two m, 1 each, CH=CH).

Anal. Calcd for $C_{22}H_{34}O$: C, 84.02; H, 10.90. Found: C, 84.03; H, 10.88.

Hydroxy Ketone 10. A. A solution of 222 mg (0.71 mmol) of the ketone **9**, 10 mg of *p*-toluenesulfonic acid monohydrate, and 1 mL of ethylene glycol in 50 mL of benzene was heated under reflux in an argon atmosphere for 50 h in an apparatus equipped with a Dean-Stark water separator and molecular sieves (4A). After cooling, 10 mL of saturated aqueous $NaHCO_3$ was added to the mixture, and isolation of the product by ether extraction[11] afforded 248 mg (98%) of the crystalline ketal. Crystallization of a portion of this material from Et_2O–CH_3OH gave colorless crystals: mp 142–143 °C; NMR ($CDCl_3$) δ 0.64 (s, 3), 0.69 (d, 3, *J* = 6 Hz), 0.81 (s, 3), 1.02 (s, 3), 3.80 (s, 4, $-OCH_2CH_2O-$), 5.13 and 5.45 (two m, 1 each, CH=CH).

Anal. Calcd for $C_{24}H_{38}O_2$: C, 80.39; H, 10.80. Found: C, 80.21; H, 10.66.

B. To a solution of 1.2 g (17 mmol) of 2-methyl-2-butene in 1 mL of THF at −78 °C under argon atmosphere was added dropwise in 10 min 7.15 mL (8.5 mmol) of 1.19 M BH_3–THF in THF solution. The mixture was then warmed to 3 °C, and stirring was continued for 4 h. This stirred solution was cooled again at −78 °C for 30 min, at 3 °C for 2 h, and at room temperature for 22 h. This mixture was cooled in an ice bath, and 8 mL of 3 N aqueous NaOH and 10 mL of 30% aqueous H_2O_2 were cautiously added. The mixture was stirred vigorously at 55–60 °C for 1 h. After cooling 20 mL of saturated aqueous $NaHCO_3$ solution was added, and the product was isolated by $HCCl_3$ extraction.[11] The crude product was separated by chromatography on 20 g of silica gel. From the fractions eluted with 10% EtOAc–*n*-hexane 40 mg (20%) of 17a-norfusidan-3-ethylene ketal was obtained. From the fraction eluted with 50% *n*-hexane–EtOAc 213 mg (81%) of the crude mixture of the 17- and 17a-hydroxy derivatives was obtained. This mixture was used for the next oxidation reaction without separation.

C. To a stirred suspension of 330 mg (3.3 mmol) of chromium trioxide in 10 mL of dry CH_2Cl_2 which was cooled with an ice bath was added dropwise 577 mg (0.59 mL, 7.3 mmol) of dry pyridine, and the mixture was stirred at room temperature for 15 min. To this mixture was added dropwise a solution of 208 mg (0.55 mmol) of the above mixture of hydroxy derivatives in 5 mL of CH_2Cl_2, and the mixture was stirred for an additional 15 min. After treatment of the mixture with 40 mL of saturated aqueous $NaHCO_3$, the product, isolated by ether extraction,[11] amounted to 188 mg (90%) of a crude crystalline mixture of ketones, which was used directly for the next reaction without further purification.

D. To a stirred solution of 188 mg (0.5 mmol) of the above ketone mixture in 20 mL of THF which was cooled with an ice bath was added 635 mg (2.5 mmol) of $Li(t\text{-}BuO)_3AlH$, and the mixture was stirred at 3 °C for 2 h and at room temperature for 15 h. The mixture was cooled with an ice bath, and the excess reagent was decomposed with 1.25 mL of 2 N aqueous NaOH. The mixture was filtered through 10 g of silica with suction, and the filter was washed with CH_2Cl_2. Removal of the solvent afforded 190 mg of crude crystalline mixture of hydroxy derivatives. This material was dissolved in 20 mL of acetone and 2 mL of 2 N hydrochloric acid, and the solution was stirred at room temperature for 2 h. Isolation of the product by 10% CH_2Cl_2–Et_2O extraction[11] and purification by chromatography on 21 g of silica gel with 50% *n*-hexane–EtOAc gave 55 mg (total yield from olefinic ketone **9** was 25%) of a less polar product which was identified as a mixture of 17(a)α- and 17(a)-β-hydroxy derivatives. Subsequently, 88 mg (total yield from olefinic ketone **9** was 39%) of a more polar product was identified as 17a-norfusidan-3-on-17β-ol (**10**). Crystallization of a portion of this material from CH_2Cl_2–Et_2O gave colorless crystals: mp 197–198 °C; IR ($CHCl_3$) 3590, 3250–3550 (OH), 1695 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.97, 1.00, 1.07 (three s, 3 each), 1.01 (d, 3, *J* = 6 Hz), 3.55 (br m, 1, R_2CHOH).

Anal. Calcd for $C_{22}H_{36}O_2$: C, 79.46; H, 10.91. Found: C, 79.49; H, 11.00.

Unsaturated Ketone 11. A. From Degradation Sequence. 1. To a solution of 47 mg (0.14 mmol) of keto alcohol **10** in 3 mL of dry DMF under an argon atmosphere was added 30.6 mg (0.45 mmol) of imidazole and 60.2 mg (0.4 mmol) of t-$BuMe_2SiCl$, and the mixture was stirred at room temperature for 6 h. After evaporation of the DMF under reduced pressure and treatment of the residue with 3 mL of saturated brine, the product, isolated by 20% CH_2Cl_2–Et_2O ether extraction[11] and purified by chromatography on 20 g of silica gel with 20% EtOAc–n-hexane, amounted to 58 mg (92%) of the crystalline silyl ether. Crystallization of a portion of this material from CH_2Cl_2–Et_2O gave colorless crystals: mp 200–201 °C; IR ($CHCl_3$) 1695 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.04 (s, 6), 0.88 (s, 12), 0.98 (s, 3), 1.02 (d, 3, J = 7 Hz), 1.08 (s, 3), 3.2–3.7 (br m, 1, $R_2CHOSiMe_2$-t-Bu).

Anal. Calcd for $C_{28}H_{50}O_2Si$: C, 75.27; H, 11.28. Found: C, 75.20; H, 11.33.

2. To a suspension of 47 mg (1.1 mmol) of rinsed 56% sodium hydride in mineral oil in 0.5 ml of benzene under argon atmosphere was added 3 mg (4 μL) of CH_3OH and the mixture was stirred at room temperature for 30 min. A solution of 48 mg (0.11 mmol) of the above ketone in 2.5 mL of benzene and 82 mg (0.09 mL, 1.1 mmol) of ethyl formate were added, and the mixture was stirred at room temperature for 12 h. The excess sodium hydride was destroyed with H_2O. The aqueous layer was acidified with 2 N hydrochloric acid, and the product was isolated by CH_2Cl_2 extraction. This process afforded 50 mg of crystalline material which was used directly in the next reaction without further purification: IR ($CHCl_3$) 1575, 1625 cm^{-1} (br absorption); NMR ($CDCl_3$) δ 0.05 (s, 6), 0.80 (s, 3), 0.88 (s, 12), 1.11 (s, 3), 1.18 (d, 3, J = 7 Hz), 3.2–3.7 (br m, 1, $R_2CHOSiMe_2$-t-Bu), 8.53 (m, 1, C=CHOH).

3. A solution of 50 mg of the crude formyl ketone from above and 27 mg (0.16 mmol) of 98% dichlorodicyanobenzoquinone in 3 mL of dry benzene was stirred at room temperature for 30 min. The mixture was then passed through a column of 20 g of silica gel, and the fraction eluted with 33% EtOAc–n-hexane (200 ml) was collected. Evaporation of the solvent gave 43 mg of product. Separation of the crude product by preparative TLC (silica gel, 20% EtOAc–n-hexane) afforded 11 mg of starting ketone and 30 mg of crystalline enone aldehyde: IR ($CHCl_3$) 1675, 1695, 1725 cm^{-1} [COC(CHO)=C]; NMR ($CDCl_3$) δ 0.05 (s, 6), 0.88 (s, 12), 0.92 (s, 3), 1.15 (s, 3), 1.18 (d, 1, J = 6.5 Hz), 3.2–3.7 (br m, 1, $R_2CHOSiMe_2$-t-Bu), 8.08 (s, 1, CH=C–CO), 9.91 (s, 1, CHO).

4. A solution of 30 mg (0.063 mmol) of the above enone aldehyde and 64.5 mg (0.07 mmol) of tris(triphenylphosphine)rhodium chloride in 3 mL of dry benzene was heated under reflux in an argon atmosphere for 2 h. After cooling, the product was separated by preparative TLC (silica gel, 20% EtOAc–n-hexane), and amounted to 20 mg (total yield from hydroxy ketone **10** was 39% of the enone **11**). Crystallization of a portion of this material from CH_2Cl_2–CH_3OH gave colorless crystals: mp 192–193 °C; IR ($CHCl_3$) 1660 cm^{-1} (COCH=CH); NMR ($CDCl_3$) δ 0.00 (s, 6), 0.82 (s, 12), 0.92 (s, 3), 1.06 (s, 3), 1.07 (d, 1, J = 6.5 Hz), 5.75 and 7.27 (two d, 1 each, COCH=CH, J = 10 Hz); mass measured $M^+ - 57$, 387.

Anal. Calcd for $C_{28}H_{48}O_2Si$: C, 75.61; H, 10.88. Found: C, 75.55; H, 10.87.

The TLC, IR, NMR, and mass spectra of this authentic fusidic acid derivative were identical with those of the synthetic sample prepared above.

B. From Synthetic Sequence. A solution of 0.35 M lithium diisopropylamide in 14% hexane–THF was prepared by adding 1.4 mL (3.5 mmol) of a solution of 2.52 M n-butyllithium in hexane solution to a solution of 390 mg (0.54 mL, 3.9 mmol) of diisopropylamine in 8 mL of THF at −78 °C. The volume of the solution was adjusted to 10 mL using a volumetric flask at room temperature.

To a stirred solution of 14 mg (0.033 mmol) of the enone **18** in 1.5 mL of THF was added 0.14 mL (0.049 mmol) of 0.35 M lithium diisopropylamide in 14% n-hexane–THF at 78 °C under an argon atmosphere, and the mixture was stirred at −78 °C for 10 min, after which it was allowed to warm up to room temperature. After stirring at room temperature for 15 min, 460 mg (0.2 mL, 3.25 mmol) of CH_3I was added in one portion to the mixture, and it was stirred at room temperature for 30 min. Isolation of the product by CH_2Cl_2 extraction[11] and purification of the crude product by preparative TLC (silica gel, 10% EtOAc–n-hexane) gave 11 mg (76%) of ketone **11**. Crystallization of this material from CH_2Cl_2–CH_3OH gave the ketone **11** as colorless crystals: mp 186–187 °C; IR ($CHCl_3$) 1660 cm^{-1} (COCH=CH); NMR ($CDCl_3$) δ 0.00 (s, 6), 0.82 (s, 12), 0.92 (s, 3), 1.06 (s, 3), 1.07 (d, 1, J = 6.5 Hz), 5.75 and 7.27 (two d, 1 each, COCH=CH, J = 10 Hz); mass measured $M^+ - 57$, 387.

Anal. Calcd for $C_{28}H_{48}O_2Si$: C, 75.61; H, 10.88. Found: C, 75.57; H, 10.81.

This product was identical with the compound derived from the natural fusidic acid in respect to TLC, IR, NMR, and mass spectra.

3β-Hydroxy-6bβ,12aα,12bβ,-trimethyl-1,2,3,4,4aα,5,6,6aβ,-6b,7,11,12,12a,12b-tetradecahydro-9(8*H*)-chrysenone. To a cooled (3 °C) solution of 170 mg (0.54 mmol) of the enedione **12**[2] in 42 mL of dry THF and 8.5 mL of dry benzene under an argon atmosphere was added a solution of 688 mg (2.71 mmol) of $Li(t\text{-}BuO)_3AlH$ in 10.5 mL of dry THF, and the solution was stirred for 110 min. After the addition of 1.13 mL (2.82 mmol) of 10% aqueous NaOH, the reaction mixture was stirred for 1 h at room temperature and then filtered through 10 g of silica gel with the aid of 150 mL of EtOAc. After removal of the solvent at reduced pressure, there remained 166 mg (67%) of crude, crystalline enone alcohol, mp 193–196 °C, which was sufficiently pure to be used directly in the following experiments. An analytical sample, obtained after crystallization of a portion of this material from CH_2Cl_2–CH_3OH, melted at 199–200 °C; tlc)1:1 benzene–EtOAc) R_f 0.24; IR ($CHCl_3$) 3600 (OH), 1650 (unsaturated C=O), and 1625 cm^{-1} (sh C=C); NMR ($CDCl_3$) δ 0.93 (s, 6, 2 CH_3), 1.24 (s, 3, CH_3), 3.50 (br m, 1, C-17α H), and 5.82 (s, 1, C-4 H).

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.74; H, 10.13.

Olefinic Ketal 13. A. A solution of 138 mg (0.44 mmol) of the above crude enone alcohol, 1.4 mL of ethylene glycol, and 14 mg of p-toluenesulfonic acid monohydrate in 125 mL of benzene was heated at reflux under a Dean-Stark water separator for 3 h. After cooling, the product was isolated by ether extraction including a base wash[11] and purified by chromatography on 20 g of silica gel with 3:1 benzene–EtOAc. In this manner there was obtained 147 mg (94%) of the hydroxy ketal, mp 178–181 °C, the analytical sample of which, obtained after three crystallizations from CH_2Cl_2–EtOH, melted at 183–184 °C: TLC (1:1 benzene–EtOAc) R_f 0.39; IR ($CHCl_3$) 3600 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.89 (s, 3, CH_3), 1.00 (s, 3, CH_3), 1.09 (s, 3, CH_3), 3.94 (s, 4, OCH_2CH_2O), and 5.37 (d, J = 5 Hz, 1, C-6 H).

Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.06. Found: C, 76.48; H, 10.20.

B. To a solution of 688 mg (1.9 mmol) of the above hydroxy ketal in 25 mL of dry DMF under argon atmosphere was added with stirring 390 mg (5.7 mmol) of imidazole and 570 mg (3.8 mmol) of t-$BuMe_2SiCl$, and the mixture was allowed to react at room temperature for 15 h. After evaporation of the DMF under reduced pressure and then treatment of the residue with 20 mL of saturated brine, the product was isolated by ether extraction.[11] Purification of the crude product by chromatography on 50 g of silica gel with 33% EtOAc–n-hexane afforded 895 mg (99%) of the crystalline silyl ether **13**. Crystallization of a portion of this material from ether–ethanol gave colorless crystals: mp 146–147 °C; NMR ($CDCl_3$) δ 0.04 (s, 6), 0.88 (s, 12), 0.99 (s, 3), 1.09 (s, 3), 3.2–3.7 (br m, 1, $R_2CHOSiMe_2$-t-Bu), 3.93 (s, 4), 5.31 (m, 1, RCH=C).

Anal. Calcd for $C_{29}H_{50}O_3Si$: C, 73.36; H, 10.62. Found: C, 73.34; H, 10.50.

Epoxy Ketal 14. To a stirred solution of 895 mg (1.9 mmol) of the ketal **13** and 320 mg (3.8 mmol) of anhydrous $NaHCO_3$ in 20 mL of CH_2Cl_2 under an argon atmosphere at 3 °C was added 770 mg (3.8 mmol) of 85% m-chloroperbenzoic acid, and the mixture was stirred at 3 °C for 1 h. The mixture was diluted with 100 mL of ether, and the ethereal phase was washed with 20 mL of 10% aqueous $Na_2S_2O_3$, 5% aqueous $NaHCO_3$ (20 mL), and saturated brine (two 20-mL portions). The aqueous layer were extracted with either (two 50-mL portions), and the combined ethereal layers were dried over $MgSO_4$ and evaporated. Purification of the crude product by chromatography on 50 g of silica gel with 33% EtOAc–n-hexane afforded 917 mg (98%) of the crystalline epoxide **14**. Crystallization of a portion from ether–ethanol gave colorless crystals: mp 161–162 °C; NMR ($CDCl_3$) δ 0.04 (s, 6), 0.84 (s, 3), 0.88 (s, 9), 1.06 (s, 3), 1.13 (s, 3), 3.09 (m, 1, RCHOC), 3.2–3.7 (br m, 1, $R_2CHOSiMe_2$-t-Bu), 3.94 (s, 4).

Anal. Calcd for $C_{29}H_{50}O_4Si$: C, 70.97; H, 10.27. Found: C, 70.92; H, 10.14.

Ketal Ketone 16. To a stirred solution of 900 mg (1.83 mmol) of the epoxide **14** in 55 mL of dry CH_2Cl_2 which was cooled with an ice bath was added under argon atmosphere 313 mg (276 μL, 3.25 mmol) of boron trifluoride etherate. After stirring for 3 min at 3 °C, the reaction mixture was quenched with 5 mL of Et_3N and 40 mL of saturated aqueous $NaHCO_3$, and the product was isolated by ether extraction.[11] The mixture of the products (913 mg) was separated by chromatography on 60 g of silica gel with 25% EtOAc–n-hexane and two main products were isolated.

The less polar crystalline product, 298 mg (33%), was identified as 17a-homo-30-nor-5α-fusida-17β-$tert$-butyldimethylsilyloxy-6-keto-3-ethylene ketal (**16**). Crystallization of a portion from

CH_2Cl_2–CH_3OH gave colorless crystals: mp 169–170 °C; IR ($CHCl_3$) 1695 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.05 (s, 6), 0.88 (s, 12), 1.31 (s, 6), 3.2–3.7 (br m, 1, $R_2CHOSiMe_2$-*t*-Bu), 3.92 (s, 4).

Anal. Calcd for $C_{29}H_{45}O_4Si$: C, 70.97; H, 10.27. Found: C, 71.04; H, 10.16.

The other polar product, 231 mg (36%), was tentatively assigned as unsaturated hydroxy ketal **15**: oil; IR ($CHCl_3$) 3490, 3300–3550 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.00 (s, 6), 0.76 (s, 3), 0.85 (s, 9), 0.97 (s, 3), 1.08 (s, 3), 3.4–3.8 (br m, 2, R_2CHOH and $R_2CHOSiMe_2$-*t*-Bu), 3.90 (s, 4), 5.12 (m, 1, RCH=C).

Anal. Calcd for $C_{29}H_{35}O_4Si$: C, 70.97; H, 10.27. Found: C, 71.09; H, 10.18.

Ketone 17. A. To a stirred solution of 300 mg (0.61 mmol) of the ketone **16** in 80 mL of THF which was cooled with an ice bath was added under an argon atmosphere a solution of 930 mg (3.66 mmol) of $Li(t\text{-}BuO)_3AlH$ in 20 mL of THF. The mixture was stirred for 30 min, and then allowed to warm to room temperature for 4 h. The reaction mixture was cooled with an ice bath and excess reagent was decomposed with ca. 3 mL of saturated brine. The mixture was filtered and the filter cake was washed with EtOAc. Extraction of the product with EtOAc and purification by chromatography on alumina with CH_2Cl_2 afforded 263 mg (88%) of the corresponding alcohol. Crystallization of a portion of this material from CH_2Cl_2–CH_3OH gave colorless crystals: mp 205–206 °C; IR ($CHCl_3$) 3600 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.03 (s, 6), 0.88 (s, 9), 0.93 (s, 3), 1.07 (s, 3), 1.13 (s, 3), 3.3–3.7 (br m, 1, $R_2CHOSiMe_2$-*t*-Bu), 3.93 (s, 4, and m, 1, $-OCH_2CH_2O-$ and R_2CHOH).

Anal. Calcd for $C_{29}H_{52}O_4Si$: C, 70.75; H, 10.64. Found: C, 70.77; H, 10.72.

B. To a stirred solution of 115 mg (0.16 mL, 1.12 mmol) of diisopropylamine in 4 mL of THF at −78 °C under an argon atmosphere was added dropwise 0.47 mL (1.12 mmol) of 2.4 M *n*-butyllithium solution in *n*-hexane, and the mixture was stirred at −78 °C for 30 min and at room temperature for 30 min. To this solution of lithium diisopropylamide in THF–*n*-hexane was added under an argon atmosphere at room temperature a solution of 185 mg (0.38 mmol) of the above alcohol in 4 mL of THF. After stirring for 30 min at room temperature, 2 ml of HMPA and 638 mg (0.65 mL, 3.75 mmol) of $ClPO[N(CH_3)_2]_2$ were added, and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into 50 mL of saturated aqueous $NaHCO_3$ and stirring was continued for 30 min before extraction. The product was isolated by ether extraction.[11] The oily product was dried and used for the next reaction without further purification.

To a solution of the above crude phosphoramidate derivative and 300 mg of (4 mmol) of *t*-BuOH in 20 mL of ethylamine and 2 mL of THF was added 35 mg (5 mg-atoms) of lithium, and the mixture was stirred under reflux for 1 h. Excess lithium was destroyed with NH_4Cl and most of the ethylamine was evaporated. The residue was treated with 10 mL of saturated brine, and the product was isolated by ether extraction.[11] Purification of the crude product by chromatography on silica gel with 25% EtOAc–*n*-hexane afforded 152 mg (85%) of crystalline 6-deoxyketal. Crystallization of a portion of this material from Et_2O–CH_3OH gave colorless crystals: mp 154–156 °C; NMR ($CDCl_3$) δ 0.03 (s, 6), 0.84 (s, 3), 0.88 (s, 12), 1.12 (s, 3), 3.3–3.7 (m, 1, $R_2CHOSiMe_2$-*t*-Bu), 3.93 (s, 4).

Anal. Calcd for $C_{29}H_{52}O_3Si$: C, 73.05; H, 10.99. Found: C, 73.02; H, 10.97.

C. To a stirred solution of 217 mg (0.46 mmol) of the above ketal in 20 mL of acetone at 3 °C was added 1.25 mL of 2 N hydrochloric acid (2.5 mmol), and then the mixture was stirred at room temperature for 1.5 h. Isolation of the product by ether extraction[11] afforded the corresponding hydroxy ketone, which on further purification by crystallization from CH_2Cl_2–CH_3OH, gave 125 mg (87%) of pure hydroxy ketone: mp 179–180 °C; IR ($CHCl_3$) 1700 (C=O), 3590, 3200–3550 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.88, 0.97, 1.10 (3 s, 3 each), 3.5 (m, 1, R_2CHOH).

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.10; H, 10.71.

D. To a solution of 120 mg (0.38 mmol) of the above hydroxy ketone in 5 mL of dry DMF under an argon atmosphere were added with stirring 82 mg (1.2 mmol) of imidazole and 150 mg (1.0 mmol) of *t*-$BuMe_2SiCl$, and the mixture was stirred at room temperature for 24 h. After evaporation of the DMF under reduced pressure and then treatment of the residue with 20 mL of saturated brine, the product was isolated by 25% CH_2Cl_2–Et_2O extraction.[11] Purification of the crude product by chromatography on silica gel with 33% EtOAc–*n*-hexane afforded 153 mg (100%) of crystalline silyl ether **17**. Crystallization of a portion of this material from CH_2Cl_2–CH_3OH gave pure silyl ether **17**: mp 195–196 °C; IR ($CHCl_3$) 1695 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.04 (s, 6), 0.87 (s, 12), 0.96 (s, 3), 1.09 (s, 3), 3.25–3.7 (br m, 1, $R_2CHOSiMe_2$-*t*-Bu).

Anal. Calcd for $C_{27}H_{48}O_2Si$: C, 74.93; H, 11.18. Found: C, 74.97; H, 11.17.

Unsaturated Ketone 18. A. To the stirred suspension of 24.5 mg (0.57 mmol) of rinsed 56% hydride in mineral oil in 0.5 mL of benzene under argon atmosphere was added 3 mg (0.3 μL) of CH_3OH and the mixture was stirred at room temperature for 30 min. Then a solution of 49 mg (0.113 mmol) of ketone **17** in 2.5 mL of dry benzene and 42.5 mg (0.043 mL, 0.57 mmol) of ethyl formate was added, and the mixture was stirred at room temperature for 6 h.

The excess sodium hydride was destroyed with H_2O, and the aqueous layer was acidified with 2 N hydrochloric acid. Isolation of the product by CH_2Cl_2 extraction[11] afforded 5.1 mg of the crystalline formyl ketone which was used directly in the next reaction without further purification: IR ($CHCl_3$) 1575, 1630 cm^{-1} (br absorption) (COC=CHOH); NMR ($CDCl_3$) δ 0.04 (s, 3), 0.77 (s, 3), 0.97 (s, 12), 1.09 (s, 3), 3.5–3.7 (m, 1, $R_3CHOSiMe_3$-*t*-Bu), 8.64 (s, 1, C=CHOH).

B. A solution of 51 mg of the crude formyl ketone above and 31.5 mg (0.13 mmol) of 98% dichlorodicyanobenzoquinone in 5 mL of dry benzene was stirred at room temperature for 1 h. The mixture was then passed through a column of 10 g of silica gel, and the fraction eluted with 33% EtOAc–*n*-hexane (300 mL) was collected. Evaporation of the solvent gave 43 mg of the residue. Purification of the crude product by preparative TLC (silica gel, 25% EtOAc–*n*-hexane) afforded 37 mg of crystalline enone aldehyde: IR ($CHCl_3$) 1670, 1685, 1720 cm^{-1} [–COC(CHO)=C]; NMR ($CDCl_3$) δ 0.04 (s, 6), 0.91 (s, 12), 0.96 (s, 3), 1.16 (s, 3), 2.46 (m, 2, $COCH_2$–), 3.3–3.7 (br m, 1, $R_2CHOSiMe_2$-*t*-Bu), 8.20 (s, 1, CH=CCO), 10.02 (s, 1, CHO).

C. A solution of 37 mg (0.08 mmol) of the above enone aldehyde and 82 mg (0.088 mmol) of tris(triphenylphosphene)rhodium chloride in 3.5 mL of dry benzene was heated under reflux in an argon atmosphere for 2 h. After cooling, the product was separated by preparative TLC (silica gel, 25% EtOAc–*n*-hexane) and 25 mg (total yield from the ketone **17** was 56%) of crystalline enone **18** was obtained. Crystallization of a portion of this material from Et_2O–CH_3OH gave the pure enone **18**: mp 203–204 °C; IR ($CHCl_3$) 1660 cm^{-1} (COCH=CH); NMR ($CDCl_3$) δ 0.04 (s, 6), 0.92 (s, 12), 1.00 (s, 3), 1.11 (s, 3), 2.37 (m, 2 H, CH_2CO), 5.79 and 7.32 (two d, 1 each, CH=CHCO, J = 10 Hz).

Anal. Calcd for $C_{27}H_{46}O_2Si$: C, 75.28; H, 10.77. Found: C, 75.16; H, 10.54.

Registry No.—**1**, 6990-06-3; **1** (R = H; R′ = Me), 21157-24-4; **2**, 14424-45-4; **3**, 61446-33-1; **3** alcohol, 61436-93-9; **3** alcohol tetraacetate, 61436-94-0; **4**, 14185-98-9; **5**, 61436-95-1; **5** 3,16-diacetate, 61436-96-2; **6**, 61436-97-3; **6** 3-acetate, 61436-98-4; **7**, 61436-99-5; **7** 3 acetate, 61437-00-1; **8**, 61437-01-2; **8** phosphorodiamidate, 61446-32-0; **8** 11-deoxy silyl ether, 61437-02-3; 8 diol, 61446-30-8; **9**, 61437-03-4; **9** alcohol, 61437-04-5; **9** ethylene ketal, 61437-05-6; **9** ketal 17,17a-dihydro-17-ol, 61437-06-7; **9** ketal 17,17a-dihydro-17a-ol, 61437-07-8; **9** ketal 17,17a-dihydro-17-one, 61462-87-1; **9** ketal 17,17a-dihydro-17a-one, 61437-08-9; **9** 17,17a-dihydro-17aα-ol, 61437-09-0; **9** 17,17a-dihydro-17aβ-ol, 61437-10-3; **10**, 61446-10-4; **10** TBS, 61446-11-5; **11**, 61446-12-6; **11** formyl ketone, 61446-13-7; 11 enone aldehyde, 61446-14-8; **12**, 61446-15-9; 12 17β-ol, 61446-16-0; **13**, 61446-17-1; **13** 17β-ol, 61446-18-2; **14**, 61446-19-3; **15**, 61446-20-6; **16**, 61446-21-7; **16** ol, 61446-22-8; **16** phosphoramidate, 61476-92-4; **17**, 61446-23-9; **17** ol, 61446-24-0; 17 ketal, 61446-25-1; 17 formyl ketone, 61446-26-2; **17** enone aldehyde, 61446-27-3; **18**, 61446-28-4; **19**, 61446-29-5; *t*-$BuMe_2SiCl$, 18162-48-6.

References and Notes

(1) The authors are grateful for the support of this investigation by Public Health Service Research Grant AM 14160 from the National Institute of Arthritis and Metabolic Diseases and the Hoffmann-La Roche Foundation.
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(8) Boiling points are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 237B grating infrared spectrometer and nuclear magnetic resonance (NMR) spectra were recorded using a Varian T-70 spectrometer. Chemical shifts are reported as δ values in parts per million relative to Me_4Si (δ 0.0 ppm) as an internal standard. Deuteriochloroform for NMR

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and chloroform for IR spectra were filtered through neutral alumina before use.

Vapor phase chromatographic (VPC) analyses were determined on either a Hewlett-Packard 5750 equipped with a flame ionization detector or a Varian 920 equipped with a thermal conductivity detector using helium as the carrier gas under the indicated conditions. The indicated liquid phase was absorbed on 60–80 mesh Chromosorb W AW DMCS.

Silica gel columns used the 0.05–0.2 mm silica gel manufactured by E. Merck and Co., Darmstadt, Germany. Acidic silica gel refers to Silicar CC-4 special "for column chromatography", sold by Mallinckrodt Chemical Works, St. Louis, Mo. Preparative medium-pressure chromatography was performed using glass columns of the indicated length and diameter with fittings supplied by Laboratory Data Control, Riviera Beach, Fla., and an instrument minipump supplied by Milton Roy Co., St. Petersburg, Fla. (instrumentation designed by R. H. Mueller, those laboratories, and copies are available on request). The columns were packed with silica gel H "for TLC acc. to Stahl" (10–40 μ) manufactured by E. Merck and Co., Darmstadt, Germany. Solvents were degassed under water aspirator vacuum prior to use.

Analytical thin layer chromatography was conducted on 2.5 × 10 cm precoated TLC plates, silica gel 60 F-254, layer thickness 0.25 mm, manufactured by E. Merck and Co., Darmstadt, Germany.

"Dry" solvents were dried immediately prior to use. Ether and tetrahydrofuran (THF) were distilled from lithium aluminum hydride; pyridine, triethylamine, diisopropylamine, *N*-isopropylcyclohexylamine, trimethylchlorosilane (Me_3SiCl), hexamethylphosphoramide (HMPA), and benzene were distilled from calcium hydride; dichloromethane, methyl iodide, and hexane were distilled from phosphorus pentoxide. "Petroleum ether" refers to the "analyzed reagent" grade hydrocarbon fraction, bp 30–60 °C, which is supplied by J. T. Baker Co., Phillipsburg, N.J., and was not further purified.

Standard solutions of *tert*-butyldimethylchlorosilane (*t*-$BuMe_2SiCl$) in hexane (ca. 3.3 M) or HMPA (ca. 1.5 M) were employed.

Reactions were run under an argon atmosphere arranged with a mercury bubbler so that the system could be alternately evacuated and filled with argon and left under a positive pressure.

Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(9) Generously supplied by Dr. G. O. Godtfredsen (Leo Pharmaceutical Co.) and A. Brossi (Hoffmann-La Roche and Co.).

(10) H. Immer and K. Huber, *Helv. Chim. Acta*, **54**, 1347 (1971).

(11) In cases where the products were isolated "by solvent extraction", the procedure generally followed was to dilute the reaction mixture with the indicated solvent or to extract the aqueous solution with several portions of the indicated solvent; then the combined organic layers were washed with several portions of water followed by saturated brine. The organic layer was dried over anhydrous sodium or magnesium sulfate, then filtered, and the solvent was evaporated from the filtrate under reduced pressure (water aspirator) using a rotary evaporator. The use of the terms "base wash" or "acid wash" indicate washing the organic solution with saturated aqueous sodium bicarbonate solution or with dilute aqueous hydrochloric acid, respectively, prior to the aforementioned wash with water.

Carbon-13 Nuclear Magnetic Resonance Studies on a New Antitubercular Peptide Antibiotic LL-BM547β

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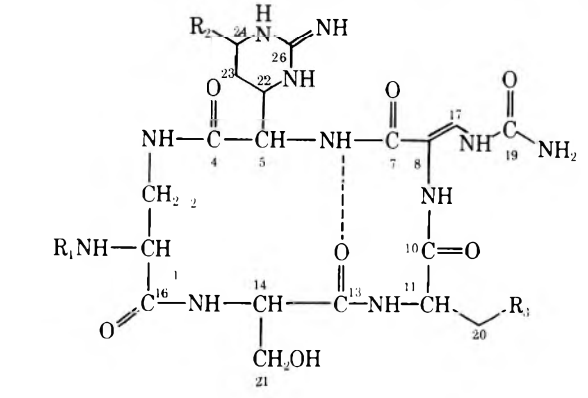
Lederle Laboratories, A Division of American Cyanamid Company, Pearl River, New York 10965

Received October 26, 1976

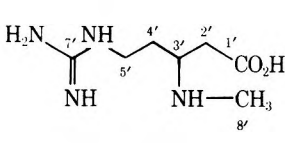
LL-BM547β, a new member of the viomycin family of antibiotics, is described. ^{13}C NMR studies on the antibiotic itself and on a hydrolytic product show that this antibiotic contains the new amino acid N^{β}-methyl-β-arginine as the appendaged amino acid.

The antitubercular agent viomycin was first described in 1951.[1] Since that time other members of the same family have been isolated, namely the capreomycins[2] and the tuberactinomycins.[3] The structures of tuberactinomycin N[4] and viomycin[5] have been determined by x-ray crystallography.

A *Nocardia* species, Lederle culture BM547, produces two antibiotic components that belong to this same chemical class. By ^{13}C NMR spectroscopy, in conjunction with hydrolytic studies, LL-BM547β was shown to be I. The novelty of I stems from the fact that the appendaged amino acid is *N*-methyl-β-arginine as opposed to β-lysine or γ-hydroxy-β-lysine in the known members (Table I) of this family. The minor component, LL-BM547α or II, was identified as the known de-β-lysylviomycin.[6]



R = H, β-lysine
R = OH, γ-hydroxy-β-lysine



N^{β}-methyl-β-arginine

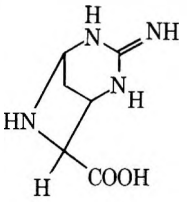
Isolation of I and II. The antibiotic components of culture BM547 in common with most water-soluble basic substances can be removed from the broth filtrate by passage over a weak cation exchange resin in the sodium cycle. The neutralized acid eluate from this resin may be applied directly to a dextran exchanger in the ammonium cycle. I and II may then be selectively eluted from this resin by using an ammonium chloride salt gradient as eluent. The eluate may be desalted over a granular carbon column. The pure antibiotic materials are recovered in about 50–60% yield from carbon columns by elution with 50% aqueous acetone solution. The solid antibiotic is obtained from this eluate by either lyophilization or precipitation with acetone.

Characterization of I and II. These two antibiotics, in common with all the other members of this peptide antitubercular group, have a vinyl urea chromophore which absorbs

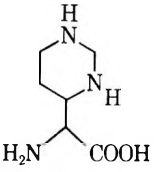
Table I. Summary of the Known Antitubercular Peptide Antibiotics

Antibiotic	R_1	R_2	R_3
LL-BM547β (I)	N^{β}-CH_3-β-arginyl	OH	OH
LL-BM547α (II) delysylviomycin	H	OH	OH
Viomycin	β-Lysyl	OH	OH
Capreomycin	β-Lysyl	H	H
Tuberactinomycin A	γ-OH-β-lysyl	OH	OH
Tuberactinomycin N	γ-OH-β-lysyl	H	OH
Tuberactinomycin O	β-Lysyl	H	OH

Table II. Amino Acid Profile of Antitubercular Peptide Antibiotics[a]



viomycidine



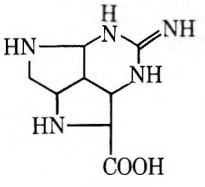
capreomycidine

Antibiotic	Ala	Ser	DAPA	β-Lys	γ-OH-β-Lys	N^β-CH_3-β-Arg	Vio	Cap
LL-BM547β (I)		2	1			1	1	
LL-BM547α (II)		2	1				1	
Viomycin		2	1	1			1	
Capreomycin	1	1	1	1				1
Tuberactinomycin A		2	1		1		1	
Tuberactinomycin N		2	1		1			1
Tuberactinomycin O		2	1	1				1

[a] Ala, alanine; Ser, serine; DAPA, diaminopropionic acid; β-Lys, β-lysine; γ-OH-β-Lys, γ-hydroxy-β-lysine, N^β-CH_3-β-arginine; Vio, viomycidine; Cap, capreomycidine.

strongly at 268 nm. Upon addition of base there is a characteristic shift to 281 nm. This chromophore is of great practical use in the recovery and purification of these compounds. The IR curves of members of this family are frequently superimposable and consequently of no use in identifying individual members. TLC on silica gel using such developing systems as 10% ammonium acetate–acetone–ammonia (90:100:0.67) or 7% ammonium bicarbonate–acetone–ammonia (90:100:1) can be used to distinguish among several family members. The spots on these layers are readily detected by UV absorption or by heating following application of ninhydrin spray reagent. The ^{1}H NMR curves of these materials clearly illustrate some characteristic markers but they are not generally useful in structural elucidation. The vinyl proton of the α,β-unsaturated urea chromophore is observed in the spectra of all members as a singlet at about δ 8.0. The spectra of I, II, and viomycin all exhibit sharp, distinct signals at δ 5.22 and 5.04 which may be attributed to protons at positions C_{24} and C_5 of the arbitrarily numbered diagram shown above. In the spectrum of I a sharp singlet at δ 2.70 for an *N*-methyl group is diagnostic.

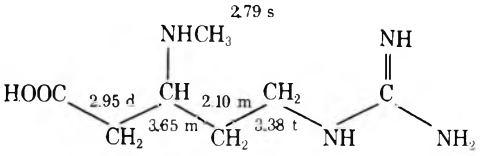
Acidic Hydrolysis. Table II shows the amino acid profile of members of this family of antibiotics. In addition to the indicated amino acids each member also yields 1 mol of ammonia, carbon dioxide, and urea during hydrolysis. Examination of the acid hydrolysate of I by TLC on silica gel revealed the presence of serine and diaminopropionic acid and a material which gave a yellow reaction with ninhydrin. This latter material has been shown to be viocidic acid[7] and the



viocidic acid

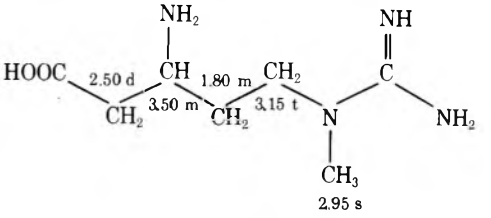
structure shows its relationship with proline, thus accounting for the yellow reaction with ninhydrin. It is an artifact of secondary hydrolysis due to the reactivity of the guanidinocarbinol group.

On silica gel thin layers the Sakaguchi reagent did not react with any product of the hydrolysis. However, TLC of the hydrolysate on cellulose followed by treatment with Sakaguchi reagent showed the presence of two strongly positive materials. One of these is presumably viomycidine. Separation of



N^β-methyl-β-arginine hydrochloride

these compounds in preparative quantities proved to be tedious. The more polar of the two compounds was recovered and shown by ^{1}H NMR and ^{13}C NMR to be N^β-methyl-β-arginine hydrochloride with a specific rotation in water of +20°. The ^{1}H NMR data of this compound are detailed below as are those of the model compound, blastidic acid, obtained by hydrolysis of the antibiotic blasticidin.[8]



blastidic acid

Blasticidic acid is known to be Sakaguchi negative[9] and since the new amino acid is strongly positive, the *N*-methyl substituent must be on the β-amino group.

^{13}C NMR Studies. ^{13}C NMR spectroscopy is by far the most effective diagnostic technique for the characterization of individual members of this antibiotic family. We obtained 25.2-MHz pulsed FT ^{13}C NMR spectra on five members, namely I, II, viomycin, capreomycin, and tuberactinomycin A.[10] The unequivocal structure models provided by the x-ray work already mentioned[4,5] are crucial to the effective use of data from these spectra. Multiplicities of the various carbon atoms in I and viomycin were determined by off-resonance spin decoupling. All the assignments are given in Tables III and IV and in the following discussion the rationale for these assignments is outlined.

Assignment of Carbons in the Macroring. The arbitrary numbering of the various positions in the macroring and in the side chains is shown in the diagram above. Carbons 1 and 2 with doublet and triplet multiplicities, respectively, present in the spectra of all five compounds are best assigned by a process of elimination. In the spectra of four of the antibiotics, that of capreomycin being the exception, four of the carbonyl carbons are bunched between 170.85 and 173.38 ppm. The

Table III. ^{13}C NMR Data on C Atoms of Macroring in I, II, and Related Compounds

Carbon no.	I[a]	II[b]	Viomycin[c]	Capreomycin[d]	Tuberactinomycin A[e]
1	52.83 (d)	51.85	52.78 (d)	51.92	52.83
2	41.13 (t)	40.44	41.23 (t)	40.28	41.27
4	172.6 (s)	172.57	172.57 (s)	172.76	172.74
10	173.40 (s)	173.19	173.38 (s)	176.29	173.47
	55.06 (d)	55.23	55.06 (d)	55.66	55.01
5, 11, 14	55.32 (d)	55.61	55.32 (d)	56.23	55.25
	52.02 (d)	57.06	57.07 (d)	11 at 54.15	57.02
7	167.90 (s)	167.86	167.90 (s)	168.0	168.0
8	105.74 (s)	105.76	105.78 (s)	105.90	105.60
13	171.30 (s)	171.35	171.26 (s)	172.00	170.85
16	171.60 (s)	168.01	172.06 (s)	176.6	171.45

[a] Registry no., 61394-76-1. [b] Registry no., 51628-30-9. [c] Registry no., 32988-50-4. [d] Registry no., 61394-77-2. [e] Registry no., 33103-21-8.

Table IV. ^{13}C NMR Data on Side Chain Carbons of I, II, and Related Antibiotics

Carbon no.	I	II	Viomycin	Capreomycin	Tuberactinomycin A
17	135.58 (d)	135.62	135.53 (d)	135.79	135.70
19	154.26 (s)	156.32	154.26 (s)	155.32	154.35
20	59.86 (t)	59.88	59.88 (t)	18.86	59.88
21	63.31 (t)	63.35	63.35 (t)	68.33	63.23
22	46.83 (d)	46.90	46.88 (d)	49.20	46.83
23	29.93 (t)	30.09	30.09 (t)	23.53	30.14
24	70.83 (d)	70.84	70.87 (d)	49.83	70.87
26	157.20 (s)	156.96	157.00 (s)	157.0 (b)	157.26
1′	171.6 (s)		171.65 (s)	172.0	171.79
2′	34.87 (t)		37.03 (t)	36.93	31.02
3′	54.69 (d)		49.18 (d)	49.26	53.52
4′	29.93 (t)		23.69 (t)	23.59	68.96
5′	38.32 (t)		29.78 (t)	29.77	37.64
6′			39.82 (t)	39.77	34.82
7′	157.5 (s)				
8′	31.28 (q)				

macroring H bonding between the C_{13} carbonyl and the amide proton of position 6 as detected by x-ray work is certain to be present in all five compounds; hence the lowest values around 171 ppm are assigned to C_{13}. The high value near 173 ppm in I, II, viomycin, and tuberactinomycin A is replaced by a still higher value of 176.26 ppm in capreomycin. These values are assigned to C_{10} since in the first four compounds there is the high probability of H bonding between the hydroxymethyl group of C_{11} and the C_{10} carbonyl to form a six-membered ring. No other amide carbonyl is suitably situated for this kind of bonding. The high value in capreomycin is then explained since alanine replaces serine in this portion of the macroring. The value 172.6 is common to all five antibiotics; consequently this is assigned to C_4, which is the position least likely to be affected by the variations between the compounds. Compound I, viomycin, capreomycin, and tuberactinomycin A all show a signal close to 172 ppm which is lacking in the spectrum of II. These values are assigned to C_{16} since II has a free amino group attached to the adjacent C_1 and hence in this compound this signal is shifted to 168 ppm (β shift). The singlet near 168 ppm common in the spectra of all five compounds belongs to the conjugated carbonyl at C_7.[11] The signal at 105.8 ppm with similar characteristics is clearly the conjugated olefinic C_8. Carbons C_5, C_{11}, and C_{14} all with doublet multiplicity are assigned the values clustered between 55 and 57 ppm without further individual characterization except for C_{11} in capreomycin at the low value of 54.15 ppm due to the lack of the β oxygen function.

Assignment of Carbon Atoms of Side Chains. The vinyl C_{17} and the urea carbonyl C_{19} are readily assigned to the signals at 135.6 and 154.3 ppm, respectively. A triplet carbon peak at 59.8 ppm in each spectrum except that of capreomycin must be assigned to C_{20}. While capreomycin lacks this signal, it has a peak at 18.86 ppm unmatched in the others which belongs to methyl carbon C_{20} in this compound. A peak with triplet multiplicity at 63.3 ppm common to all five spectra is assigned to C_{21}. Carbons C_{22}, C_{23}, and C_{24} are assigned as shown in Table IV since in capreomycin the hydroxy group of C_{24} is missing and the α and β effects of the oxygen atom are observed by comparison of C_{22} and C_{23} in the spectrum of this compound with the corresponding signals in the spectra of the others. The guanidino C_{26} is located at about 157 ppm and is clearly visible in all spectra except that of capreomycin, where it is so broad as to be barely detectable. All of the carbons of the amino acid side chains may be picked out readily since they are all missing in the spectrum of II. With the exceptions of the carbonyl $C_{1'}$, which is around 172 ppm, and the guanidine $C_{7'}$ in I, which is found near 157 ppm, all the others appear as intense peaks between 69 and 22 ppm. Their intensities alone set them apart from other carbons in the spectra in the same range. The assignments of $C_{2'}$ through $C_{5'}$ in I, viomycin, capreomycin, and tuberactinomycin A and $C_{6'}$ in the last three of these compounds are readily made by spectral comparisons taking into account perturbation shifts due to N-methylation in I and α and β effects due to the presence of the γ-hydroxy group in tuberactinomycin A.[12] The one remaining signal at 31.28 ppm with quartet multiplicity in the spectrum of I obviously belongs to the *N*-methyl carbon.

We obtained ^{13}C NMR spectra on the hydrochloride salts of *N*-methyl-β-arginine and β-lysine and the data are shown in Table V. The agreement between the chemical shift values for the free acid salts and the corresponding values in the antibiotics I, viomycin, and capreomycin is quite good as seen by comparison of Tables IV and V.

Studies against *Mycobacterium tuberculosis* in mice showed I to be as effective as either viomycin or streptomycin.

Table V. ^{13}C NMR Data on the Hydrochloride Salts of N^β-Methyl-β-arginine and β-Lysine

Carbon	N^β-Methyl-β-arginine[a]	β-Lysine[b]
1′	174.55 (s)	174.56 (s)
2′	34.60 (t)	36.54 (t)
3′	54.32 (d)	48.63 (d)
4′	29.78 (t)	23.63 (t)
5′	38.28 (t)	29.73 (t)
6′		39.82 (t)
7′	157.64 (s)	
8′	31.22 (q)	

[a] Registry no. (HCl), 61394-78-3. [b] Registry no. (HCl), 37894-33-0.

However, the tolerated dose of LL-BM547β was 32 times less than that of streptomycin or 16 times less than that of viomycin. Other relevant biological data are given below.

Experimental Section

IR spectra were taken on in Infracord spectrophotometer, UV spectra were made using a DU Beckman spectrophotometer with recorder attachment, ^{1}H NMR spectra were made on a Varian A100 instrument, and ^{13}C NMR work was carried out on a Varian XL-100 spectrometer. HPLC was carried out on a Chromatronix Model 3520 equipped with a Schoeffel 770 spectrophotometric detector.

Isolation of I and II. Lederle culture BM547 was grown in a 300-L fermentor in a medium consisting of 2% molasses, 1% glucose, 0.5% Bactopeptone, and 0.1% $CaCO_3$ at pH 7.2. Inoculum was prepared in two steps from an agar slant using a medium of 0.5% tryptone, 0.5% yeast extract, 0.3% beef extract, and 1% dextrose. The tank was agitated by impeller at 190 rpm, aerated at 0.5 v v^{-1} min^{-1}, and allowed to incubate for about 140 h. The broth was filtered using diatomaceous earth and 100 L of filtrate was passed over 1 L of weak cation exchanger[14a] in the Na^+ cycle. The resin was washed with water and with acetate buffer at pH 4.8 until the pH of the effluent was unchanged. The resin was then eluted with 0.36 N H_2SO_4 and the eluate adjusted to pH 6.0 using warm $Ba(OH)_2$ solution. After filtration the solution was concentrated to 1 L and 2 L of acetone was added. The resultant precipitate was recovered and dried to 5.5 g of off-white solid. This solid was taken up in 100 mL of H_2O and charged to 500 mL of dextran resin[14b] in the Na^+ cycle. This column was eluted with a gradient of 0.6–6.0% NH_4Cl in H_2O. Elution was monitored by UV absorption at 268 nm and fractions of 60–65 mL volume were collected. Fractions 45–55 were combined and shown to be very rich in II by TLC on silica gel using the system 7% NH_4HCO_3 (90:100:1). Fractions 56–60 were combined and passed over 120 mL of granular carbon.[14] The carbon was then washed with 1200 mL of H_2O and eluted with 360 mL of 50:50 acetone–H_2O. UV measurement indicated that recovery off the carbon column was 62% of charge. The acetone–water eluate was concentrated to 100 mL of aqueous phase and freeze dried to yield 1.2 g of white solid. The OD of this preparation at a concentration of 25 μg/mL in H_2O at 268 nm was 0.73. For HPLC 20 μg was charged to a silica gel column[14c] and developed using a gradient of 20–50% B in A where A was absolute alcohol and B was 10% NH_4OAc solution with pH adjusted to 8.5 using concentrated NH_4OH. This test indicated that the solid was 97% of a major component with traces of two minor components. The major component was I, $[\alpha]^{25}D$ −33 ± 2° (*c* 0.69, H_2O). Microanalytical elemental analyses values for I, while quite reproducible, were consistently low in the carbon and nitrogen values. A typical analysis gave values such as the following.

Anal. Calcd for $C_{26}H_{45}N_{15}O_{10}\cdot 3HCl$: C, 37.29; H, 5.85; N, 25.10; Cl, 12.61. Found: C, 34.78; H, 5.88; N, 22.34; Cl, 12.58.

Fractions 45–55 above, which were shown to be rich in II, were processed by granular carbon to yield about 300 mg of solid. Cuts such as these from several columns were combined and rechromatographed over dextran resin[14b] in the Na^+ cycle and eluted with a gradient of 0.4–4% NH_4Cl. This column was again monitored by UV. Fraction volumes were 80–85 mL and fractions 34–43 were passed over 80 mL of granular carbon and worked as before to get 300 mg of white solid which by TLC was about 95% II with less than 5% I present. The OD of a 25 μg/mL solution in H_2O was 0.69, $[\alpha]^{25}D$ −28° (*c* 1.07, H_2O).

Anal. Calcd for $C_{19}H_{31}N_{11}O_9\cdot 2HCl$: C, 36.36; H, 4.94; N, 24.56. Found: C, 35.32; H, 5.76; N, 22.34.

As in the case of I, the carbon and nitrogen values are low. The biological activity of II is less than that of I or viomycin.[13]

Hydrolysis of I. Approximately 5.0 g of I was refluxed for 16 h in 200 mL of 6 N HCl. The solvent was evaporated off under reduced pressure and the residue treated with H_2O and evaporated to dryness several times until the sharp odor of HCl was no longer detected. The residual 6 g of oil was taken up in 75 mL of H_2O and passed over 30 g of cation-exchanger of 200–400 mesh in the H^+ form.[14d]

The column was eluted with a gradient of 0.3–4 N HCl and fraction volumes were in the range 40–50 mL. Elution progress was followed by paper chromatography using the system *t*-BuOH–H_2O–HOAc (2:1:1), by TLC on silica gel using 10% NH_4OAc–acetone–concentrated NH_4OH (90:100:0.67), and by cellulose TLC using $CHCl_3$–MeOH–NH_4OH–H_2O (1:4:2:1). Fractions 9–12 contained serine and 15–23 contained diaminopropionic acid (DAPA). Fractions 24–35 contained two Sakaguchi-positive materials as detected by cellulose TLC and one ninhydrin-yellow material as detected by paper chromatography. These fractions were combined and charged to 23 g of cation exchange resin[14a] (16–50 mesh) in the H^+ cycle. The column was eluted with H_2O and the eluate charged to 75 mL of dextran resin[14b] in the NH_4^+ form. Elution was carried out using a gradient of 0.5–3% ammonium formate. Fraction volumes were in the range 35–40 mL. Fraction 44–51 contained the Sakaguchi-positive material and these were freeze dried to about 500 mg of residue which was charged to 20 g of cation exchanger in the H^+ form (100–200 mesh).[14e] Elution was carried out using a gradient of 0.1–1.0 N HCl. Fraction volumes were 15–18 mL and the Sakaguchi-positive material appeared in fractions 20–23. Fraction 23 was evaporated to dryness several times, then reconstituted in H_2O and freeze dried to yield 20 mg of N^β-methyl-β-arginine hydrochloride salt which by TLC was essentially pure, $[\alpha]^{25}D$ +20 ± 2° (c 0.75, H_2O).

The material gave a clean ^{1}H NMR spectrum (D_2O): δ 2.10 m (2 H, C_3 methylene), 2.79 s (3 H, NCH_3), 2.92 d (2 H, C_2 methylene), 3.38 t (2 H, C_4 methylene), 3.65 m (1 H, C_3 methine).

Fractions 20–22 described above were combined and concentrated and chromatographed over 100 g of cellulose powder[14f] using the upper phase of $CHCl_3$–MeOH–concentrated NH_4OH (2:1:1) as the stationary phase and the lower phase as developing solvent. Fraction volumes of 60–65 mL were collected and fraction 95 contained about 200 mg of essentially pure *N*-methyl-β-arginine. Some of this material was converted to the hydrochloride salt and used for ^{13}C NMR work to get clean spectra. In our hands the material failed to crystallize.

Hydrolysis of II. About 100 mg of II was hydrolyzed in 10 mL of 6 N HCl at 100 °C for 16 h. At the same time a similar hydrolysis was carried out on viomycin. Chromatography of the acid-free hydrolysates showed the presence of serine, DAPA, and β-lysine in viomycin, while the hydrolysate of II showed only serine and DAPA.

Acknowledgments. We wish to thank Mr. A. C. Dornbush and associates for biological assays, Dr. J. Thomas and Mrs. N. Kuck for in vivo testing data, Mr. L. Brancone and associates for microanalytical data, Mr. W. Fulmor and associates for spectral and rotation data, Mr. A. J. Shay and Mr. M. Dann and associates for large-scale fermentations and recoveries, and Dr. H. Tresner for advice on nomenclature of microorganisms. Finally we thank Dr. W. Curran for the ^{13}C NMR data on β-lysine.

Registry No.—I 3HCl, 61473-86-7; II 2HCl, 61473-87-8.

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(9) Monosubstituted guanidino compounds give a positive red color with the Sakaguchi reagent whereas disubstituted guanidino compounds are negative. Viomycin and viomycidine are exceptions since they contain the

reactive guanidino carbinol or amino groups.
(10) Viomycin and capreomycin are commercially available as the sulfates. Tuberactinomycin A was isolated from a *Streptoverticillum* species (Lederle culture B0471). It is worth mentioning that hydrochloride or sulfate salts of these compounds give good ^{13}C NMR spectra whereas the carbonate salts give poorer quality spectra.
(11) G. L. Levy and G. L. Nelson, "^{13}C NMR for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972, p 123.
(12) J. B. Stothers, "Carbon 13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972, p 142.
(13) For comparison purposes the minimal inhibitory concentrations in μg/mL of I, II, and viomycin are given against two bacterial species in the agar dilution assay. *Mycobacterium smegmatis* ATCC 607: I, 2.5; II, 25; viomycin, 2.5. *Klebsiella pneumoniae*: I, 10; II, 100; viomycin, 25.
(14) (a) IRC-50 resin from Rohm and Haas Co., Philadelphia, Pa. (b) CM-Sephadex C-25 obtainable from Pharmacia Fine Chemicals, Inc., Piscataway, N.J. (c) Vydac column No. SS-2-500 A-107 from Spectra Physics, Santa Clara, Calif. (d) AG 50W-X4 from Bio-Rad Laboratories, Richmond, Calif. (e) Amberlite CG-50 is supplied by Mallinckrodt, St. Louis, Mo. (f) Cellulose CF11 from Whatman, Inc., Clifton, N.J.

Facile Synthesis of Amino Acid and Peptide Esters under Mild Conditions via Cesium Salts

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Received October 8, 1976

A facile procedure for the preparation of a wide variety of esters derived from protected amino acids and peptides under mild conditions is described. The carboxylic acid to be esterified is first titrated to pH 7 with cesium carbonate or cesium bicarbonate and the neutral salt obtained is then allowed to react with different alkyl halides to form the corresponding esters. The reaction is simple, easily scaled up, and proceeds without observable racemization. Many amino acid and peptide esters that might be difficult to prepare by other methods have been made by this method. The usefulness of this procedure is further demonstrated by the synthesis of methionine-enkephalin.

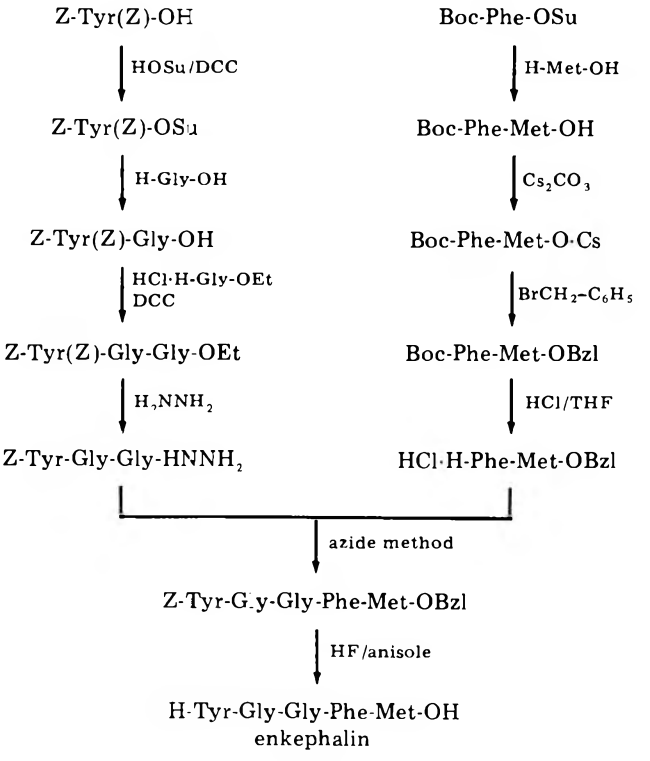
Many useful processes for esterification of carboxylic acids have been reported in the literature.[1-10] However, a great need still exists for a versatile and facile procedure to prepare esters under mild conditions. Such a procedure should be applicable to compounds that are sensitive to acidic, basic, or thermic conditions without depending on exotic expensive reagents. Recently, in an effort to reduce the number of side reactions encountered in solid-phase peptide synthesis,[11] a method for total esterification of Merrifield resins (chloromethylated copolystyrene–1% divinylbenzene) with the cesium salts of Boc-amino acids[12] was investigated.[13] The reaction was found to proceed rapidly and quantitatively under mild conditions. The process has since been satisfactorily utilized to prepare β-phenacyl aspartate[14] and Boc-valyl-4-(oxymethyl)phenylacetic acid.[15] Preparation of other polymer-bound benzyl esters[13,16] and polymer-bound α-methylphenacyl esters has also been described.[17] In the following, we describe the application of this principle to the synthesis of protected amino acid and protected peptide esters in solution.

Reaction of suitably protected amino acid or peptide cesium salts with alkyl halides yielded the desired esters readily under neutral conditions at room temperature. No racemization was observed during this process. The reactions were easily carried out and the yields were generally very high.

In Table I, α-carboxylic esters of amino acids and peptides prepared in this study are listed. The general procedure is as follows. The carboxylic acid to be esterified is first converted into its cesium salt by titration to neutrality with aqueous $CsHCO_3$ or Cs_2CO_3. The latter reagent is more economical. After evaporation to dryness the neutral salt is treated with an alkyl halide in DMF to form the corresponding ester. For example, the benzyl esters I–XII (Table I) were obtained within a short period of time by stirring equivalent amounts of benzyl bromide and the cesium salts of Boc-amino acids or Boc-peptides in DMF at room temperature.

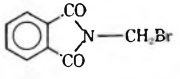
The combination of amine protection by the *tert*-butyloxycarbonyl group and carboxyl protection by the benzyl ester has been the most widely used tactic in peptide synthesis.[18-20] The scope and versatility of this useful approach is now further enhanced by the facile introduction of the benzyl ester group into protected peptides, as shown in Scheme I, with a synthesis of methionine-enkephalin as an example. Thus, Boc-Phe-Met-OH was readily converted in high yield into its benzyl ester Boc-Phe-Met-OBzl (VII) by the cesium salt

Scheme I. Synthesis of H-Tyr-Gly-Gly-Phe-Met-OH (Enkephalin)



† Rockefeller University.

Table I. Preparation of Protected Amino Acid and Peptide Esters via Cs-Salt Method: RX + R'COO·Cs → R'COOR + CsX

RX	Registry no.	R'COOH	R'COOR	Registry no.	% yield	Mp, °C	$[\alpha]^{25}D$, deg	% C[i]	% H[i]	% N[i]
$C_6H_5CH_2Br$	100-39-0	Boc-Asn-OH	Boc-Asn-OBzl (I)	13512-57-7	90.3[a]	120–122	−17.29[f]	59.61	6.88	8.69
								59.76	6.81	8.82
$C_6H_5CH_2Br$		Boc-Gln-OH	Boc-Gln-OBzl (II)	61543-21-3	86.3[a]	108–110	−22.69[f]	60.70	7.19	8.33
								60.72	7.30	8.35
$C_6H_5CH_2Br$		Boc-Trp-OH	Boc-Trp-OBzl (III)	57229-67-1	86.5[b]	140–142	−2.02[g]	70.03	6.64	7.10
								70.25	6.60	6.92
$C_6H_5CH_2Br$		Boc-Arg(Tos)-OH	Boc-Arg(Tos)-OBzl (IV)	61543-20-2	88.1[c]	Amorphous	+2.81[h]	57.90	6.61	10.80
								57.84	6.77	10.72
$C_6H_5CH_2Br$		Boc-Phe-Gly-OH	Boc-Phe-Gly-OBzl (V)	42280-29-5	79.5[c]	132–134	−8.61[f]	66.97	6.84	6.79
								67.18	6.90	6.64
$C_6H_5CH_2Br$		Boc-Phe-Phe-OH	Boc-Phe-Phe-OBzl (VI)	16879-80-4	82.0[c]	121–122	−1.59[g]	71.69	6.72	5.57
								71.86	6.72	5.56
$C_6H_5CH_2Br$		Boc-Phe-Met-OH	Boc-Phe-Met-OBzl (VII)	61543-22-4	86.2[c]	99–100	−3.43[h]	64.11	7.04	5.76
								64.16	6.99	5.97
$C_6H_5CH_2Br$		Boc-Pro-Pro-OH	Boc-Pro-Pro-OBzl (VIII)	29776-70-3	96.0[c]	Oil	−103.63[h]	65.65	7.51	6.96
								65.31	7.49	6.78
$C_6H_5CH_2Br$		Boc-Gly-Glu(OBzl)-OH	Boc-Gly-Glu(OBzl)-OBzl (IX)	61570-89-6	75.0[a]	Oil	−17.82[h]	64.45	6.66	5.78
								64.58	6.44	6.06
$C_6H_5CH_2Br$		Boc-Val-Cys(2-NO_2-Bzl)-OH	Boc-Val-Cys(2-NO_2-Bzl)-OBzl (X)	61543-23-5	67.3[c]	120–122	−65.64[g]	59.43	6.47	7.70
								59.53	6.54	7.73
$C_6H_5CH_2Br$		Boc-Leu-Val-Thr(Bzl)-OH	Boc-Leu-Val-Thr(Bzl)-OBzl (XI)	61543-24-6	85.5[a]	68–72	−31.02[h]	66.75	8.07	6.86
								66.71	8.08	6.81
$C_6H_5CH_2Br$		Boc-Ala-Ala-Ala-Lys(Z)-Ala-OH	Boc-Ala-Ala-Ala-Lys(Z)-Ala-OBzl (XII)	61543-25-7	72.9[c]	226–228	−29.41[f]	60.46	7.21	11.13
								60.42	7.29	11.04
2-$NO_2C_6H_4CH_2Cl$	612-23-7	Boc-Glu(OBzl)-Glu(OBzl)-OH	Boc-Glu(OBzl)-Glu(OBzl)-O(2-NO_2Bzl) (XIII)	61543-26-8	89.1[c]	108–110	+3.79[g]	62.50	5.97	6.07
								62.60	5.88	6.05
CH_3I	74-88-4	Boc-Ile-Leu-OH	Boc-Ile-Leu-OMe (XIV)	61543-27-9	81.0[d]	144–146	−26.00[g]	60.30	9.56	7.82
								60.50	9.61	7.93
CH_3I		Z-Lys(Z)-Phe-Phe-Gly-OH	Z-Lys(Z)-Phe-Phe-Gly-OMe (XV)	61570-88-5	80.4[d]	178–180	−24.35[f]	66.22	6.33	8.98
								66.06	6.30	8.94
$C_6H_5COCHMeBr$	2114-00-3	Z-Gly-OH	Z-Gly-OMPA (XVI)	61543-28-0	79.1[b]	Oil		66.85	5.61	4.10
								66.88	5.71	4.08
$C_6H_5COCHMeBr$		Z-Ala-OH	Z-Ala-OMPA (XVII)	61543-29-1	81.7[d]	Oil	−21.71[g]	67.59	5.96	3.94
								67.49	5.73	3.85
Ph_3CCl	76-83-5	Fmoc-Gly-OH	Fmoc-Gly-OTrt (XVIII)	61570-87-4	40.1[c]	173–175		80.13	5.42	2.60
								80.15	5.27	2.54
Ph_3CCl		Z-Ile-Leu-OH	Z-Ile-Leu-OTrt (XIX)	61543-30-4	64.2[e]	152–154	−54.57[h]	75.46	7.14	4.51
								75.66	7.08	4.47
Me_3CBr	507-19-7	Z-Ala-OH	Z-Ala-OBut (XX)	50300-96-4	14[c]	Oil	−10.18[g]	64.50	7.58	5.01
								64.44	7.42	4.98
$MeOC_6H_4CH_2Cl$	824-94-2	Boc-Trp-OH	Boc-Trp-OPMB (XXI)	61543-31-5	68.5[c]	100–102	−4.08[g]	67.91	6.65	6.60
								68.12	6.50	6.42
$MeOC_6H_4CH_2Cl$		Z-Ile-Leu-OH	Z-Ile-Leu-OPMB (XXII)	61543-32-6	73.6[c]	112–116	−19.42[h]	67.45	7.68	5.62
								67.54	7.68	5.58
	5332-26-3	Boc-Ala-Ala-OH	Boc-Ala-Ala-OPIM (XXIII)	61543-33-7	81.4[b]	96–98	−19.15[g]	57.27	6.01	10.02
								57.13	5.84	9.99
		Z-Ile-Leu-OH	Z-Ile-Leu-OPIM (XXIV)	61543-34-8	87.6[b]	151–153	−11.12[f]	64.79	6.56	7.82
								64.75	6.49	7.71

[a] Reaction time 6 h. [b] Reaction time 1 h. [c] Reaction time 17 h. [d] Reaction time 30 min. [e] Reaction time 64 h. [f] c 1, DMF. [g] c 1, EtOAc. [h] c 1, $CHCl_3$. [i] Anal. (calcd over found).

method which was subsequently condensed with the tripeptide Z-Tyr-Gly-Gly-$HNNH_2$ via the azide method.[21] The protected pentapeptide Z-Tyr-Gly-Gly-Phe-Met-OBzl was obtained as a crystalline pure compound. It is interesting that there was no indication for thioether alkylation at the methionine residue during the synthesis of VII. Apparently, carboxyl group benzylation proceeded much faster than thioether alkylation. The absence of S-alkylation was similarly observed during the synthesis of Boc-Val-Cys(2-NO_2-Bzl)-OBzl (X).

To ascertain the absence of gross racemization during esterification, the Manning and Moore test[22] was applied to a sample of crude Boc-Phe-Phe-OBzl (VI). A small amount of D isomer (0.30% D-Phe) was found. However, this value coincided within experimental variation with the D-Phe content (0.27%) of the hydrolyzed starting material Boc-Phe-Phe-OH. It is therefore concluded that racemization during the preparation of this ester, if any, was below the limit of detection by this test. Since phenylalanine is more racemization prone than most other amino acids the generalization that esterification of α-amino acids via the cesium salt proceeds generally free of observable racemization appears justified.

Similar to benzyl esters, methyl esters of protected peptides can be prepared efficiently from their cesium salts and methyl iodide. The reaction was found to proceed rapidly, requiring only a few minutes for completion (see compounds XIV, XV). Presumably, ethyl iodide could be used in a similar fashion for the preparation of peptide ethyl esters. The photolyzable 2-nitrobenzyl ester[23,24] and α-methylphenacyl esters[25] were also obtained by the cesium salt method using the readily available 2-nitrobenzyl chloride and α-bromopropiophenone, respectively, as alkylating agents. Reaction of amino acids or peptide cesium salts with triphenylmethyl chloride provided trityl esters[26-28] in moderate yields (see compounds XVIII and XIX). Z-Ala-OBut (XX) was prepared from the cesium salt of Boc-Ala-OH with 2-bromo-2-methylpropane, although the yield was low, probably owing to the instability and low reactivity of this alkylating agent. As illustrated by the synthesis of XXI and XXII, *p*-methoxybenzyl esters[29] were satisfactorily obtained from cesium salts and *p*-methoxybenzyl chloride.[30] This ester may become more important as a temporary blocking group for the carboxylic function since the selective removal of the Boc group by *p*-toluenesulfonic acid in the presence of *p*-methoxybenzyl ester has recently been described.[31] The cesium ester method was equally suitable for the preparation of phthalimidomethyl esters[32] as exemplified by the synthesis of XXIII and XXIV. The phthalimidomethyl ester is an attractive protection for carboxyl group in peptide synthesis since it can be removed selectively in the presence of many other widely used blocking groups under very mild conditions.[18-20]

In conclusion, the cesium salt method provides facile preparation of a wide variety of esters of protected amino acids and peptides under mild, neutral conditions at room temperature. The procedure is simple, easily scaled up, and proceeds without observable racemization. Its great versatility suggests that the procedure might be useful beyond amino acid and peptide chemistry.

Experimental Section

Melting points are uncorrected. Thin layer chromatography was carried out on precoated silica gel plates (Merck, F-254) with the solvent systems given previously.[33] Elemental analyses and physiochemical measurements (IR, UV, $[\alpha]^{25}_D$, NMR) were performed by the Hoffmann-La Roche Physical Chemistry Department. All the new compounds described in these experiments have been examined by UV, IR, and NMR spectrophotometry. Each compound gave spectra agreeing with its structure.

Amino acid derivatives were either purchased from Bachem Inc., Marina Del Rey, Calif., or prepared in our laboratories. All the optically active amino acids were of the L configuration. Benzyl bromide, o-nitrobenzyl chloride, 2-bromo-2-methylpropane, α-bromopropiophenone, methyl iodide, and *p*-methoxybenzyl alcohol were obtained from Aldrich Chemical Co. and triphenylmethyl chloride and *N*-bromomethylphthalimide were the products of Eastman Organic Chemicals. Cesium carbonate was bought from Atomergic Chemical Co., Long Island, N.Y. *p*-Methoxybenzyl chloride was prepared from *p*-methoxybenzyl alcohol according to the literature procedure.[30] Other chemicals and solvents used were reagent grade products available from commercial sources.

Since the procedures utilized to make the esters listed in Table I are very similar from one to the other, the synthesis of only a few representative compounds will be described in the following examples.

A. General Examples of Esterification. Boc-Asn-OBzl (I). Boc-Asn-OH (11.6 g, 47.5 mmol) was dissolved in 200 mL of MeOH and 20 mL of water was added. The solution was titrated to pH 7.0 (pH paper) with a 20% aqueous solution of Cs_2CO_3 (~55 mL). The mixture was evaporated to dryness and the residue reevaporated twice from 120 mL of DMF (45 °C). The white solid cesium salt obtained was stirred with 8.9 g (52 mmol) of benzyl bromide in DMF (120 mL) for 6 h. On evaporation to dryness and treatment with a large volume of water (500 mL) the product solidified. It was taken into ethyl acetate, washed with water, dried over Na_2SO_4, evaporated to a solid mass, and crystallized from ethyl acetate with petroleum ether: yield 13.8 g (90.3%); mp 120–122 °C; $[\alpha]^{25}_D$ −17.29° (*c* 1, DMF).

Anal. Calcd for $C_{16}H_{22}N_2O_5$ (322.36): C, 59.61; H, 6.88; N, 8.69. Found: C, 59.76; H, 6.81; N, 8.82.

Boc-Glu(OBzl)-Glu(OBzl)-O(2-NO_2-Bzl) (XIII). H-Glu(OBzl)-OH (4.74 g, 20 mmol) was finely ground in a mortar and pestle and stirred with 8.7 g of Boc-Glu(OBzl)-OSu[34] (20 mmol) and NMM (4.8 mL) in DMF (150 mL) for 36 h. The clear solution obtained was evaporated to a syrup and treated with a large volume of water. The oily product was taken up in ethyl acetate, washed with 5% HOAc followed by water (three times), dried over Na_2SO_4, and evaporated to dryness. The colorless, clear oil (12.2 g) failed to crystallize. TLC indicated that the product, Boc-Glu(OBzl)-Glu(OBzl)-OH, is homogeneous, $[\alpha]^{25}_D$ −7.59° (*c* 1, DMF).

Anal. Calcd for $C_{29}H_{36}N_2O_9$ (556.60): C, 62.57; H, 6.52; N, 5.03. Found: C, 62.37; H, 6.34; N, 5.01.

The oily Boc-Glu(OBzl)-Glu(OBzl)-OH (6.0 g, 10.8 mmol) was dissolved in 100 mL of EtOH when 10 mL of H_2O was added. The solution was then titrated to pH 7 with 20% Cs_2CO_3 and evaporated to dryness. The residue was reevaporated twice from DMF (100 mL) and the cesium salt obtained was stirred with 1.88 g (11 mmol) of o-nitrobenzyl chloride in 50 mL of DMF for 17 h. Evaporation of the solvent and treatment of the residue with water gave a crude solid product. It was collected by suction, dissolved in ethyl acetate, washed with water, dried over Na_2SO_4, and evaporated to a solid mass. Crystallized from ethyl acetate and petroleum ether: yield 6.66 g (89.1%); mp 108–110 °C $[\alpha]^{25}_D$ +3.79° (*c* 1, EtOAc).

Anal. Calcd for $C_{36}H_{41}N_3O_{11}$ (691.73): C, 62.51; H, 5.97; N, 6.07. Found: C, 62.60; H, 5.88; N, 6.05.

Z-Lys(Z)-Phe-Phe-Gly-OCH_3 (XV). Z-Lys(Z)-Phe-Phe-Gly-OH[35] (1.0 g, 1.3 mmol) was dissolved in 50 mL of THF and 5 mL of water was added. The solution was neutralized to pH 7 with 20% Cs_2CO_3 and evaporated to dryness as described above to give the cesium salt. It was then stirred with 0.22 g (1.55 mmol) of CH_3I in DMF (20 mL) for 30 min. Upon removal of the solvent by evaporation and treatment with water, a solid product was obtained. It was collected and washed with water on the funnel and dried to a white powder. Crystallized from THF and water: yield 0.82 g (80.4%); mp 178–180 °C; $[\alpha]^{25}_D$ −24.35° (*c* 1, DMF).

Anal. Calcd for $C_{43}H_{49}N_5O_9$ (779.90): C, 66.22; H, 6.33; N, 8.98. Found: C, 66.06; H, 6.30; N, 8.94.

Z-Ala-OMPA (XVII). Z-Ala-OH (1.12 g, 5 mmol) was converted into its cesium salt as described above and stirred with 1.17 g (5.5 mmol) of α-bromopropiophenone for 30 min in DMF (25 mL). Workup as usual gave an oil (1.45 g, 81.7%) which failed to crystallize, $[\alpha]^{25}_D$ −21.71° (*c* 1, EtOAc).

Anal. Calcd for $C_{20}H_{21}NO_5$ (355.38): C, 67.59; H, 5.96; N, 3.94. Found: C, 67.49; H, 5.73; N, 3.85.

Z-Ile-Leu-OTrt (XIX). Z-Ile-Leu-OH[34] (1.0 g, 2.64 mmol) was converted into its cesium salt as described above and stirred with 1.0 g (3.6 mmol) of triphenylmethyl chloride for 64 h in DMF (15 mL). Workup as usual gave a solid material which was crystallized from ethyl acetate and petroleum ether: yield 1.05 g (64.2%); mp 152–154 °C; $[\alpha]^{25}_D$ −54.57° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{39}H_{44}N_2O_5$ (620.77): C, 75.46; H, 7.14; N, 4.51. Found: C, 75.66; H, 7.08; N, 4.47.

Z-Ile-Leu-OPMB (XXII). Z-Ile-Leu-OH (1.0 g, 2.64 mmol) was converted into its cesium salt and reacted with 0.47 g (3.0 mmol, freshly prepared) of *p*-methoxybenzyl chloride for 17 h in DMF (10 mL). Workup as usual gave a crude solid which was crystallized from THF and petroleum ether: yield 0.97 g (73.6%); mp 112–116 °C; $[\alpha]^{25}_D$ −19.42° (c 1, $CHCl_3$).

Anal. Calcd for $C_{28}H_{38}N_2O_6$ (498.62): C, 67.45; H, 7.68; N, 5.62. Found: C, 67.54; H, 7.68; N, 5.58.

Z-Ala-OBut (XX). Z-Ala-OH (2.33 g, 10 mmol) and solid Cs_2CO_3 (3.25 g, 10 mmol) were ground together in a mortar and pestle and the resulting fine powder was stirred in DMF (30 mL) with 2.85 g (20 mmol) of 2-bromo-2-methylpropane for 17 h. The solvent was then removed by evaporation and the residue was treated with water.[36] The product was taken into ethyl acetate and washed with water, 15% $NaHCO_3$, and water followed by drying (Na_2SO_4). Evaporation of the solvent left a clear, colorless oil (0.39 g, 14%): homogeneous on TLC; $[\alpha]^{25}_D$ −10.18° (c 1, EtOAc).

Anal. Calcd for $C_{15}H_{21}NO_4$ (279.33): C, 64.50; H, 7.58; N, 5.01. Found: C, 64.44; H, 7.42; N, 4.98.

Boc-Ala-Ala-OPIM (XXIII). Boc-Ala-Ala-OH (1.3 g, 5 mmol) was converted into its cesium salt in the usual manner (20% Cs_2CO_3 and aqueous MeOH; DMF) and stirred with 1.32 g (5.5 mmol) of *N*-bromomethylphthalimide for 1 h in DMF (15 mL). Removal of the solvent and treatment with water gave a solid which was worked up as usual and crystallized from ethyl acetate and petroleum ether: yield 1.70 g (81.4%) mp 96–98 °C $[\alpha]^{25}_D$ −19.15° (c 1, EtOAc).

Anal. Calcd for $C_{20}H_{25}N_3O_7$ (419.42): C, 57.27; H, 6.01; N, 10.02. Found: C, 57.13; H, 5.84; N, 9.99.

H-Cys(2-NO_2-Bzl)-OH. Cysteine hydrochloride monohydrate (17.56 g, 100 mmol) was dissolved in 200 mL of 1 N NaOH that had been purged with argon gas for 15 min. To this mixture, 17.4 g (102 mmol) of *o*-nitrobenzyl chloride in 100 mL of peroxide-free dioxane[37] was added dropwise under argon during 90 min. The solution was stirred for an additional 60 min and the pH adjusted to 6.2. A heavy suspension of crystalline product formed. The solid was collected and washed with water, *i*-PrOH, and ether: yield 22.0 g (85.6%); mp 198–200 °C.

Anal. Calcd for $C_{10}H_{12}N_2O_4S$ (256.28): C, 46.87; H, 4.72; N, 10.93; S, 12.51. Found: C, 47.02; H, 4.74; N, 10.94; S, 12.62.

Boc-Val-Cys(2-NO_2-Bzl)-OBzl (X). Boc-Val-OSu (3.15 g, 10 mmol) and 2.56 g (10 mmol) of H-Cys(2-NO_2-Bzl)-OH were allowed to react in DMF (75 mL) for 36 h in the presence of 1.5 mL of Et_3N. Evaporation of the solvent and trituration of the residue gave a gum which was taken up in ethyl acetate, washed with water, dried over Na_2SO_4, and evaporated to a slightly yellowish oil (4.2 g) that failed to crystallize. It was thus converted into the cesium salt as described above and treated with 1.62 g of benzyl bromide in a manner similar to that for the preparation of VII. The mixture was left stirring overnight and worked up as usual to give a solid which was crystallized from ethyl acetate and petroleum ether: yield 3.67 g (67.3%); mp 120–122 °C; $[\alpha]^{25}_D$ −65.64° (c 1, EtOAc).

Anal. Calcd for $C_{27}H_{35}N_3O_7S$ (545.64): C, 59.43; H, 6.47; N, 7.70. Found: C, 59.53; H, 6.54; N, 7.73.

Boc-Gly-Glu(OBzl)-OBzl (IX). H-Glu(OBzl)-OH (1.19 g, 5 mmol), finely ground, was stirred with 1.43 g (5.25 mmol) of Boc-Gly-OSu and 0.7 mL (5 mmol) of Et_3N in DMF (35 mL) for 36 h. The clear solution obtained was evaporated to a syrup and treated with acidified water. The oily product was taken up in ethyl acetate, washed with 5% AcOH followed by water, dried over Na_2SO_4, and evaporated to dryness. The colorless, clear oil failed to crystallize. TLC indicated that the product Boc-Gly-Glu(OBzl)-OH was homogeneous, $[\alpha]^{25}_D$ +0.55° (c 1.8, MeOH).

Anal. Calcd for $C_{19}H_{26}N_2O_7$ (394.43): C, 57.86; H, 6.64; N, 7.10. Found: C, 57.88; H, 6.74; N, 6.98.

The oily Boc-Gly-Glu(OBzl)-OH was dissolved in 35 mL of EtOH when 5 mL of water was added. The solution ws then titrated to pH 7 with 20% Cs_2CO_3 and evaporated to dryness. The residue was reevaporated twice from DMF (25 mL) and the cesium salt obtained was stirred with 0.86 g (5 mmol) of benzyl bromide for 6 h. The solvent was then removed by evaporation and the residue treated with water. The product was taken into ethyl acetate, washed with water, and dried over Na_2SO_4. Evaporation of the solvent left a clear, colorless oil, which failed to crystallize. TLC indicated that the product Boc-Gly-Glu(OBzl)-OBzl (1.82 g, 75%) was homogeneous, $[\alpha]^{25}_D$ −17.82° (c 2.1, MeOH).

Anal. Calcd for $C_{26}H_{32}N_2O_7$ (484.56): C, 64.45; H, 6.66; N, 5.78. Found: C, 64.58; H, 6.44; N, 6.06.

B. Synthesis of Methionine-Enkephalin. Z-Tyr(Z)-OSu. Z-Tyr(Z)-OH[38] (5 g, 11.1 mmol) in THF was cooled in an ice bath and treated with 1.54 g (13.3 mmol) of HOSu and 2.52 g (12.2 mmol) of DCC. The mixture was gently stirred at 0 °C for 1 h and at 25 °C for 2.5 h. The insoluble by-product was then filtered off and the filtrate evaporated at 30 °C to leave a solid mass, recrystallized from *i*-PrOH: yield 5.9 g (97.2%); mp 153–154 °C; $[\alpha]^{25}_D$ +8.77° (c 1, $CHCl_3$).

Anal. Calcd for $C_{29}H_{26}N_2O_9$ (546.54): C, 63.73; H, 4.79; N, 5.12. Found: C, 63.94; H, 5.07; N, 5.17.

Z-Tyr(Z)-Gly-OH. Glycine (0.75 g, 10 mmol) was dissolved in 4.9 mL of 40% Triton B in MeOH (10.5 mmol), evaporated at 35 °C to a white solid residue, reevaporated twice from DMF (50 mL), and mixed with 6.01 g (11 mmol) of Z-Tyr(Z)-OSu in DMF. The reaction mixture was stirred for 17 h during which time some additional Et_3N was added occasionally to maintain the pH at about 8.0 (moist pH paper). Acetic acid was added to about pH 3 and the solvents removed under reduced pressure. The product was extracted into ethyl acetate, washed with 5% HOAc and water, dried over Na_2SO_4, and evaporated to a white solid, crystallized from ethyl acetate with petroleum ether: yield 4.8 g (94.7%); mp 174–176 °C; $[\alpha]^{25}_D$ −20.08° (c 1, DMF).

Anal. Calcd for $C_{27}H_{26}N_2O_8$ (506.52): C, 64.03; H, 5.17; N, 5.53. Found: C, 63.99; H, 5.13; N, 5.45.

Z-Tyr(Z)-Gly-Gly-OEt. Glycine ethyl ester HCl (1.27 g, 9.1 mmol) was allowed to react with 4.6 g (9.1 mmol) of Z-Tyr(Z)-Gly-OH, 2.07 g (10 mmol) of DCC, and 1.02 mL (9.1 mmol) of NMM in a mixture of DMF and CH_2Cl_2 at 0 °C for 1 h and then at 25 °C for 24 h. After removal of the by-product and the solvent, the syrup obtained was dissolved in ethyl acetate, washed with water, dried (Na_2SO_4), and evaporated to dryness. The product was crystallized from ethyl acetate and petroleum ether: yield 5.1 g (94.8%); mp 89–91 °C.

Anal. Calcd for $C_{31}H_{33}N_3O_9$ (591.62); C, 62.93; H, 5.62; N, 7.10. Found: C, 62.97; H, 5.52; N, 7.21.

Z-Tyr-Gly-Gly-HNNH$_2$. Z-Tyr(Z)-Gly-Gly-OEt (4.4 g, 7.44 mmol) was dissolved in EtOH (50 mL) and treated with 5 mL of H_2NNH_2. The product precipitated as a granular solid during overnight standing, recrystallized from EtOH: yield 2.5 g (75.8%); mp 198–201 °C; $[\alpha]^{25}_D$ −21.86 (c 1, DMF).

Anal. Calcd for $C_{21}H_{25}N_5O_6$ (443.46): C, 56.89; H, 5.68; N, 15.79. Found: C, 56.60; H, 5.80; N, 15.62.

Boc-Phe-Met-OH. Methionine (3.5 g, 24.45 mmol) was dissolved in 11.57 mL (25.4 mmol) of 40% Triton B and evaporated to an oil. It was reevaporated twice with DMF (45 mL) and the salt obtained was stirred with 9.35 g (26.9 mmol) of Boc-Phe-OSu in DMF (0 °C, 1 h; 25 °C, 17 h). The mixture was adjusted to pH 3 and worked up as usual to give an oil which was crystallized from ethyl acetate and petroleum ether: yield 7.5 g (80.7%); mp 137–139 °C; $[\alpha]^{25}_D$ +23.01° (c 1, $CHCl_3$).

Anal. Calcd for $C_{19}H_{28}N_2O_5S$ (396.50): C, 57.56; H, 7.12; N, 7.06; S, 8.09. Found: C, 57.82; H, 7.25; N, 7.14; S, 8.26.

Boc-Phe-Met-OBzl (VII). Boc-Phe-Met-OH (6.0 g, 15.12 mmol) was converted into its cesium salt as described above except that all the operations were performed under an argon atmosphere. The white solid salt was dissolved in DMF (50 mL, purged with argon for 15 min) and treated with 2.72 (15.8 mmol) of benzyl bromide added dropwise during a 30-min period of time. The reaction mixture was worked up as usual, after 17 h of gentle stirring, to give a solid which was crystallized from ethyl acetate with petroleum ether: yield 6.4 g (86.2%); mp 99–100 °C; $[\alpha]^{25}_D$ −3.43° (c 1, $CHCl_3$).

Anal. Calcd for $C_{26}H_{34}N_2O_5S$ (486.63): C, 64.11, H, 7.04; N, 5.76; S, 6.59. Found: C, 64.16; H, 6.99; N, 5.97; S, 6.68.

HCl·H-Phe-Met-OBzl. Boc-Phe-Met-OBzl (4.38 g, 9.02 mmol) was treated with freshly prepared peroxide-free[37] 4.0 N HCl in THF for 90 min. Evaporation of the excess HCl and solvent gave a white solid which was crystallized from EtOH and ether: yield 2.66 g (69.7%); mp 140–142 °C; $[\alpha]^{25}_D$ −8.57° (c 1, 0.1 N HCl).

Anal. Calcd for $C_{21}H_{27}N_2O_3S$ Cl (422.97): C, 59.63; H, 6.43; N, 6.62; S, 7.58; Cl, 8.38. Found: C, 59.50; H, 6.44; N, 6.57; S, 7.49; Cl, 8.45.

Z-Tyr-Gly-Gly-Phe-Met-OBzl. Z-Tyr-Gly-Gly-HNNH$_2$ (2.0 g, 4.51 mmol) was dissolved in 45 ml of DMF, cooled to −20 °C and treated with 5.65 mL of 4.0 N HCl in THF followed by 9.1 mL of 10% isoamyl nitrite in DMF. After 30 min, the mixture was cooled down to −30 °C when 3.79 mL of Et_3N and HCl·H-Phe-Met-OBzl (1.9 g, 4.51 mmol) were added. The mixture was stirred gently at 4 °C for 32 h during which time some more Et_3N was added in order to maintain the pH slightly basic. Evaporation of the solvent and trituration of the residue gave a yellowish powder which was taken up in ethyl acetate, washed with H_2O, dried over Na_2SO_4, and evaporated to a smaller volume when crystallization began. Recrystallized from ethyl acetate: yield 2.40 g (66.9%); mp 182–185 °C; $[\alpha]^{25}_D$ −26.82° (c 1, DMF).

Anal. Calcd for $C_{42}H_{47}N_5O_9S$ (797.93): C, 63.22; H, 5.94; N, 8.78;

S, 4.02. Found: C, 63.16; H, 5.83; N, 8.83, S, 4.13.

H-Tyr-Gly-Gly-Phe-Met-OH (Methionine-Enkephalin). The protected pentapeptide Z-Tyr-Gly-Gly-Phe-Met-OBzl (2.4 g, 3.0 mmol) was treated with HF[39] (35 mL) at 0 °C for 45 min in the presence of 13.3 mL of anisole and 6.6 mL of diethyl sulfide. After removal of the acid, the residue was taken up in 5% HOAc, washed a few times with peroxide-free ether, and lyophilized to give 2.01 g of crude product. It showed two minor impurities on TLC which were eliminated after passing through a Sephadex G-10 column (5 × 100 cm) using 0.2 M HOAc as eluent: yield 0.99 g; $[\alpha]^{25}_D$ +23.80° (c 1, 5% HOAc).

Anal. Calcd for $C_{27}H_{35}N_5O_7S \cdot H_2O$ (591.68): C, 54.80; H, 6.30; N, 11.83. Found: C, 54.90; H, 6.14; N, 11.69.

Amino Acid Anal.[40] Gly, 2.00; Met, 0.98; Tyr, 1.00; Phe, 1.00.

Racemization Test for Boc-Phe-Phe-OBzl Prepared by the Cesium Salt Method. Samples of Boc-Phe-Phe-OH and *unpurified* crude Boc-Phe-Phe-OBzl obtained from Boc-Phe-Phe-OH by the cesium salt method were hydrolyzed separately in 6 N HCl at 135 °C for 4 h. They were then evaporated to dryness and separately made up to a concentration of 6 μmol/mL (Phe) with pH 10.2 borate buffer. Derivatization and analyses of these samples were carried out according to Manning and Moore[22] with the results: Boc-Phe-Phe-OH contained 0.27% D-phenylalanine after hydrolysis whereas Boc-Phe-Phe-OBzl (crude) contained 0.30% D-phenylalanine after hydrolysis. Thus, within the experimental variation, they contained equal amounts of D-phenylalanine.

Acknowledgments. The authors wish to thank Dr. R. B. Merrifield for suggestions and discussions; Dr. F. Scheidl, Dr. T. Williams, Dr. V. Toome, Mr. S. Traiman (Hoffmann-La Roche Inc.), and their colleagues for physicochemical measurements; and Dr. J. M. Manning (The Rockefeller University) for a sample of L-Glu-D-Phe. B.F.G. received NIH support through Grants HL-12157 and HL-17961.

Registry No.—Boc-Asn-OH Cs salt, 61543-35-9; Boc-Gln-OH Cs salt, 61543-36-0; Boc-Trp-OH Cs salt, 61543-37-1; Boc-Arg(Tos)-OH Cs salt, 61543-38-2; Boc-Phe-Gly-OH Cs salt, 61543-39-3; Boc-Phe-Phe-OH Cs salt, 61543-40-6; Boc-Phe-Met-OH Cs salt, 61543-41-7; Boc-Pro-Pro-OH Cs salt, 61543-42-8; Boc-Gly-Glu(OBzl)-OH Cs salt, 61543-43-9; Boc-Val-Cys(2NO_2-Bzl)-OH Cs salt, 61543-44-0; Boc-Leu-Val-Thr(Bzl)-OH Cs salt, 61543-45-1; Boc-Ala-Ala-Ala-Lys(Z)-Ala-OH Cs salt, 61570-86-3; Boc-Glu(OBzl)-Glu(OBzl)-OH Cs salt, 61543-46-2; Boc-Ile-Leu-OH, 61543-47-3; Z-Lys(Z)-Phe-Phe-Gly-OH, 61604-89-5; Z-Gly-OH, 61543-48-4; Z-Ala-OH, 61543-49-5; Fmoc-Gy-OH, 61543-50-8; Z-Ile-Leu-OH, 61543-51-9; Boc-Ala-Ala-OH, 61543-52-0; H-Glu(OBzl)-OH, 1676-73-9; Boc-Glu(OBzl)-OSu, 32886-40-1; Boc-Glu(OBzl)-Glu(OBzl)-OH, 32886-41-2; H-Cys(2-NO_2-Bzl)-OH, 61543-53-1; Cys HCl, 52-89-1; Boc-Val-OSu, 3392-12-9; Boc-Gy-OSu, 3392-07-2; Boc-Gly-Glu(OBzl)-OH, 56357-41-6; Z-Tyr(Z)-OSu, 6461-23-0; Z-Tyr(Z)-OH, 29713-96-0; HOSu, 6066-82-6; Z-Tyr(Z)-Gly-OH, 14297-20-2; Gly, 56-40-6; Z-Tyr(Z)-Gly-Gly-OEt, 61543-54-2; Gly-OEt HCl, 623-33-6; Z-Tyr-Gly-Gly-$HNNH_2$, 61543-55-3; Boc-Phe-Met-OH, 61543-56-4; Met, 63-68-3; Boc-Phe-OSu, 3674-06-4; HCl·H-Phe-Met-OBzl, 61543-57-5; Z-Tyr-Gly-Gly-Phe-Met-OBzl, 61543-58-6; H-Tyr-Gly-Gly-Phe-Met-OH, 58569-55-4.

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(12) Abbreviations used: Boc, *tert*-butyloxycarbonyl; But, *tert*-butyl; Bzl, benzyl; Bpoc, 2-(biphenylyl)-2-propyloxycarbonyl; Fmoc, 9-fluorenylmethyloxycarbonyl; MPA, α-methylphenacyl; 2-NO_2-Bzl, 2-nitrobenzyl; PIM, phthalimidomethyl; Trt, trityl; Z, benzyloxycarbonyl; NMM, *N*-methylmorpholin; TLC, thin layer chromatography; THF, tetrahydrofuran; HOSu, *N*-hydroxysuccinimide; DCC, dicyclohexylcarbodiimide; HOBT, *N*-hydroxybenzotriazole; FMB, *p*-methoxybenzyl; DMF, dimethylformamide.
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The Limits of Reaction of Radioactive Dicyclohexylcarbodiimide with Amino Groups during Solid-Phase Peptide Synthesis[1,2]

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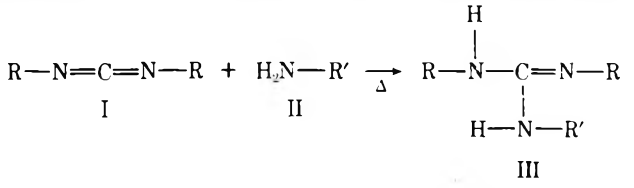
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Received October 18, 1976

[1-^{14}C]Dicyclohexylcarbodiimide ([^{14}C]DCC) was synthesized and the extent of its reaction with N^{α}-amino groups during solid-phase peptide synthesis was determined by radioisotopic analysis. The limit of detection was below 0.2%. No measurable reaction occurred between [^{14}C]DCC and unprotonated valine which was esterified to a polystyrene–divinylbenzene resin (Val-Res). Similarly, no reaction occurred during normal [^{14}C]DCC-mediated coupling reactions such as those between Boc-Gly and Val-Res, Boc-Ala and Gly-Val-Res, or Boc-Lys(2,4-Cl_2Z) and Pro-Ala-Ile-Arg(Tos)-Arg(Tos)-Leu-Res. Therefore, this is not a significant side reaction and cannot account for the rises in picrate monitoring values that have been observed in some syntheses. [^{14}C]DCC reacted extensively with the protonated form of Val-Res to give [1-^{14}C]*N,N'*-dicyclohexylamidino-valine-resin (Dca-Val-Res). Cyclization and cleavage by diisopropylethylamine (DIEA) gave [2-^{14}C]-1-cyclohexyl-2-cyclohexylamino-4-isopropyl-4,5-dihydro-5-imidazolone. Reaction of [^{14}C]DCC with HCl·Gly-Val-Res gave the amidino peptide, which was stable to DIEA in CH_2Cl_2 but was transesterified with DIEA in methanol to give [^{14}C]Dca-glycyl-valine methyl ester hydrochloride. [^{14}C]Dca-Gly-Val-Res·HCl took up 1 equiv of picrate by the picrate monitoring method. It did not react with Boc-Ala + DCC following treatment with DIEA, but in the presence of a quaternary ammonium hydroxide (Triton B) it was acylated by Boc-Ala + DCC or by the symmetrical anhydride of Boc-Ala.

Monitoring data have suggested the occurrence of a side reaction during solid-phase peptide synthesis[3,4] that leads to a product which will titrate by the picrate method,[5,6] but which is terminated for further chain growth. Thus, in a long synthesis, the titration after coupling continued to rise slowly but the total titration after deprotection remained constant. It seemed possible that a reaction of dicyclohexylcarbodiimide (DCC, I) with the α-amino group could account for this effect.

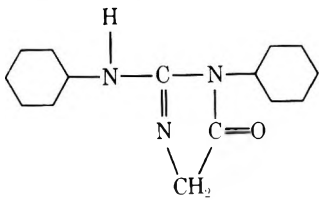
It has been known from early work[7-13] that diimides can react with amines to give guanidines, III. If this were to occur



I II III

during the coupling step of a solid-phase synthesis, in competition with the reaction of DCC with the carboxyl component, it would give a basic, titratable guanidine group which might remain protonated after the neutralization step with a tertiary amine and be resistant to further acylation reactions, just as in the case of unprotected arginine.

Muramatsu et al.[8] showed that glycine ethyl ester reacts with DCC in triethylamine to form 1-cyclohexyl-2-cyclohexylamino-4,5-dihydro-5-imidazolone (IV), and DeTar et al.[11]



IV

found that HBr·Gly-ONp reacted with DCC in acetonitrile to give the corresponding hydrobromide, whereas HCl·Gly-OEt and HBr·Ser-Gly-ONp reacted with DCC, but did not cyclize in the absence of tertiary amine. They predicted that the reactions were fast enough to be a source of by-products in certain peptide syntheses.

Soon after the DeTar publications we[14] tested the possibility that this might occur during solid-phase syntheses. Glycyloxymethyl-copoly(styrene–divinylbenzene) (Gly-Res) was treated with 4 equiv of DCC for 2 h, followed by addition of 4 equiv of Boc-Ala for 2 more h. After hydrolysis, the amino acid analysis showed equal amounts of glycine and alanine. Thus, the coupling had gone essentially to completion and no significant amount (<5%) of the side reaction appeared to have occurred. In a further test, Boc-Gly-Res (0.178 mmol/g) was deprotected with HCl and HOAc, neutralized with Et_3N, and treated for 2 h with 4 equiv of DCC in dimethylformamide. After acid hydrolysis, 0.178 mmol/g of glycine was found, indicating no formation of the acid-stable *N,N'*-dicyclohexylamidinoglycine (Dca-Gly) by reaction with DCC. In contrast, when HCl·Gly-Res was treated (without neutralization) with DCC in dimethylformamide the glycine recovered after hydrolysis decreased by 11% and when the reaction was carried out in dichloromethane glycine was reduced to 0.058 mmol/g, consistent with the presence of 67% of the guanidine derivative. Since the reaction did not occur to a measurable extent under normal coupling conditions or during treatment of the neutral amino acid-resin with DCC it was concluded at that time that this was not a significant side reaction of solid-phase synthesis.

A more sensitive way to detect and quantitate low levels of incorporation of DCC was necessary before the new evidence from monitoring data could be tested. For that purpose [1-^{14}C]dicyclohexylcarbodiimide ([^{14}C]DCC) was synthesized and examined for reaction with resin-bound amino acids and peptides under a variety of conditions.

Results and Discussion

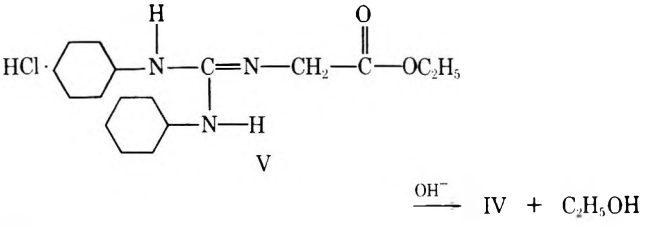
Experiments with Nonradioactive DCC. In order to compare the extent of reaction of DCC with amino groups in solution or on a resin support and to confirm some of the earlier work, a number of exploratory experiments were performed using unlabeled reagent.

It was found that reaction of DCC with unprotonated Gly-OEt in CH_2Cl_2 was very slow while in the case of Gly-Res no reaction was observed within the accuracy of the assay (<5%, amino acid analysis after hydrolysis). On the other hand, the hydrochlorides of amino acid esters reacted readily, either in solution or on a solid support, although the solution reaction appeared to be more rapid and complete. The product of the reaction of HCl·Gly-OEt with DCC, Dca-Gly-OEt·HCl[2] (V), cyclized at a rapid rate when base was added, to give IV. This reaction could also be adapted for the cleavage of Dca-amino acids esterified to a resin support. Thus, when

Table I. Reaction of [^{14}C]DCC with the Amino Component during a Solid-Phase Synthesis

Run	Amino component[a] (1 equiv)	Carboxyl component (4 equiv)	[^{14}C]DCC,[b] equiv	% reaction[c] Resin	Acid hydrol	DIEA filtrate
1	Boc-Val-R		4	0.2		
2	Val-R		4	0.2	0.1	0.1
3	Val-R	Boc-Gly	2	0.1	0.1	0.2
4	Val-R	Boc-Gly	4	0.1	0.1	0.2
5	Val-R	Boc-Gly	6	0.1		
6	Val-R	Boc-Ile	4	0.2	0.1	0.1
7	Gly-Val-R	Boc-Ala	4	0.3	0.1	
8	Ala-Gly-Val-R	Boc-Leu	4	0.2	0.1	

[a] These experiments were carried out on 200-mg samples of resin containing 0.076 mmol Val/g. [b] Specific activity 10.8 mCi/mol. [c] The reactions were for 2 h at room temperature. The percent reaction in each case is calculated from the radioactivity and is expressed as moles of DCC/100 mol Val.

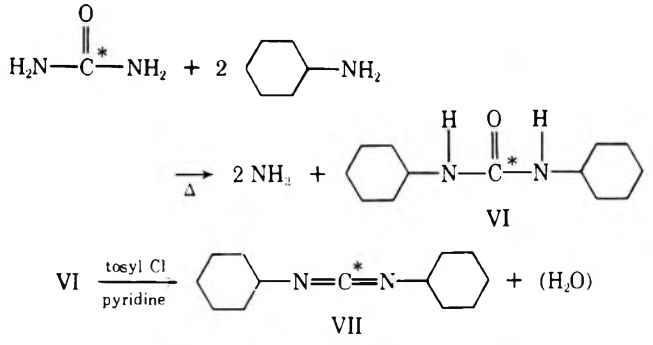


V

$\xrightarrow{OH^-}$ IV + C_2H_5OH

HCl·Dca-Gly-Res was suspended in CH_2Cl_2 and DIEA was added, IV was released into solution where it was readily identified by thin layer chromatography. When HCl·Val-Gly-Res (Val:Gly, 0.96:1) was treated for 18 h with 1 equiv of DCC in dichloromethane and then hydrolyzed, a Val:Gly ratio of 0.49:1 was found. This indicated that DCC also could react with peptide-resin hydrochlorides to a significant extent.

Experiments with Radioactive DCC. A sample of [1-^{14}C]DCC was prepared from [^{14}C]urea and cyclohexylamine according to the procedure of Amiard and Heymes:[15,16]



VI

VII

The purified distilled product had the correct chemical and physical properties and a specific activity of 10.8 mCi/mol.

The potential incorporation of [^{14}C]DCC into a resin-bound product was assessed by scintillation counting in three ways: (1) the resin was suspended in Aquasol and counted directly; (2) the resin was hydrolyzed and the filtrate was counted; (3) the resin was treated with diisopropylethylamine (DIEA) and the filtrate was counted. The latter was a useful diagnostic method for detecting the presence of the addition product between DCC and the α-amino group of an amino acid-resin because amidino amino acid esters are rapidly and selectively cyclized to give dihydroimidazolones.[8,11] The three methods gave essentially the same results, although at very low levels of reaction the variability was rather large.

Lack of Reaction of [1-^{14}C]DCC with Unprotonated Resin-Bound Amino Groups. It was first shown that [^{14}C]DCC could be satisfactorily removed from the resin beads by washing. Boc-Val-Res (200 mg) was shaken for 2 h in CH_2Cl_2 containing [^{14}C]DCC (2×10^6 cpm). After six washes with 4 mL of CH_2Cl_2 the recovery of radioactivity was essentially quantitative and the counts in subsequent washes had dropped to background levels. The washed Boc-Val-Res contained only 4 cpm/mg, equivalent to 0.2% of the valine (Table I). This value tends to set the lower level of sensitivity of the method.

The reaction of DCC with an amino acid resin was tested by treating Val-Res with 4 equiv of [^{14}C]DCC in CH_2Cl_2 for 2 h. The mixture was filtered and washed thoroughly and a weighed aliquot was counted. A second aliquot was hydrolyzed in 6 N HCl–dioxane for 24 h and the filtrate was counted. A third aliquot was treated with 10% DIEA in CH_2Cl_2 for 24 h and the filtrate was counted (Table I). The reaction of DCC with an amino acid resin under normal coupling conditions was then examined by mixing Val-Res with 4 equiv of Boc-Gly, followed in 5 min by 4 equiv of [^{14}C]DCC. After 2 h the resin was filtered, thoroughly washed, and examined for incorporation of counts. The data from this and related experiments are summarized in Table I.

The results showed no significant incorporation of ^{14}C above background and therefore less than 0.2% of the α-amino group of the amino acid resin could have reacted with DCC alone or under the normal conditions of a coupling reaction with a Boc-amino acid. These data lower the level of detectability of the potential side reaction by a factor of 10 below that which we could estimate previously by amino acid analyses, and they allow the conclusion that it probably is not a side reaction of practical importance.

The possibility that a hindered, and therefore much slower, coupling reaction might favor a competing reaction of the amine component with the DCC was tested by substituting Boc-Ile for Boc-Gly. We had shown previously that the rate of coupling of Boc-Ile to Val-Res was six times slower than the coupling of Boc-Gly to Val-Res.[17] The data of runs 4 and 6, Table I, showed no significant uptake of [^{14}C]DCC during either of these two coupling reactions. There was no difference in ^{14}C incorporation when the ratios of [^{14}C]DCC to Boc-Gly to Val-Res were 2:4:1, 4:4:1, or 6:4:1 and, furthermore, it was found that addition of triethylamine or pyridine did not change the extent of [^{14}C]DCC incorporation. It was also found that DCC did not react significantly with the amino component during normal coupling reactions between Boc-amino acids and resin-bound di- or tripeptides (runs 7 and 8).

Finally, a direct comparison was made between the extent of DCC incorporation and the picrate monitoring value during the synthesis of a heptapeptide. First the protected peptide, Boc-Pro-Ala-Ile-Arg(Tos)-Arg(Tos)-Leu-Res, corresponding to residues 32–37 of calf thymus histone H4, was synthesized. The picrate value was equal to 3.9% of the total peptide chains. The peptide was deprotected, neutralized, and coupled with 4 equiv each of Boc-Lys(2,4-Cl_2Z)[18] and [^{14}C]DCC. The re-

Table II. Reaction of [^{14}C]DCC with Protonated Valine Resin[a]

Run	Resin (1 equiv)	Amino acid (4 equiv)	Other, equiv	[^{14}C]DCC, equiv	Time, h	% reaction Resin	Hydrol	DIEA
1	HCl·Val-R			4	24	86	84	93
2	HCl·Val-R			4	2	23		
3	TFA·Val-R			4	2	19		
4	Val-R		0.1 TFA	4	2	3.6	3.3	3.3
5	Val-R		1.0 TFA + 1.0 DIEA	4	2	0.9	0.7	0.6
6	Val-R	Boc-Gly	0.1 TFA	4	2	0.1		
7	Val-R	Boc-Gly	1.0 TFA	4	2	0.1		

[a] These experiments were carried out on 200-mg samples of resin containing 0.076 mmol Val/g. See Table I.

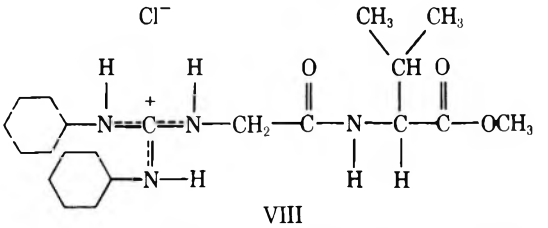
sulting protected heptapeptide, Boc-Lys(2,4-Cl_2Z)-Pro-Ala-Ile-Arg(Tos)-Arg(Tos)-Leu-Res, showed a picrate value of 6.8%, indicating an increase of 2.9% in the number of chains that could be titrated with picric acid. However, the ^{14}C counts corresponded to less than 0.1% of the peptide chains and could not account for the apparent rise in titratable groups that was indicated by the picrate method.[19]

Reaction of [1-^{14}C]DCC with Protonated Val-Res. Boc-Val-Res was deprotected with 50% TFA[2] in CH_2Cl_2, washed, treated with 4 equiv of [^{14}C]DCC for 2 h, washed thoroughly, and counted. In separate experiments the deprotected TFA·Val-Res was converted into the hydrochloride and then treated as before with [^{14}C]DCC for 2 h and for 24 h. The results of these runs are summarized in Table II. In 2 h both the trifluoroacetate and the hydrochloride of Val-Res reacted significantly with DCC (19 and 23%) and in 24 h an 86% yield was obtained from the hydrochloride. The product of the reaction was deduced to be *N,N'*-dicyclohexylamidinovaline-resin (Dca-Val-Res). All of the ^{14}C counts found on the resin beads were released into solution by acid hydrolysis. The hydrolysate contained 15% free valine, accounting for the fraction of Val-Res that had not reacted with DCC and supporting the expectation that the addition product does not give rise to the free amino acid upon acid hydrolysis.

The presence of only 0.1 equiv of TFA catalyzed the reaction of DCC with Val-Res to the extent of about 3% in 2 h (run 4) and the addition of 1 equiv of TFA plus 1 equiv of DIEA produced 0.6–0.9% reaction. In contrast, neither 0.1 nor 1.0 equiv of TFA was effective in catalyzing the reaction of DCC with Val-Res when excess Boc-Gly was present (runs 6 and 7). In these two runs the measured counts were not significantly above background. This is an important observation because it shows that a carryover, by failure to neutralize or by mechanical means, of even as much as 1 equiv of acid into the coupling reaction would not give rise to a termination reaction by DCC during a normal solid-phase synthesis.

Rate of Cyclization of [^{14}C]Dca-Val-Res·HCl by DIEA. Samples of [^{14}C]Dca-Val-Res·HCl were treated with 10% DIEA in CH_2Cl_2 for periods of 1 min to 5 h; 83% of the ^{14}C counts were released from the resin in 1 min by cyclization with the amine and the release was essentially quantitative within 1 h. The cyclization product was crystallized and characterized as 1-cyclohexyl-2-cyclohexylamino-4-isopropyl-4,5-dihydro-5-imidazolone. Since the cyclization reaction is very fast it was not possible to neutralize the HCl·Dca-Val-Res and study its susceptibility to coupling with Boc-amino acids or other acylating agents. However, those studies could be carried out on the corresponding amidino derivatives of di- and tripeptide resins.

[^{14}C]Dca-Gly-Val-Res and [^{14}C]Dca-Ala-Gly-Val-Res. Synthesis, Structure, and Properties. [^{14}C]Dca-Gly-Val-Res was synthesized by the reaction of [^{14}C]DCC with Gly-Val-Res·HCl. The structure of the product was deduced from the properties of the HF-cleavage products and by isolation and identification of the product of cleavage by amine-catalyzed transesterification: *N,N'*-dicyclohexylamidinoglycyl-valine methyl ester hydrochloride (VIII).



VIII

Picrate Titration. A sample of resin containing a mixture of HCl·Gly-Val-Res and HCl·Dca-Gly-Val-Res gave a picrate titration value[5] equal to the sum of the two basic groups, and similarly a sample containing HCl·Ala-Gly-Val-Res plus HCl·Dca-Ala-Gly-Val-Res gave a titration equal to the sum of the two components. These results showed that both the α-amino and α-guanidino groups will titrate.

Acylation. When a preparation of HCl·Dca-Gly-Val-Res was washed with DIEA and then treated with an excess of Boc-Ala and DCC the picrate value was equal to the amidine content. Following treatment with benzoyl chloride in pyridine the picrate value was unchanged. Similar results were obtained with HCl·Dca-Ala-Gly-Val-Res. It was concluded that amidinopeptide resins, after washing with DIEA, are resistant to acylation by DCC-activated Boc-amino acids or by benzoyl chloride, but that they take up 1 equiv of picric acid.

When a strong base such as Triton B[20] was used to deprotonate the amidinopeptide resins, acylation became possible with a DCC-activated Boc-amino acid or with a preformed symmetrical anhydride. Thus, HCl·Dca-Gly-Val-Res gave 63% of Ala-Dca-Gly-Val-Res.

Conclusions

Dicyclohexylcarbodiimide does not react to a measurable extent (<0.2%) with the amino group of resin-bound amino acids or peptides during solid-phase synthesis. Therefore this is not a significant side reaction and it cannot be responsible for the rises in picrate titration that have been observed. Dicyclohexylcarbodiimide will react with the hydrochloride or trifluoroacetate salts of resin-bound amino acids or peptides to give guanidines.

Experimental Section

[^{14}C]Urea, 55 mCi/mol, and dicyclohexylcarbodiimide were obtained from Schwarz/Mann; Boc-amino acids were from Beckman; chloromethylcopoly(styrene–1% divinylbenzene) 200–400 mesh resin beads were from Bio-Rad Laboratories. Quantitative amino acid analyses were performed on a Beckman Model 121 analyzer and ^{14}C was measured on a Beckman scintillation counter Model LS-355, using Aquasol scintillation fluid (New England Nuclear) and a 30–1000 channel. All samples were counted after standing for 24 h in the dark to allow phosphorescence to decay. Radioactivity on paper electropherograms was counted on a Packard radio chromatogram

scanner model 7201. Elemental analyses were by Mr. T. Bella. ^1H NMR spectra were obtained on a Varian 220-MHz instrument by Dr. Thomas Witherup and ^{13}C spectra were obtained on a Bruker 90-MHz instrument by Dr. William Wittbold.

Experiments with Nonradioactive DCC. Dca-Gly-OEt·HCl (V). Gly-OEt·HCl (1.4 g, 10 mmol) and 10 mL of a 1 M solution of unlabeled DCC in CH_2Cl_2 were combined and agitated in a sealed vessel at room temperature. After 20 h a clear solution had resulted and TLC on silica gel G (1-butanol–acetic acid–water, 4:1:1 v/v) indicated that HCl·Gly-OEt (R_f 0.24) had almost completely disappeared in favor of a single new spot (R_f 0.50) staining yellow with ninhydrin (10 min, 140 °C) or with the I_2/tolidine reaction. After evaporation of the solvent and treatment with ether the crude product was crystallized from 12 mL of acetone, filtered, and dried to give 2.8 g (81%) of Dca-Gly-OEt·HCl, mp 174–176 °C.

Anal. Calcd for $C_{17}H_{32}N_3O_2Cl$: C, 59.03; H, 9.33; N, 12.15. Found: C, 59.13; H, 9.21; N, 12.08.

Titration of an aqueous solution of V with NaOH to phenolphthalein gave an equivalent weight of 350 (calcd, 335). Hydrolysis (6 N HCl, 110 °C) did not release glycine from this compound. When the reaction of HCl·Gly-OEt and DCC described above was carried out with addition of 1 equiv of NEt_3, no clear solution resulted after 20 h. TLC showed that most of the starting material had remained unreacted and that three new products, one of them corresponding to V, had formed.

Conversion of V to 1-Cyclohexyl-2-cyclohexylamino-4,5-dihydro-5-imidazolone (IV). To 100 mg (0.3 mmol) of V in water, 0.1 N NaOH was added to pH ~8 (2.85 mL). The precipitate that formed instantaneously was collected, washed with water, and dried. This product was homogeneous by TLC (R_f 0.80) with $CHCl_3$–MeOH (9:1 v/v) staining yellow with the I_2/tolidine reaction, yield 64 mg (81%), after crystallization from EtOH–H_2O (1:1 v/v) mp 156–157 °C (lit.[8] 156 °C).

Anal. Calcd for $C_{15}H_{25}N_3O$: C, 68.40; H, 9.57; N, 15.96. Found: C, 68.38; H, 9.60; N, 16.03.

As judged by TLC, cyclization to give IV took place also when Dca-Gly-OEt·HCl was heated in water or 0.1 N HCl (100 °C, 14 h). Compound IV was stable under these condition and even 6 N HCl at 110 °C did not release glycine from it.

Reaction of DCC with HCl·Gly-Resin and Gly-Resin. Two 100-mg samples (A, B) of Boc-Gly-resin (770 μmol/g) were deprotected with 50% TFA, neutralized with 5% DIEA–CH_2Cl_2, and washed thoroughly with CH_2Cl_2. While A was converted to HCl·Gly-Res with a saturated solution of pyridine hydrochloride in CH_2Cl_2 and washed with CH_2Cl_2, B was left as the free base, Gly-Res. To each sample a 1 M solution of unlabeled DCC in CH_2Cl_2 (85 μL, 1.1 equiv) was added followed by enough CH_2Cl_2 to allow good mixing. The samples were agitated at room temperature and ~20-μL aliquots of the supernatants were taken periodically. As judged by TLC, nothing was released into solution in B, while in A small but increasing amounts of IV were detected. After 28 h, sample A contained 185 μmol/g Gly and B 736 μmol/g. Thus, under identical conditions, DCC had reacted with the hydrochloride to the extent of 76%, and with the free base to the extent of less than 5%.

Cleavage of Dca-Gly-Res Hydrochloride with DIEA and with HBr. A small sample of HCl·Dca-Gly-Res was treated with 5% DIEA in CH_2Cl_2 for 30 min and the supernatant was analyzed by TLC. Only one spot was detected, which cochromatographed with and stained like compound IV, R_f 0.65 with 1-butanol–acetic acid–pyridine–water, 15:10:3:2 (v/v). HCl·Dca-Gly-Res was also subjected to acidolytic cleavage conditions (30% HBr in AcOH, 30 min). In this case, two spots of about equal intensity were found in addition to Gly (R_f 0.21). One of these (R_f 0.65) was identical with IV, the other stained in the same way as IV (yellow with ninhydrin after heating to 140 °C, yellow with I_2/tolidine) but migrated slower (R_f 0.55).

Experiments with [^{14}C]DCC. Synthesis of [1-^{14}C]Dicyclohexylcarbodiimide (VII). [^{14}C]Urea (1 mCi, 55 mCi/mmol) was mixed with unlabeled urea (6.0 g, 0.10 mol), and cyclohexylamine (27.7 mL, 0.24 mol) was added. The suspension was heated to reflux (134 °C). The urea slowly dissolved and copious evolution of ammonia occurred. Refluxing was continued for a total of 2 h, while slowly increasing the temperature to 160 °C. The mixture, which solidified when removed from the bath to cool, was extracted with 1 N HCl, H_2O, ethanol, and ether. The solid residue of *N,N'*-dicyclohexylurea (VI) was recrystallized from 200 mL of absolute alcohol: yield 7.15 g (0.032 mol, 32%) (lit. 50%), total counts 7.52×10^8 cpm (36% radioactive yield); mp 229–230 °C uncorrected (lit.[15,16] 234–235 °C); mmp with authentic DCU 229–230 °C; NMR ($CDCl_3$) δ 1.09, 1.35, 1.64, 1.93 (m, ~20 H), 3.46 (m, 2 H, tertiary CH), 4.08 (d, 2 H, J = 8.2 Hz, NH).

[1-^{14}C]Dicyclohexylurea (VI, 7.3 g, 0.032 mol), 13 mL of dry pyridine, and 5.9 g (0.032 mol) of *p*-toluenesulfonyl chloride were stirred and heated at 70–75 °C for 4 h. After cooling, the product was dissolved in 20 mL of petroleum ether and the pyridine salts were filtered off and washed with petroleum ether. Diethylamine (1.2 mL) was added to the combined extracts and the mixture was heated to reflux. The solvent was removed on a rotary evaporator and the [^{14}C]DCC was distilled. The fraction distilling at a constant temperature of 134 °C (0.5 mm) [lit.[15,16] 140 °C (5 mm)] weighed 1.42 g (22%); total counts 1.49×10^8 cpm (21% radioactive yield from urea); specific activity 10.8 mCi/mol.

Anal. Calcd for $C_{13}H_{22}N_2$: C, 75.67; H, 10.75; N, 13.58. Found: C, 75.54; H, 10.70; N, 13.50.

1-Cyclohexyl-2-cyclohexylamino-4-isopropyl-4,5-dihydro-5-imidazolone. DCC (2.31 g, 11.2 mmol) in 50 mL of CH_2Cl_2 was added to HCl·Val-Res (10 g, 2.8 mmol Val) and the mixture was shaken for 24 h at 25 °C. After filtering and washing, 100 mL of 10% DIEA in CH_2Cl_2 was added with shaking for 1 h. The filtrate and washes were collected, evaporated to 10 mL, and cooled. The resulting solid was dissolved in methanol and crystallized by the addition of water; yield 230 mg. The product was recrystallized in the form of short needles from methanol–water, mp 50–51 °C (sinters), which analyzed as the monohydrate.

Anal. Calcd for $C_{18}H_{31}N_3O·H_2O$: C, 66.83; H, 10.28; N, 12.99. Found: C, 66.82; H, 10.16; N, 12.95.

Amino acid analysis of a 6 N HCl hydrolysate showed no valine (<0.5 mol %).

Synthesis of [^{14}C]Dca-Gly-Val-Res. HCl·Gly-Val-Res (0.98 g, 0.074 mmol/g) was treated with 4 equiv of [^{14}C]DCC (61 mg, 2.17×10^7 cpm/mmol) for 24 h. After filtering and washing six times with CH_2Cl_2 the peptide resin contained 1430 cpm/mg (corrected for a blank of 4.7 cpm/mg), and an acid hydrolysate contained 1403 cpm/mg, giving an average of 0.062 mmol of incorporated DCC/g. An amino acid analysis of the hydrolysate showed Val, 0.074 mmol/g; Gly, 0.012 mmol/g.

Acylation of Amidino Peptide Resins. A. A sample of resin containing, by amino acid analysis, 0.012 mmol/g of HCl·Gly-Val-Res and 0.064 mmol/g of HCl·Dca-Gly-Val-Res and giving a picrate titration value of 0.076 mmol/g was washed with DIEA and treated with 4 equiv each of Boc-Ala and DCC. The picrate value was now 0.065 mmol/g, and Ala was 0.02 mmol/g.

B. A resin containing 0.034 mmol/g of HCl·Ala-Gly-Val-Res and 0.033 mmol/g of HCl·Dca-Ala-Gly-Val-Res (picrate value, 0.072 mmol/g) was washed with DIEA and treated with Boc-Leu and DCC. The picrate titration of the product was 0.043 mmol/g. Leu-Ala-Gly-Val (0.030 mmol/g) was identified chromatographically[21] following cleavage from the resin with HF, and 0.031 mmol/g of Leu was found in an acid hydrolysate of the peptide resin.

C. A sample containing 0.139 mmol/g of HCl·Dca-Gly-Val-Res and 0.034 mmol/g of HCl·Gly-Val-Res was mixed with 4 equiv of Triton B in CH_2Cl_2, and then treated for 2 h with the symmetrical anhydride made from 4 equiv of Boc-Ala and 2 equiv of DCC. An acid hydrolysate of the product gave 0.174 mmol/g Val, 0.035 mmol/g Gly, and 0.123 mmol/g Ala, indicating the presence of 0.035 mmol/g Ala-Gly-Val-Res, 0.051 mmol/g Dca-Gly-Val-Res, and 0.088 mmol/g Ala-Dca-Gly-Val-Res.

Cleavage of [^{14}C]Dca-Gly-Val-Res with HF. A 900-mg sample of HCl·Dca-Gly-Val-Res was stirred in 10 mL of HF containing 1 mL of anisole. After 1 h at 0 °C only 7% of the ^{14}C counts were released, but after 2 h at 25 °C 93% of the counts were removed from the resin. After evaporation of the HF, the crude product was extracted into TFA, evaporated, lyophilized from H_2O, and dissolved in 1 mL of water. The mixture was fractionated on a 1 × 10 cm column of Aminex 50W-X4 in pyridine–0.2 M acetate, pH 3.2. Two radioactive components were obtained with peaks at 65 and 71 mL. Analytical paper electrophoresis in formic acid–acetic acid–H_2O (15:10:75), pH 1.5, 1000 V, 3 h, showed radioactive spots at R_{Val} 0.69 and 0.62, respectively. At pH 5.0 and 8.5 both compounds remained at the origin. Their acid hydrolysates contained 2.42 and 2.54 μmol Val/mg and no Gly. The ratios of ^{14}C/Val were 1.05 and 1.03, respectively. These data and the ^1H NMR data were consistent with the assignment of isomeric forms of Dca-Gly-Val to the two products.

[^{14}C]Dca-Gly-Val-OMe·HCl (VIII). HCl·Gly-Val-Res (5.00 g, 0.19 mmol/g) was stirred for 48 h in 50 mL of CH_2Cl_2 containing 4 equiv of [^{14}C]DCC (900 mg, 2.17×10^6 cpm/mmol), filtered, washed, and dried. The product contained 530 cpm/mg (0.24 mmol/g) of incorporated DCC. Amino acid analysis of an acid hydrolysate showed Val, 0.196 mmol/g, and Gly, 0.010 mmol/g, indicating that 95% of the Gly had been guanidinated. The HCl·Dca-Gly-Val-Res (2.0 g) was transesterified by shaking with 60 mL of 1 M diisopropylethylamine

in methanol for 24 h. The filtrate and washes were evaporated to dryness: yield 77 mg, 36% by weight; 127 μmol Val, 7.7 μmol Gly (yield 32%). Total ^{14}C counts recovered in the filtrate indicated a yield of 36%. The solid was recrystallized from ether–petroleum ether. Paper electrophoresis at pH 1.5 gave a single radioactive spot at R_{Val} 0.48 (standards of Gly-Val, Asp, and cyclic Dca-Val appeared at 0.86, 0.74, and 0.66, respectively); ^1H NMR (Varian HF, 220 MHz, Me_2SO-d_6) δ 0.91 (m, 6 H), 1.3–1.4 (broad m, cyclohexyl axial), 1.6–1.8 (broad m, cyclohexyl equatorial), 2.06 (m, 1 H, Val β-CH), 3.1 (m, tertiary CH), 4.1–4.2 (m, 3 H, α-CH), 3.8 (s, 3 H, OCH_3), 7.32 (d, 2 H, J = 8 Hz, cyclohexyl NH), 7.68 (t, 1 H, J = 7 Hz, Gly NH), 8.64 (d, 1 H, J = 8 Hz, Val NH); ^{13}C NMR (Bruker HX-90, 22.6 MHz, proton decoupled, Me_2SO) (Me_4Si δ 0) δ 19.1, 19.8 (Val, C_γ), 25.5, 33.2, 51.6 (cyclohexyl), 31.0 (Val C_β), 44.8 (Gly C_α), 54.4 (OCH_3), 58.7 (Val C_α), 155 (Guan), 167.8 (Gly C=O), 169.7 (Val C=O). ^{13}C assignments were based on the standards, cyclohexylamine, Gly-Val, and Arg·HCl.

Acknowledgment. We wish to thank Mr. Arun Dhundale for his assistance during the preliminary phase of this work.

Registry No.—IV, 5874-68-0; V, 61364-31-6; VI, 61348-54-7; VII, 57944-26-0; VIII, 61364-32-7; DCC, 538-75-0; Gly-OEt HCl, 623-33-6; Gly HCl, 6000-43-7; Gly, 56-40-6; Boc-Gly, 4530-20-5; Dca-Gly HCl, 61348-85-8; DIEA, 7087-68-5; [^{14}C]urea, 594-05-8; cyclohexylamine, 108-91-8; 1-cyclohexyl-2-cyclohexylamino-4-isopropyl-4,5-dihydro-5-imidazolone, 61348-56-9; Val HCl, 17498-50-9; [^{14}C]Dca-Gly-Val, 61348-57-0; Gly-Val HCl, 61348-59-2; Dca-Gly-Val HCl, 61348-60-5; Boc-Ala, 15761-38-3; Ala-Gly-Val HCl, 61348-58-1; Boc-Leu, 13139-15-6; Boc-Ile, 13139-16-7; Boc-Val, 13734-41-3; Boc-Gly-Val, 28334-73-8; Boc-Ile-Val, 61348-61-6; Boc-Ala-Gly-Val, 56133-97-2; Boc-Leu-Ala-Gly-Val, 61165-83-1.

References and Notes

(1) Reported in part at the 170th National Meeting of the American Chemical Society, Chicago, Ill., Aug 1975; the work was supported by Grants AM 01260 and HL 12157 from the U.S. Public Health Service and by a grant from the Hoffmann-La Roche Foundation.
(2) Abbreviations: [^{14}C]DCC, [1-^{14}C]dicyclohexylcarbodiimide; Boc, *tert*-butyloxycarbonyl; Lys(2,4-Cl_2Z), N^{ϵ}-2,4-dichlorobenzyloxycarbonyllysine; Tos, *p*-toluenesulfonyl; DIEA, diisopropylethylamine; Res, 200–400 mesh resin beads of a 1% cross-linked copolymer of styrene and divinylbenzene; Dca, *N,N'*-dicyclohexylamidino; TFA, trifluoroacetic acid; TLC, thin layer chromatography. Other nomenclature and symbols follow the Tentative Rules of the IUPAC–IUB Commission on Biochemical Nomenclature, *J. Biol. Chem.*, **241**, 2491 (1966); **242**, 555 (1967); **247**, 977 (1972).
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Cytotoxic C-Benzylated Flavonoids from *Uvaria chamae*[1]

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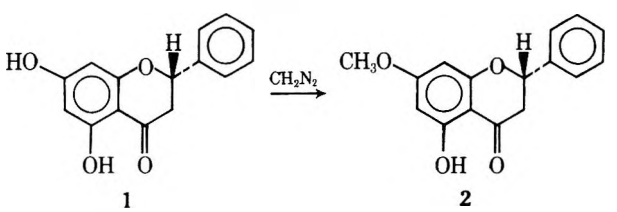
Received September 13, 1976

Ethanolic extracts of *Uvaria chamae* have demonstrated activity in vivo against P-388 lymphocytic leukemia in the mouse and in vitro against cells derived from human carcinoma of the nasopharynx (KB). Fractionation of these extracts yielded the known flavanones pinocembrin (**1**) and pinostrobin (**2**), the C-benzylated flavanones chamanetin (**3**), isochamanetin (**4**), and dichamanetin (**5**), and the C-benzylated dihydrochalcones uvaretin (**6**), isouvaretin (**7**), and diuvaretin (**8**). The structures were established by spectroscopic methods, chemical synthesis, and degradations.

In a previous communication[2] the isolation and structure elucidation of the cytotoxic C-benzylated flavanones chamanetin[3] (**3**) and isochamanetin (**4**) from the stem bark of *Uvaria chamae* were reported. We now wish to describe the total structure determination of these compounds. In addition, we wish to describe the isolation and structure elucidation of the known flavanone pinocembrin (**1**) and the dibenzylated flavanone dichamanetin (**5**) isolated from stem bark extracts as well as the known flavanone pinostrobin (**2**) and C-benzylated dihydrochalcones uvaretin (**6**), isouvaretin (**7**), and diuvaretin (**8**), which were isolated from root bark extracts.

Cytotoxicity[5] residing in ethanolic extracts of the stem bark was concentrated in the ethyl acetate fraction of an ethyl acetate–water partition. Silicic acid chromatography of this fraction starting with initial eluent benzene followed by ether–benzene mixtures resulted in the isolation of four flavanones (**1**, **3**, **4**, and **5**).

Scheme I



1 **2**

Compound **1** demonstrated UV, IR, and ^1H NMR[6] data consistent with a 5,7-dihydroxylated flavanone lacking B-ring[7] substituents. Comparison of the isolated product with an authentic sample of pinocembrin verified structure **1**.

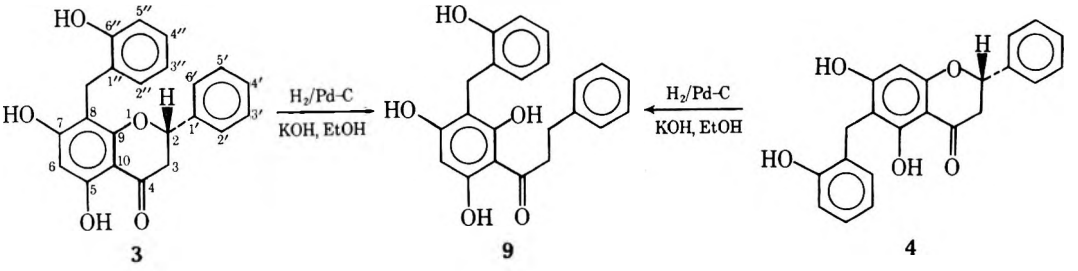
Based on spectroscopic evidence (^1H NMR data in Table I) chamanetin (**3**) and isochamanetin (**4**) were designated as isomeric *o*-hydroxybenzyl derivatives of pinocembrin.[2] Support for these assignments followed from their formation of

Table I. ^{1}H NMR Spectra of Flavanones[a]

Registry no.	Compd	H-2[b]	H-3[c]	C_5-OH	H-6	H-8	Misc
480-39-7	1	5.53, dd (3.5, 9.8)	2.67–3.60, m (14.2)	14.00	5.98	5.98	7.30–7.80,[d] m
480-37-5	2	5.50, dd (3.9, 10.2)	2.70–3.50, m (14.6)	13.90	6.13	6.13	7.50[d] 3.87[e]
	3	5.60, dd (4.5, 10.7)	2.50–3.50, m (16.5)	12.60	6.10		6.50–7.33,[d] m 3.91[f]
	4	5.68, dd (3.5, 9.8)	2.67–3.60, m (14.2)	13.53		6.26	6.67–7.50,[d] m 4.00[f]
58779-09-2	5	5.65, dd (3.9, 9.2)	2.60–3.60, m (13.7)	13.13			6.50–7.80,[d] m 3.97[f]

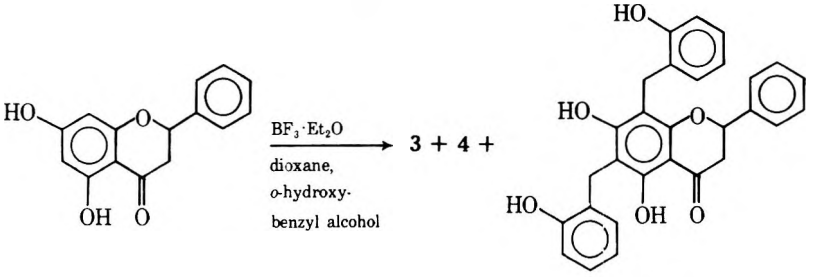
[a] Values are in parts per million in acetone-d_6 solution. Multiplicities are indicated by the usual symbols: dd, double doublet; m, multiplet. Unmarked signals are singlets. Figures in parentheses are coupling constants in hertz. [b] Center of the X portion of an ABX system; parentheses include J_{AX} and J_{BX}, respectively. [c] AB portion of an ABX system, J_{AB} is in parentheses. [d] The aromatic signals in this category represent (1) the four B-ring aromatic protons for **1** and **2**, (2) the nine B-ring and o-hydroxybenzyl aromatic protons for **3** and **4**, and (3) the 13 B-ring and o-hydroxybenzyl aromatic protons for **5**. [e] C_7–OCH_3. [f] $ArCH_2Ar$ (two protons in **3** and **4**; four protons in **5**).

Scheme II



3 9 4

Scheme III



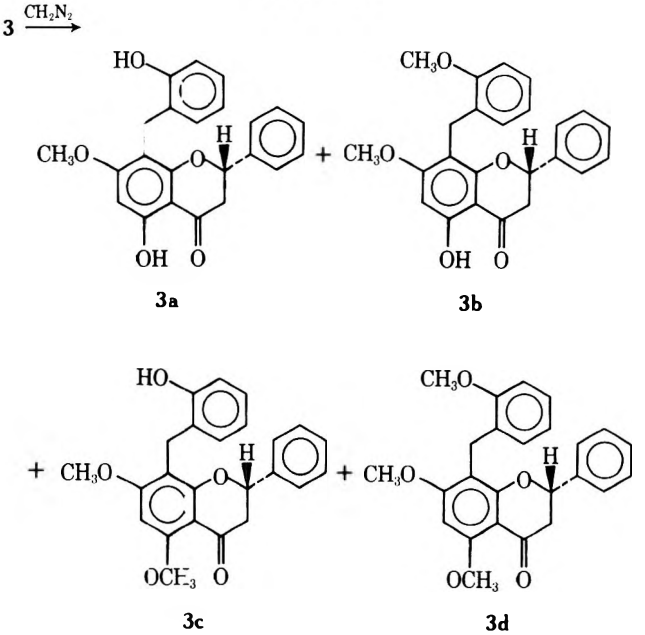
1 5

the same dihydrochalcone (**9**) upon catalytic hydrogenation (Scheme II) and their synthesis from pinocembrin and o-hydroxybenzyl alcohol using boron trifluoride etherate in dioxane (Scheme III). The dibenzylated product from this reaction was found to correspond to dichamanetin (**5**), a C-dibenzylated flavanone also isolated from stem bark extracts. The absolute stereochemistry in **3**, **4**, and **5** follows from CD data which allows assignment of the 2*S* configuration.[2,8]

Treatment of chamanetin (**3**) with ethereal diazomethane (Scheme IV) yielded four products: a monomethyl ether **3a**, two dimethyl ethers **3b** and **3c**, and a trimethyl ether **3d**. Treatment of isochamanetin (**4**) with ethereal diazomethane (Scheme V) yielded the dimethyl ethers **4a** and **4b**[9] and the trimethyl ether **4c**. Table II lists the spectroscopic data supporting the indicated methoxyl assignments in the methyl ethers of **3** and **4**.

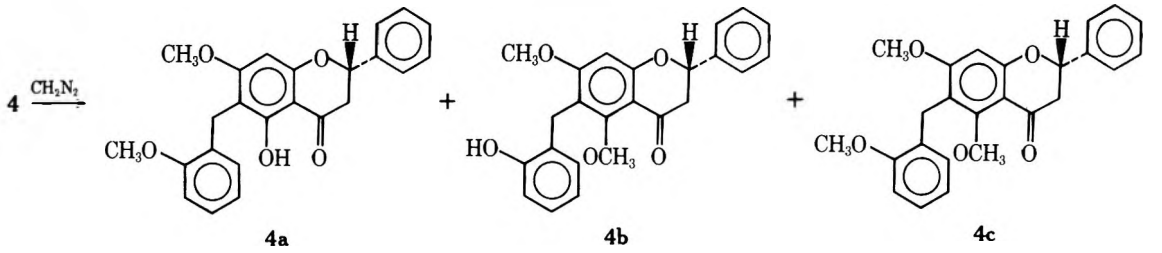
The synthesis of chamanetin and isochamanetin established them as isomeric C-benzylated flavanones. However, placement of the o-hydroxybenzyl substituent at the C-8 and C-6 positions of **3** and **4**, respectively, depended upon the interrelation of certain methyl ethers of chamanetin and isochamanetin with methyl ether derivatives of the dihydrochalcones uvaretin (**6**) and isouvaretin (**7**) which were isolated from root bark extracts.

Scheme IV



3a 3b 3c 3d

Scheme V



Scheme VI

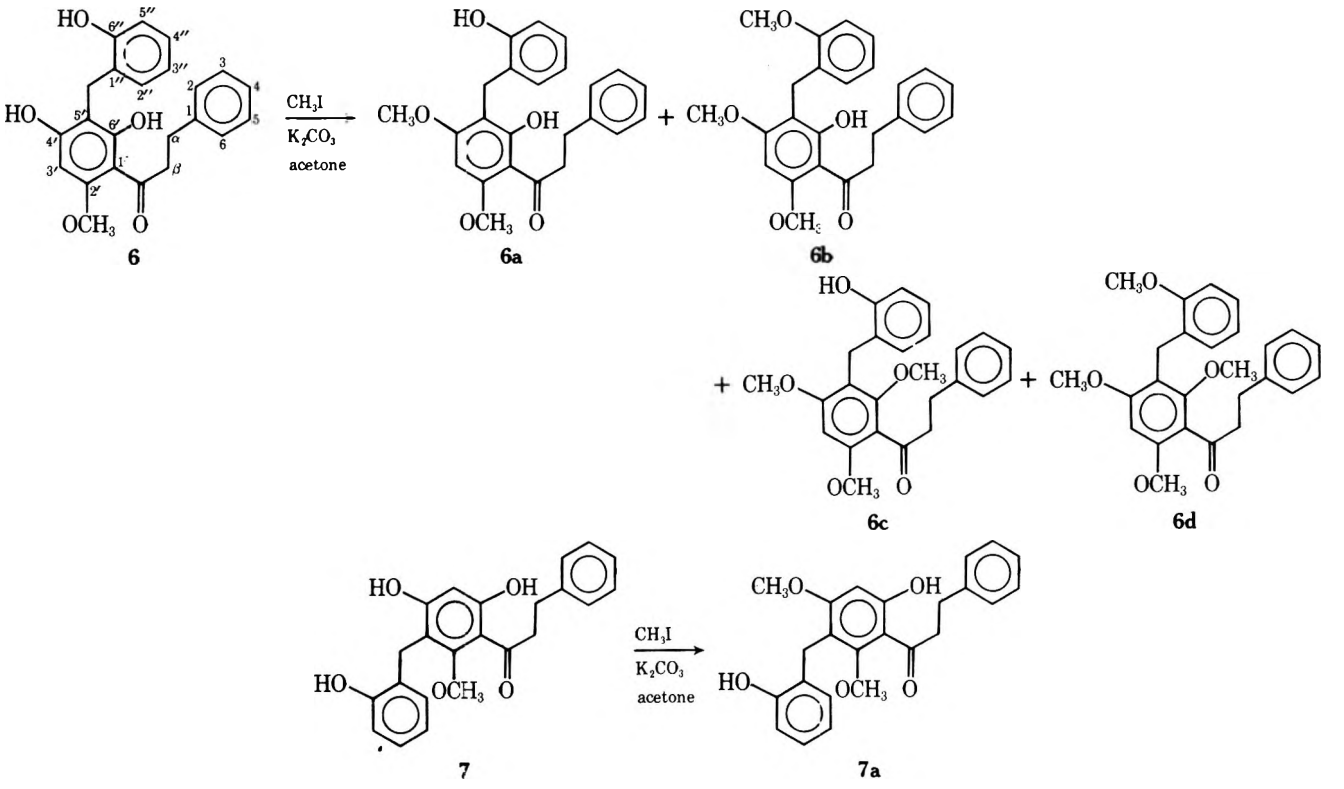


Table II. Spectral Data for 3, 4, and Their Methyl Ethers

Registry no.	Compd	^{1}H NMR[a] C_5-OH	UV NaOAc shift[b]	IR carbonyl band,[c] cm^{-1}
61462-95-1	**3**	12.60	+36	1630
61462-96-2	**3a**	13.50	*d*	1630
61462-97-3	**3b**	12.70	*d*	1640
61462-98-4	**3c**		*d*	1662
61462-99-5	**3d**		*d*	1680
61477-75-6	**4**	13.33	+28	1630
61463-00-1	**4a**	12.53	*d*	1640
61463-01-2	**4b**		*d*	1678
61463-02-3	**4c**		*d*	1670

[a] All signals are singlets. The presence of a low-field, exchangeable signal indicates the presence of a hydroxyl group at C-5 which is hydrogen bonded to the carbonyl function.[6] [b] Shift values refer to the 290-nm band (band II) in the UV spectrum. A shift of ~30 nm indicates a C-7 hydroxyl group.[6] [c] Carbonyl bands of unusually low value (<1640) are a result of hydrogen bonding with the C-5 hydroxyl. [d] No appreciable shift.

Silicic acid chromatography of the ethyl acetate fraction of the root bark yielded four flavonoids (**2**, **6**, **7**, and **8**). Compound **2** demonstrated spectral characteristics indicative of pinostrobin (**2**). Treatment of (−)-pinocembrin with ethereal diazomethane (Scheme I) gave a product identical with **2**.

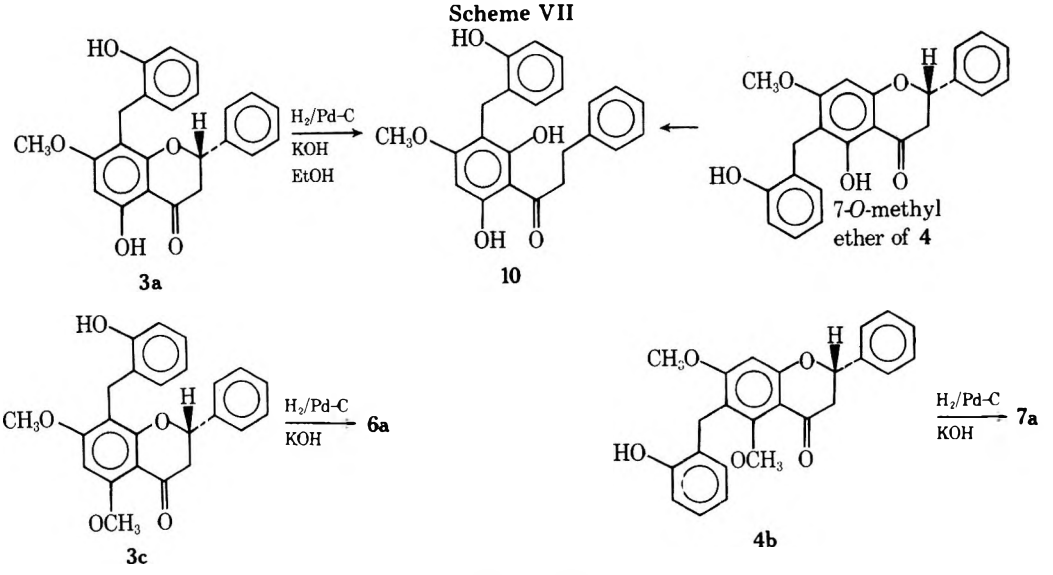
The spectral data for uvaretin (**6**) and isouvaretin (**7**) indicated them to be monomethoxylated dihydrochalcones (see ^{1}H NMR data in Table III). Uvaretin (**6**) yielded four products upon treatment with methyl iodide and potassium carbonate in acetone (Scheme VI): a monomethyl ether **6a**, two dimethyl ethers **6b** and **6c**, and a trimethyl ether **6d**.[10] Isouvaretin (**7**) formed a monomethyl ether,[11] **7a**, upon treatment with methyl iodide and potassium carbonate in acetone (Scheme VI). Recently, uvaretin has been reported from *Uvaria acuminata* and its structure has been established by x-ray crystallography.[4] Knowledge of the structure of uvaretin taken in conjunction with the following conversions (Scheme VII) allows deduction of the structures of chamanetin (**3**) and isochamanetin (**4**).

Hydrogenation of **3a** gave a product, **10**, not identical with **6** or **7**. However, similar treatment of **3c**[12] yielded the monomethyl ether of **6**, **6a**. Thus, the hydroxybenzyl substituent in **3** and **3c** must be placed at C-8. The fact that **3** and **4** have been shown to be isomeric places the hydroxybenzyl substituent of isochamanetin (**4**) at C-6.

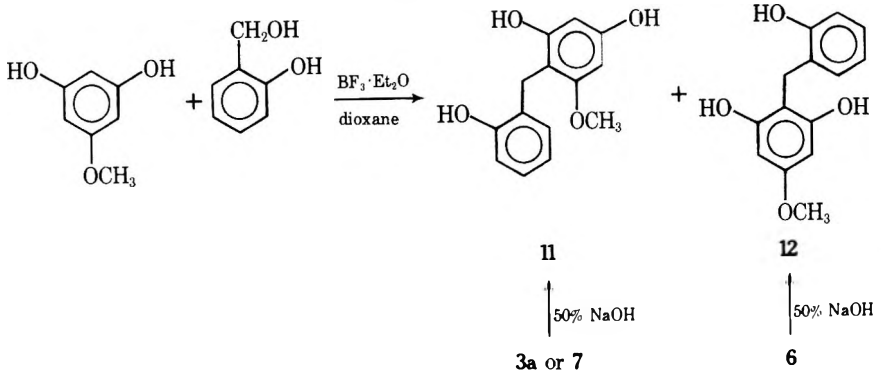
Spectroscopic evidence indicates that isouvaretin (**7**) is isomeric with **6**. Scheme VII shows that hydrogenation of **4b** gives **7a**.[13] Therefore, the same relationship that existed between **3c**, **6a**, and **6** exists between **4b**, **7a**, and **7**, thus placing the *o*-hydroxybenzyl substituent in **7** ortho to the methoxyl group. The following sequence of conversions was carried out to provide further evidence for the structure of isouvaretin (**7**).

The monomethyl ether of phloroglucinol was treated with

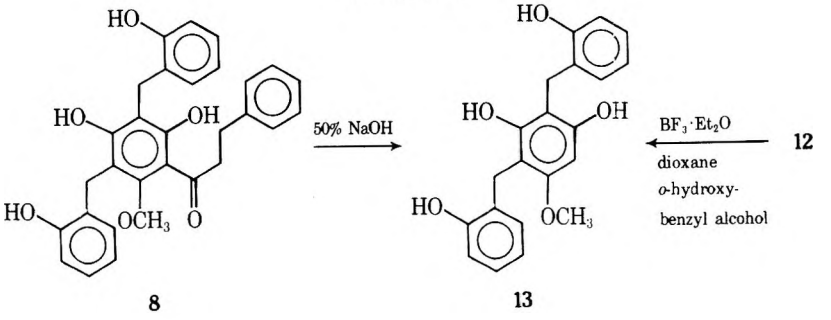
Scheme VII



Scheme VIII



Scheme IX



o-hydroxybenzyl alcohol and boron trifluoride etherate to yield two monomethoxylated, monobenzylated products **11** and **12**. Degradation of **3a** (Scheme VIII) with sodium hydroxide yielded a product identical with **11**. Thus, of the two isomeric monobenzylated products formed from the monomethyl ether of phloroglucinol, **11** is the isomer containing its benzyl group ortho to the methoxy group and **12** is the isomer with its benzyl group para to the methoxy function. As expected, similar treatment of **6** yielded **12**. Furthermore, degradation of **7** gave **11**, thus confirming structure **7** for isouvaretin.

One of the fragments of this degradative procedure, **12**, was then used to elucidate the structure of the third dihydrochalcone from the root bark, diuvaretin (**8**). The molecular formula and spectral properties (see Table III) of diuvaretin indicated it to be a 3′,5′-dibenzylated dihydrochalcone. Degradation of **8** with sodium hydroxide gave **13** which was found identical with the dibenzylated product formed from the treatment of **12** with *o*-hydroxybenzyl alcohol and boron trifluoride etherate (Scheme IX). This degradation along with spectroscopic evidence allows diuvaretin to be assigned structure **8**.

Experimental Section[14]

Isolation of Pinocembrin (1), Chamanetin (3), Isochamanetin (4), and Dichamanetin (5). The plant material used in this study was obtained and identified in Ghana by Dr. Oscar B. Dokosi, Department of Botany, University of Ghana, and Dr. Maynard W. Quimby, Department of Pharmacognosy, University of Mississippi. A voucher specimen has been deposited in the Herbarium of the Department of Pharmacognosy, School of Pharmacy, University of Mississippi.

The dried, ground stem bark (2.4 kg) was exhaustively extracted by percolation with 95% ethanol. After solvent evaporation 560 g of residue was obtained; 300 g of this residue was partitioned between 1.5 L of H_2O and 3 × 1.5 L of ethyl acetate. Evaporation of the combined ethyl acetate layers yielded 65 g of material which was adsorbed onto 50 g of Celite 545 and applied to a column containing 1 kg of silicic acid in benzene. Column fractions were monitored and combined by TLC.

Initial elution with 4 L of benzene resulted in a fraction containing 17.6 g of volatile oils. Further elution with 1.5 L of 0.1% ether in ben-

Table III. ^{1}H NMR Spectra of Dihydrochalcones[a]

Registry no.	Compd	H-α, H-β[b]	$C_{2'}$-OCH_3	$C_{6'}$-OH	H-3′	H-5′	Misc
58449-06-2	6	2.83–3.56, m	3.91	15.20	6.30		6.60–7.50[c] 3.96[d]
61463-03-4	7	2.80–3.80, m	3.77	13.13		6.25	6.50–7.50[c] 4.03[d]
61463-04-5	8	2.70–3.60, m	3.65	14.00			6.50–7.50[c] 3.93[d]

[a] Spectra for **6** and **7**, were taken in acetone-d_6 while the spectrum for **8** was taken in $CDCl_3$. Unmarked signals are singlets (m = multiplet). [b] H-α and H-β form an A_2B_2 pattern. [c] These represent aromatic protons for the B-ring and o-hydroxybenzyl groups. [d] Singlets here represent $ArCH_2Ar$ grouping.

zene, 3 L of 0.5% ether in benzene, and 2 L of 1% ether in benzene yielded a number of semicrystalline fractions.

Dichamanetin (5). Continued elution with 5 L of 1% ether in benzene yielded a 4.07-g fraction from which 1.60 g of **5** was obtained by crystallization from ethanol: mp 118–120 °C; UV λ_{max} (MeOH) 329 nm (ϵ 1.05 × 10^4) and 273 (2.10 × 10^3); CD $[\theta]_{362}$ +3640, $[\theta]_{335}$ −3120, $[\theta]_{283}$ −10 400, $[\theta]_{244}$ −5200; $[\alpha]^{25}D$ −9.75° (c 1.20, acetone); IR (KBr) bands at 3060, 1620, and 1600 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 468 (M$^+$, 82), 467 (M$^+$ − 1, 3), 364 (M$^+$ − 104, 22), 363 (M$^+$ − 105, 100), and 362 (M$^+$ − 106, 19).

Anal. Calcd for $C_{29}H_{24}O_6 \cdot C_2H_5O$: C, 72.33; H, 5.84. Found: C, 72.39; H, 5.89.

Isochamanetin (4). Elution with 4 L of 2% ether in benzene afforded a 5.03-g fraction from which 850 mg of **4** was obtained from benzene: mp 215–217 °C; uv λ_{max} (MeOH) 324 nm (ϵ 1.25 × 10^4), 296 (sh, 9.00 × 10^3), 218 (sh, 7.06 × 10^3), and 251 (4.04 × 10^3); CD $[\theta]_{328}$ +3800, $[\theta]_{289}$ −24 500, $[\theta]_{251}$ −24 100, $[\theta]_{219}$ +29 600; $[\alpha]^{25}D$ −10.5° (c 1.00, acetone); IR (KBr) bands at 3030, 1630, and 1605 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 362 (M$^+$, 100), 361 (M$^+$ − 1, 10), 344 (M$^+$ − 18, 2), 285 (M$^+$ − 77, 13), 258 (M$^+$ − 104, 22), and 256 (M$^+$ − 106).

Anal. Calcd for $C_{22}H_{18}O_5$: C, 72.93; H, 4.97. Found: C, 72.99; H, 5.02.

Pinocembrin (1). Further elution (3 L) with 4% ether–benzene resulted in a fraction from which 240 mg of **1** was crystallized from benzene: mp 194–195 °C; UV λ_{max} (MeOH) 320 nm (sh, ϵ 7.46 × 10^3) and 287 (1.55 × 10^4); CD $[\theta]_{325}$ +9420, $[\theta]_{315sh}$ +7300, $[\theta]_{284}$ −41 300, $[\theta]_{215}$ +27 400; $[\alpha]^{25}D$ −37.8° (c 0.90, MeOH); IR (KBr) bands at 3020, 1630, and 1600 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 256 (M$^+$, 100), 255 (M$^+$ − 1, 48), 179 (M$^+$ − 77, 84), 152 (M$^+$ − 104, 87), and 150 (M$^+$ − 106, 34). This compound was compared with and found identical with an authentic sample of pinocembrin[15] (melting point, mixture melting point, TLC, co-TLC, IR, and ^{1}H NMR).

Chamanetin (3). Elution with 2 L of 8% ether–benzene yielded a 2.47-g fraction from which 900 mg of **3** was obtained from benzene: mp 210–211 °C; UV λ_{max} (MeOH) 324 nm (ϵ 2.40 × 10^4) and 289 (1.05 × 10^4); CD $[\theta]_{355}$ +2260, $[\theta]_{314}$ +5080, $[\theta]_{288}$ −40 000, $[\theta]_{242}$ +3620, $[\theta]_{219}$ +34 600; $[\theta]^{25}D$ −52.5° (c 1.20, MeOH); IR (KBr) bands at 3090, 1630, and 1588 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 362 (M$^+$, 100), 361 (M$^+$ − 1, 11), 285 (M$^+$ − 77, 16), 258 (M$^+$ − 104, 37), and 256 (M$^+$ − 106, 51).

Anal. Calcd for $C_{22}H_{18}O_5$: C, 72.93; H, 4.97. Found: C, 72.96; H, 5.02.

Isolation of Pinostrobin (2), Uvaretin (6), Isouvaretin (7), and Diuvaretin (8). The dried, ground root bark (2.4 kg) was extracted by percolation with 95% ethanol. After solvent evaporation 685 g of residue was obtained; 300 g of this residue was partitioned between 1.5 L of H_2O and 3 × 1.5 L of ethyl acetate. The combined ethyl acetate fraction was evaporated to afford 110 g of residue which was adsorbed onto 100 g of Celite 545 and chromatographed on a column containing 2 kg of silicic acid in benzene. Elution with 4 L of benzene yielded a 6.0-g fraction of volatile oils.

Pinostrobin (2). Elution with an additional 1 L of benzene yielded a 132-mg fraction from which was isolated 20 mg of **2**: mp 109–110 °C (ethanol); UV λ_{max} (MeOH) 284 nm (ϵ 1.46 × 10^4); CD $[\theta]_{328}$ +820, $[\theta]_{285}$ −3880, $[\theta]_{227}$ +5180; IR (KBr) bands at 3210, 1640, and 1580 cm^{-1}. Compound **2** was compared with and found identical with the methylation product of **1**[16,17] (melting point, mixture melting point, TLC, co-TLC, IR and ^{1}H NMR).

Diuvaretin (8). Elution with an additional 3 L of benzene afforded a 12.0-g residue containing **8** as a gum which could not be induced to crystallize. Repeated chromatography over silica gel (with benzene) produced a gummy residue (9.6 g) which was pure by TLC, ^{1}H NMR, and MS: UV λ_{max} (MeOH) 331 nm (ϵ 9.40 × 10^3) and 277 (9.70 × 10^3); IR ($CHCl_3$) bands at 3600, 3310, 1620, and 1585 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 484 (M$^+$, 52), 452 (M$^+$ − 32, 6), 379 (M$^+$ − 105, 57), and 378 (M$^+$ − 106, 100).

Anal. Calcd for $C_{30}H_{28}O_6$: mol wt. 484.1886. Found: mol wt, 484.1877 (MS).

Isouvaretin (7). Elution with 4 L of 1% ether–benzene yielded 635 mg of a gummy fraction containing **7**. Repeated chromatography over silica gel (with 1% ether–benzene) yielded an oily residue which was pure by TLC, ^{1}H NMR, and MS: UV λ_{max} (MeOH) 326 nm (ϵ 8.09 × 10^3) and 278 (1.00 × 10^4); IR ($CHCl_3$) bands at 3595, 3400, 1645, and 1605 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 378 (M$^+$, 63), 347 (M$^+$ − 31, 9), 274 (M$^+$ − 104, 17), 273 (M$^+$ − 105, 100), 272 (M$^+$ − 106, 15), and 246 (M$^+$ − 132, 22).

Anal. Calcd for $C_{23}H_{22}O_5$: mol wt, 378.1467. Found: mol wt, 378.1442 (MS).

Uvaretin (6). Following elution with 3 L of 2% ether–benzene and 3 L of 4% ether–benzene a 2.65-g fraction was obtained which afforded 1.60 g of **6** from benzene: mp 164–165 °C; UV λ_{max} (MeOH) 323 nm (ϵ 1.3 × 10^4) and 295 (1.52 × 10^4); IR ($CHCl_3$) bands at 3590, 3490, 1621, and 1610 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 378 (M$^+$, 100), 274 (M$^+$ − 104, 23), 273 (M$^+$ − 105, 100), 272 (M$^+$ − 106, 29), and 246 (M$^+$ − 132, 38).

Anal. Calcd for $C_{23}H_{22}O_5$: C, 73.01; H, 5.82. Found: C, 72.85; H, 5.96.

Methylation of Pinocembrin to Give 2. A solution of 30 mg of **1** was treated with excess ethereal diazomethane for 3 h at room temperature. After evaporation the resulting crude residue was taken up in benzene and chromatographed over 20 g of silica gel in benzene. Elution with benzene and crystallization from ethanol afforded 22 mg of pinostrobin (**2**), mp 109–110 °C.[16,17]

Methylation of Chamanetin (3) to Give 3a, 3b, 3c, and 3d. Excess ethereal diazomethane was added to a solution of 200 mg of **3** in 60 mL of ether. This mixture was allowed to stand at room temperature for 4 days. After evaporation of the solvent the residue was dissolved in benzene and chromatographed over 22 g of silica gel.

Elution with benzene yielded 58 mg of the dimethyl ether **3b** as needles from ethanol: mp 139–140 °C; UV λ_{max} (MeOH) 335 nm (ϵ 3.60 × 10^3) and 288 (7.20 × 10^3); CD $[\theta]_{329}$ +4360, $[\theta]_{311}$ +5430, $[\theta]_{287}$ −21 500, $[\theta]_{240}$ +6200, $[\theta]_{222}$ + 1300; $[\alpha]^{25}D$ −83.2° (c 0.90, benzene); IR (KBr) bands at 3200, 1640, and 1590 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 390 (M$^+$, 100), 389 (M$^+$ − 1, 10), 359 (M$^+$ − 31, 27), 313 (M$^+$ − 77, 16), and 286 (M$^+$ − 104, 8); ^{1}H NMR ($CDCl_3$) δ 12.70 (s, 1 H, exchanges D_2O), 7.33 (s, 5 H), 6.50–7.33 (m, 4 H), 6.17 (s, 1 H), 5.50 (X of ABX, 1 H), 3.97 (s, 2 H), 3.82 (s, 3 H), 3.79 (s, 3 H), and 2.50–3.16 (AB of ABX, 2 H).

Anal. Calcd for $C_{24}H_{22}O_5$: C, 73.85; H, 5.64. Found: C, 73.71; H, 5.70.

Elution with 1% ether–benzene afforded the monomethyl ether **3a** as needles from methanol: mp 146–148 °C; UV λ_{max} (MeOH) 338 nm (ϵ 4.60 × 10^3) and 289 (1.87 × 10^4); CD $[\theta]_{332}$ +860, $[\theta]_{311}$ +1290, $[\theta]_{287}$ −4320, $[\theta]_{235}$ −1330, $[\theta]_{212}$ +3020; $[\alpha]^{25}D$ −107.5° (c 1.70, acetone); IR (KBr) bands at 3230, 1630, and 1594 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 376 (M$^+$, 100), 375 (M$^+$ − 1, 7), 299 (M$^+$ − 77, 9), 272 (M$^+$ − 104, 28), and 270 (M$^+$ − 106, 66); ^{1}H NMR (acetone-d_6) δ 13.50 (s, 1 H, exchanges D_2O), 7.52 (s, 5 H), 6.60–7.33 (m, 4 H), 6.20 (s, 1 H), 5.50 (X of ABX, 1 H), 4.00 (s, 3 H), 3.82 (s, 2 H), and 2.67–3.50 (AB of ABX, 2 H).

Anal. Calcd for $C_{23}H_{20}O_5$: C, 73.40; H, 5.32. Found: C, 73.27; H, 5.35.

Elution with 32% ether–benzene gave 41 mg of the trimethyl ether **3d** as needles from ethanol: mp 148–150 °C; UV λ_{max} (MeOH) 323 nm (sh, ϵ 5.20 × 10^3), 285 (1.74 × 10^4), and 237 (1.79 × 10^4); CD $[\theta]_{332}$ +14 600, $[\theta]_{287}$ −32 700, $[\theta]_{241}$ −12 900; $[\alpha]^{25}D$ −73.4° (c 1.00, benzene);

IR (KBr) bands at 3220, 1680, and 1604 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 404 (M^+, 100), 403 ($M^+ - 1$, 7), 327 ($M^+ - 77$, 10), and 300 ($M^+ - 104$); ^1H NMR ($CDCl_3$) δ 7.37 (s, 5 H), 6.80–7.50 (m, 4 H), 6.50 (s, 1 H), 5.50 (X of ABX, 1 H), 3.93 (s, 8 H), 3.80 (s, 3 H), and 2.80–3.00 (AB of ABX, 2 H).

Anal. Calcd for $C_{25}H_{24}O_5$: mol wt, 404.1624. Found: mol wt, 404.1633 (MS).

Elution with 50% ether–benzene afforded 22 mg of the dimethyl ether **3c** as plates from methanol: mp 205–209 °C; UV λ_{max} (MeOH) 320 nm (sh, ϵ 9.80×10^3), 285 (2.91×10^4), and 238 (2.85×10^4); CD $[\theta]_{335}$ +26 300, $[\theta]_{286}$ −56 400, $[\theta]_{239}$ −25 200; $[\alpha]^{25}D$ −4.6° (*c* 3.20, benzene); IR (KBr) bands at 3130, 1662, and 1596 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 390 (M^+, 100), 389 ($M^+ - 1$, 21), 313 ($M^+ - 77$, 28), 286 ($M^+ - 104$, 70), and 284 ($M^+ - 106$, 24); ^1H NMR (Me_2SO-d_6) δ 7.60 (s, 5 H), 6.60–7.20 (m, 4 H), 6.52 (s, 1 H), 5.56 (X of ABX, 1 H), 3.95 (s, 3 H), 3.92 (s, 3 H), 3.88 (s, 2 H), and 2.80–3.10 (AB of ABX, 2 H).

Anal. Calcd for $C_{24}H_{22}O_5$: C, 73.85; H, 5.64. Found: C, 73.70; H, 5.74.

Treatment of 40 mg of **3a** with excess diazomethane for 5 h followed by chromarography over silica gel yielded 15 mg of a compound identical with **3c** (melting point, mixture melting point, TLC, co-TLC, IR, and ^1H NMR).

Methylation of Isochamanetin (4) to Give 4a, 4b, and 4c. Treatment of 187 mg of **4** with excess diazomethane for 10 h, evaporation of solvent, and chromatography over 19 g of silica gel afforded three methyl ethers.

Elution with benzene gave the dimethyl ether **4a**: mp 202–204 °C (ethanol); uv λ_{max} (MeOH) 338 nm (ϵ 2.91×10^3), 290 (1.71×10^4), and 237 (ϵ 1.70×10^4); CD $[\theta]_{333}$ +7310, $[\theta]_{314sh}$ −2770, $[\theta]_{288}$ −26 400, $[\theta]_{239}$ +9320, $[\theta]_{218}$ +29 400;$[\alpha]^{25}D$ −47.1° (*c* 1.50, benzene); IR (KBr) bands at 3220, 1640, and 1610 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 390 (M^+, 100), 389 ($M^+ - 1$, 9), 359 ($M^+ - 31$, 13), 313 ($M^+ - 77$, 11), and 286 ($M^+ - 104$, 10); ^1H NMR ($CDCl_3$) δ 12.53 (s, 1 H, exchanges D_2O), 7.50 (s, 5 H), 6.70–7.60 (m, 4 H), 6.20 (s, 1 H), 5.51 (X of ABX, 1 H), 3.98 (s, 2 H), 3.93 (s, 3 H), 3.82 (s, 3 H), and 2.70–3.50 (AB of ABX, 2 H).

Anal Calcd for $C_{24}H_{22}O_5$: C, 73.85; H, 5.64. Found: C, 73.37; H, 5.65.

The trimethyl ether **4c** was eluted with 2% ether–benzene and 10 mg was crystallized from ethanol: mp 176–179 °C; UV λ_{max} 276 nm (ϵ 3.54×10^2), 237 (sh, 4.72×10^2), and 225 (7.09×10^3); CD $[\theta]_{340}$ +25 900, $[\theta]_{310}$ −34 100, $[\theta]_{280}$ +6310, $[\theta]_{237}$ +21 100; $[\alpha]^{25}D$ +14.1° (c 0.90, benzene); IR (KBr) bands at 1670 and 1605 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 404 (M^+, 100), 403 ($M^+ - 1$, 6), 389 ($M^+ - 15$, 71), 327 ($M^+ - 77$, 9), and 300 ($M^+ - 104$, 60); ^1H NMR ($CDCl_3$) δ 7.50 (s, 5 H), 6.70–7.60 (m, 4 H), 6.47 (s, 1 H), 5.54 (X of ABX, 1 H), 4.06 (s, 2 H), 3.97 (s, 3 H), 3.82 (s, 3 H), 3.75 (s, 3 H), and 2.70–3.50 (AB of ABX, 2 H).

Anal. Calcd for $C_{25}H_{24}O_5$: C, 74.26; H, 5.94. Found: C, 74.04; H, 6.07.

Elution with 16% ether–benzene provided 114 mg of the dimethyl ether **4b** which remained as a gum after repeated attempts at crystallization (pure by TLC, ^1H NMR, and MS): UV λ_{max} (MeOH) 324 nm (ϵ 4.32×10^3) and 288 (1.73×10^4); CD $[\theta]_{340}$ +20 000, $[\theta]_{313}$ −32 800, $[\theta]_{280}$ +8790, $[\theta]_{232}$ +21 600, $[\theta]_{214}$ +14 400; $[\alpha]^{25}D$ −7.8° (c 1.20, benzene); IR ($CHCl_3$) bands at 3415, 1678, and 1602 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 390 (M^+, 53), 389 ($M^+ - 1$, 4), 375 ($M^+ - 15$, 12), 359 ($M^+ - 31$, 38), 358 ($M^+ - 32$, 51), 313 ($M^+ - 77$, 5), 286 ($M^+ - 104$, 16), and 284 ($M^+ - 106$, 28); ^1H NMR ($CDCl_3$) δ 7.45 (s, 5 H), 6.70–7.60 (m, 4 H), 6.43 (s, 1 H), 5.47 (X of ABX, 1 H), 4.01 (s, 3 H), 3.93 (s, 3 H), 3.90 (s, 2 H), and 2.70–3.40 (AB of ABX, 2 H).

Anal. Calcd for $C_{24}H_{22}O_5$: mol wt, 390.1480. Found: mol wt, 390.1467 (MS).

Methylation of Dichamanetin (5). Treatment of 400 mg of **5** with excess diazomethane for 4 days yielded a residue after removal of solvent. This was chromatographed over 21 g of silica gel. Elution with 1% ether–benzene gave 95 mg of the tetramethyl ether after crystallization from ethanol: mp 122–124 °C; UV λ_{max} (MeOH) 326 nm (ϵ 3.93×10^3), 277 (sh, 1.52×10^4), and 272 (1.60×10^4); CD $[\theta]_{350}$ +25 400, $[\theta]_{314}$ −24 500, $[\theta]_{278}$ +5240, $[\theta]_{243sh}$ +2100, $[\theta]_{230}$ −2620, $[\theta]_{215}$ +18 300; $[\alpha]^{25}D$ +12.8° (*c* 1.00, benzene); IR (KBr) bands at 1685 and 1595 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 524 (M^+, 100) and 509 ($M^+ - 15$, 16); ^1H NMR ($CDCl_3$) δ 6.70–7.50 (m, 13 H), 5.67 (X of ABX, 1 H), 4.13 (s, 4 H), 3.97 (s, 3 H), 3.82 (s, 3 H), 3.78 (s, 3 H), 3.58 (s, 3 H), and 2.85–3.10 (AB of ABX, 2 H).

Anal. Calcd for $C_{33}H_{32}O_6$: C, 75.57; H, 6.11. Found: C, 75.40; H, 6.23.

Methylation of Uvaretin (6) to Give 6a, 6b, 6c, and 6d. K_2CO_3 (10 mg) was suspended in a stirred acetone solution of 40 mg of **6**. Methyl iodide (1 mL) was added to this suspension over 2.5 h. The solvent was evaporated and 15 mL of ether added. Filtration and chromatography of the Na_2SO_4-dried ether fraction over silica gel (2% ether–benzene) provided 18 mg of the monomethyl ether **6a** as needles from ethanol: mp 138–140 °C; UV λ_{max} (MeOH) 289 nm (ϵ 1.81×10^4); IR ($CHCl_3$) bands at 3490, 1621, and 1605 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 392 (M^+, 88), 288 ($M^+ - 104$, 20), 287 ($M^+ - 105$, 100), and 260 ($M^+ - 132$, 36); ^1H NMR ($CDCl_3$) δ 15.80 (s, 1 H, exchanges D_2O), 7.33 (s, 5 H), 6.83–7.66 (m, 4 H), 6.08 (s, 1 H), 4.03 (s, 3 H), 3.93 (s, 5 H), and 2.83–3.66 (A_2B_2, 4 H).

Anal. Calcd for $C_{24}H_{24}O_5$: C, 73.47; H, 6.12. Found: 73.42; H, 6.21.

Compound **6** (90 mg) was treated with 4.5 mL of methyl iodide and 135 mg of K_2CO_3 as before. Chromatography of the resulting residue over 19 g of silica gel produced three additional methyl ethers.

The dimethyl ether, **6b** (16 mg), mp 129–131 °C (ethanol), was eluted with 2% ether–benzene: UV λ_{max} (MeOH) 288 nm (ϵ 2.01×10^4); IR ($CHCl_3$) bands at 3500, 1621, and 1598 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 406 (M^+, 62), 302 ($M^+ - 104$, 19), 301 ($M^+ - 105$, 100), and 274 ($M^+ - 132$, 34); ^1H NMR ($CDCl_3$) δ 14.53 (s, 1 H, exchanges D_2O), 7.34 (s, 5 H), 6.66–7.50 (m, 4 H), 6.10 (s, 1 H), 3.80 (s, 9 H), 3.71 (s, 2 H), and 2.83–3.67 (A_2B_2, 4 H).

Anal. Calcd for $C_{25}H_{26}O_5$: C, 73.89; H, 6.40. Found: C, 73.99; H, 6.61.

Elution with 2% ether–benzene yielded 34 mg of the trimethyl ether **6d** as a gum (pure by TLC, ^1H NMR, and MS); UV λ_{max} (MeOH) 295 nm (sh, ϵ 3.19×10^3), 275 (6.22×10^3), and 269 (6.41×10^3); IR ($CHCl_3$) bands at 3392, 1702, and 1598 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 420 (M^+, 15), 316 ($M^+ - 104$, 25), 315 ($M^+ - 105$, 100), and 288 ($M^+ - 132$, 41); ^1H NMR ($CDCl_3$) δ 7.16 (s, 5 H), 6.50–7.33 (m, 4 H), 6.27 (s, 1 H), 3.90, 3.89, 3.80, 3.75 (s, 11 H), 3.43 (s, 3 H), and 3.07 (br s, 4 H).

Anal. Calcd for $C_{26}H_{28}O_5$: mol wt, 420.1937. Found: mol wt, 420.1920 (MS).

Elution with 4% ether–benzene yielded 43 mg of the dimethyl ether **6c** as a colorless gum (pure by TLC, ^1H NMR, and MS): UV λ_{max} 280 nm (sh, ϵ 3.93×10^3), 277 (sh, 6.26×10^3), and 271 (6.70×10^3); IR ($CHCl_3$) bands at 3392, 1695, and 1585 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 406 (M^+, 17), 302 ($M^+ - 104$, 21), 301 ($M^+ - 105$, 100), and 274 ($M^+ - 132$, 16); ^1H NMR ($CDCl_3$) δ 7.17 (s, 5 H), 6.50–7.33 (m, 4 H), 6.07 (s, 1 H), 3.80 (s, 2 H), 3.63, 3.64, 3.67 (s, 9 H), and 2.97 (s, 4 H).

Anal. Calcd for $C_{25}H_{25}O_5$: mol wt, 406.1780. Found: mol wt, 406.1769 (MS).

Treatment of 40 mg of **6a** with excess ethereal diazomethane yielded a compound identical with **6c** (TLC, co-TLC, and IR).

Methylation of Isouvaretin (7) to Give 7a. Treatment of 70 mg of **7** with 20 mg of K_2CO_3 and 0.5 mL of CH_3I in a manner similar to that of **6** afforded 35 mg of the monomethyl ether **7a** as rods from ethanol: mp 127–131 °C; UV λ_{max} (MeOH) 330 nm (ϵ 3.74×10^3), 282 (1.54×10^4), and 239 (1.20×10^4); IR (KBr) bands at 3410, 1630, and 1585 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 392 (M^+, 81), 361 ($M^+ - 31$, 6), 288 ($M^+ - 104$, 10), 287 ($M^+ - 105$, 57), 286 ($M^+ - 106$, 43), and 260 ($M^+ - 132$, 11); ^1H NMR $CDCl_3$) δ 13.51 (s, 1 H, exchanges D_2O), 7.25 (s, 5 H), 6.70–7.50 (m, 4 H), 6.33 (s, 1 H), 3.93 (s, 3 H), 3.82 (s, 5 H), and 2.80–3.70 (A_2B_2, 4 H).

Anal. Calcd for $C_{24}H_{24}O_5$: C, 73.47; H, 6.12. Found: C, 73.46; H, 6.18.

Hydrogenation of Chamanetin (3) to Give 9. Pd/C (10%, 25 mg) in 20 mL of ethanol and 10 mL of 0.1 N ethanolic KOH was prereduced with hydrogen at room temperature and atmospheric pressure. To this suspension was added 50 mg of **3** in 5 mL of ethanol. After 24 hydrogen uptake ceased and the catalyst was removed by filtration. The filtrate was acidified to pH 1 with 0.1 N HCl, evaporated, and chromatographed over 18 g of silica gel (32% ether–benzene) to afford 10 mg of **9** as crystals from benzene: mp 207–208 °C; UV λ_{max} (MeOH) 317 nm (sh, ϵ 1.30×10^3); IR (KBr) bands at 3120, 1640, and 1600 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 364 (M^+, 62), 346 ($M^+ - 18$, 18), 260 ($M^+ - 104$, 10), 259 ($M^+ - 105$, 25), 258 ($M^+ - 106$, 11), and 232 ($M^+ - 132$, 27); ^1H NMR (acetone-d_6) δ 7.33 (s, 5 H), 6.70–7.60 (m, 4 H), 6.20 (s, 1 H), 3.97 (s, 2 H), and 2.85–3.80 (A_2B_2, 4 H).

Anal. Calcd for $C_{22}H_{20}O_5$: mol wt, 364.1311. Found: mol wt, 364.1332 (MS).

Hydrogenation of 3a to Give 10. Compound **3a** (40 mg) was dissolved in ethanol and added to a suspension of 20 mg of 10% Pd/C and 6 mL of 0.1 N ethanolic KOH. This was then hydrogenated in the same manner as **3** and chromatographed over silica gel (2% ether–benzene) to give 12 mg of **10**: mp 190–192 °C; UV λ_{max} 350 nm (sh, ϵ

1.29×10^3) and 283 (7.40×10^3); IR (KBr) bands at 3100, 1640, and 1594 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 378 (M^+, 62), 274 ($M^+ - 104$, 8), 273 ($M^+ - 105$, 68), 272 ($M^+ - 106$, 16), and 246 ($M^+ - 132$, 23); ^1H NMR (acetone-d_6) δ 7.30 (s, 5 H), 6.50–7.50 (m, 4 H), 6.23 (s, 1 H), 3.87 (s, 5 H), and 2.80–3.70 (A_2B_2, 4 H).

Anal. Calcd for $C_{23}H_{22}O_5$: mol wt, 378.1467. Found: mol wt, 378.1481 (MS).

Hydrogenation of 3c, 4, and 4b. Compound **3c** (40 mg in 5 mL of ethanol) in 20 mg of 10% Pd/C and 4 mL of 0.1 N ethanolic KOH was hydrogenated and worked up as before. Chromatography over 18 g of silica gel (1% ether–benzene) afforded 12 mg of a compound identical with **6a** (melting point, mixture melting point, TLC, co-TLC, IR, and ^1H NMR).

Compound **4** (50 mg in 5 mL of ethanol) in 25 mg of 10% Pd/C and 10 mL of 0.1 N ethanolic KOH was hydrogenated and worked up as before. Silica gel chromatography (32% ether–benzene) provided 10 mg of a compound identical with **9** (melting point, mixture melting point, TLC, co-TLC, IR, and ^1H NMR).

Compound **4b** (40 mg in 5 mL of ethanol) in 20 mg of 10% Pd/C and 5 mL of 0.1 N ethanolic KOH was hydrogenated and worked up as before. Silica gel chromatography (1% ether–benzene) gave 25 mg of a compound identical with **7a** (melting point, mixture melting point, TLC, co-TLC, IR, and ^1H NMR).

Degradation of 3a to Give 11. Compound **3a** (100 mg) was dissolved in 10 mL of 50% aqueous NaOH, refluxed for 45 min, and allowed to cool to room temperature. The mixture was then acidified to pH 1 with 6 N HCl and extracted with 3 × 20 mL of ether. After drying of the combined ether phases over Na_2SO_4 and evaporation, the residue was chromatographed over 20 g of silica gel. Elution with 16% ether–benzene gave 50 mg of **11** from ethanol–benzene: mp 180–182 °C; UV λ_{max} (MeOH) 270 nm (ϵ 3.00×10^3) and 223 (5.00×10^3); IR (KBr) bands at 3200, 1640, and 1600 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 246 (M^+, 38), 245 ($M^+ - 1$, 2), and 140 ($M^+ - 106$, 100); ^1H NMR (acetone-d_6) δ 6.50–7.50 (m, 4 H), 6.00 (s, 2 H), 3.99 (s, 2 H), and 3.72 (s, 3 H).

Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.29; H, 5.69. Found: C, 68.13; H, 5.85.

Degradation of Uvaretin (6) to Give 12. Compound **6** (100 mg) was dissolved in 10 mL of 50% NaOH and treated in a manner similar to that described for **3a**. Chromatography over silica gel (4% ether–benzene) gave 65 mg of **12**: mp 171–173 °C; UV λ_{max} (MeOH) 269 nm (ϵ 2.88×10^3) and 219 (6.73×10^3); IR (KBr) bands at 3300, 1640, and 1600 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 246 (M^+, 100), 245 ($M^+ - 1$, 2), and 140 ($M^+ - 106$, 83); ^1H NMR (acetone-d_6) δ 6.50–7.50 (m, 4 H), 5.97 (s, 2 H), 3.82 (s, 2 H), and 3.57 (s, 3 H).

Anal. Calcd for $C_{14}H_{14}O_4$: mol wt, 246.0892. Found: mol wt, 246.0862 (MS).

Degradation of Isouvaretin (7) to Give 11. Compound **7** (100 mg) was dissolved in 10 mL of 50% NaOH and treated as before (refluxed for 2 h). Chromatography over silica gel (16% ether–benzene) yielded 45 mg of a compound identical with **11** (melting point, mixture melting point, TLC, co-TLC, IR, and ^1H NMR).

Degradation of Diuvaretin (8) to Give 13. Compound **8** (170 mg) was dissolved in 17 mL of 50% NaOH and treated as before. Chromatography over silica gel (4% ether–benzene) gave 70 mg of a gum, **13**, pure by TLC, ^1H NMR, and MS: UV λ_{max} (MeOH) 267 nm (sh, ϵ 5.49×10^3) and 262 (5.84×10^3); IR ($CHCl_3$) bands at 3605, 3280, 1629, and 1619 cm^{-1}; low-resolution mass spectrum *m/e* (rel abundance) 352 (M^+, 9) and 243 ($M^+ - 109$, 100); ^1H NMR δ ($CDCl_3$) 6.60–7.70 (m, 8 H), 5.92 (s, 1 H), 3.90 (s, 2 H), 3.87 (s, 2 H), and 3.63 (s, 3 H).

Anal. Calcd for $C_{21}H_{20}O_5$: mol wt, 352.1311. Found: mol wt, 352.1292 (MS).

Synthesis of Chamanetin (3), Isochamanetin (4), and Dichamanetin (5). (±)-Pinocembrin[18] (500 mg) was dissolved in 10 mL of purified dioxane[19] and heated to 60 °C. A solution of 300 mg of *o*-hydroxybenzyl alcohol in 5 mL of dioxane and 1 mL of boron trifluoride etherate was added over 25 min. An additional 1 mL of boron trifluoride etherate in 2 mL of dioxane was then added. After standing at 60 °C for 30 min the cooled solution was diluted with 15 mL of ether and extracted with 6 × 20 mL of H_2O. The ether layer was dried over Na_2SO_4, evaporated, and applied to a column of 20 g of silica gel in benzene. Elution with 1% ether–benzene yielded 15 mg of a dibenzylated product identical with **5** (melting point, mixture melting point, TLC, co-TLC, and IR). A monobenzylated product was eluted with 2% ether–benzene and was identical with **4** (melting point, mixture melting point, TLC, co-TLC, and IR). Elution with 4% ether–benzene yielded 260 mg of pinocembrin while the 8% ether–benzene eluate yielded 10 mg of a product identical with **3** (melting point, mixture melting point, TLC, co-TLC, and IR).

Synthesis of 11 and 12. Phloroglucinol monomethyl ether[20] (1.14 g) was dissolved in 20 mL of dioxane and heated to 50 °C. A solution of 660 mg of *o*-hydroxybenzyl alcohol and 2 mL of boron trifluoride etherate dissolved in 25 mL of dioxane was added over 30 min. An additional 1 mL of boron trifluoride etherate in 5 mL of dioxane was then added. After 30 min the solution was allowed to cool, diluted with 20 mL of ether, and extracted with 6 × 20 mL of H_2O. The combined ether layers were then dried over Na_2SO_4 and evaporated. Chromatography of the resulting residue over 40 g of silica gel (4% ether–benzene) yielded 195 mg of a product identical **12** (melting point, mixture melting point, TLC, co-TLC, IR, and ^1H NMR). Elution with 8% ether–benzene gave 272 mg of phloroglucinol monomethyl ether while elution with 16% ether–benzene gave 240 mg of a product identical with **11** (melting point, mixture melting point, TLC, co-TLC, IR, and ^1H NMR).

Synthesis of 13. To a solution of 400 mg of **12** in 5 mL of dioxane at 60 °C was added 200 mg of *o*-hydroxybenzyl alcohol and 2 mL of boron trifluoride etherate. After standing at 60 °C for 1 h the reaction mixture was worked up as before and the resulting residue was chromatographed over 22 g of silica gel. Elution with 8% ether–benzene gave 135 mg of a product identical with **13** (melting point, mixture melting point, TLC, co-TLC, IR, and ^1H NMR).

Acknowledgments. This investigation was supported by Grant CA-15590, awarded by the National Cancer Institute, DHEW, and in part by the Research Institute of Pharmaceutical Sciences (RIPS), School of Pharmacy, University of Mississippi. The authors wish to thank Dr. I. R. C. Bick for provision of a generous sample of pinocembrin and Dr. Stephen Billets (RIPS) for high-resolution mass spectral analyses. W.L.L. acknowledges a fellowship from the American Foundation for Pharmaceutical Education.

Registry No.—**5**, tetramethyl ether, 61463-05-6; **6a**, 58449-08-4; **6b**, 58449-09-5; **6c**, 61463-06-7; **6d**, 61463-07-8; **7a**, 61463-08-9; **9**, 61463-09-0; **10**, 61463-10-3; **11**, 61463-11-4; **12**, 61463-12-5; **13**, 61463-13-6; (±)-pinocembrin, 61490-55-9; phloroglucinol monomethyl ether, 2174-64-3; *o*-hydroxybenzyl alcohol, 90-01-7.

References and Notes

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(2) C. D. Hufford and W. L. Lasswell, Jr., *J. Org. Chem.*, **41**, 1297 (1976).
(3) The names uvaretin and isouvaretin were originally chosen for these novel C-benzylated flavanones. The name uvaretin was also assigned to a C-benzylated dihydrochalcone[4] appearing in a paper published after our communication appeared in print. By mutual agreement with the authors of ref 4 we have decided to change the names of these flavanones from those originally chosen (uvaretin and isouvaretin) to chamanetin and isochamanetin since the received date of the paper in ref 4 preceded that of our communication.
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(5) Tumor-Inhibitory activity and cytotoxicity were assayed under the auspices of the National Cancer Institute by procedures described in *Cancer Chemother. Rep., Part 3*, **3**, 1 (1972). KB test values (ED_{50}, μg/mL) follow: **1**, 21 (25); **3**, 5.2 (16); **4**, 2.4 (5.3); **5**, 1.2 (4.8); **6**, 1.0 (2.6); **7**, 1.9 (2.8); **8**, 2.0 (2.4). PS cell culture values (ED_{50}, μg/mL) follow: **1**, 10.5 (19); **3**, 2.4 (2.7); **4**, 2.2 (4.1); **5**, 1.4 (1.8); **6**, 1.0 (0.83); **7**, 1.9 (2.3); **8**, 0.84 (0.96).
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(9) Brief treatment of **4** with diazomethane failed to produce a monomethyl ether.
(10) **6a** and **6b** have been reported previously.[4] However, the evidence presented in ref 4 for the monomethyl ether of **6** does not rule out the possibility that the introduced methoxyl group might be located in the hydroxybenzyl moiety. **6a** correctly represents the monomethyl ether of **6** because of the conversion of **3c** to **6a** which is described later. **6b** correctly represents one of the dimethyl ethers based on spectroscopic evidence. **6c** correctly represents one of the dimethyl ethers based on its spectroscopic properties as well as its formation from methylation of **6a**.
(11) The structure assigned to the monomethyl ether of **7** follows from the hydrogenation of **4b** to **7a** which is described later.
(12) In a separate experiment treatment of **3a** with diazomethane yielded **3c** (melting point, mixture melting point, TLC, co-TLC, and IR).
(13) Although attempts to make the 7-*O*-methyl ether of **4** failed, its hydrogenation product would be identical with **10** since **3a** and the 7-*O*-methyl ether of **4** are *o*-hydroxybenzyl isomers at the C-8 and C-6 positions, respectively.
(14) Melting points were determined on either a Thomas-Hoover or a Fisher-Johns 355 melting point apparatus and are uncorrected. Elemental analyses were performed by Scandanavian Microanalytical Laboratories, Herlev,

Denmark. Infrared spectra were obtained on either a Beckman IR-33 or a Perkin-Elmer 257 spectrophotometer and ultraviolet spectra were obtained on a Beckman Acta III spectrophotometer. The CD spectra were taken in methanol on a JASCO J-40 recording spectropolarimeter and optical rotation measurements were performed on a Perkin-Elmer 141 polarimeter. Mass spectra were obtained on a Du Pont CEC-492 mass spectrometer. ^{1}H NMR spectra were recorded on a JEOL C-60HL spectrometer using Me_4Si as internal standard. Coupling constants were calculated using first-order approximations. Column chromatography was carried out with silicic acid AR, 100 mesh (Mallinckrodt), activated by heating at 120 °C for 12 h or silica gel 60, 70–270 mesh (Brinkmann).

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Synthesis of Deoxy Sugar. Deoxygenation of an Alcohol Utilizing a Facile Nucleophilic Displacement Step

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Received September 14, 1976

Methyl 2-amino-2-deoxy-α-D-glucopyranoside was converted in good yield to the corresponding 3-deoxy analogue. The key steps include the facile nucleophilic displacement of a 3-*O*-trifluoromethylsulfonyl function by benzenethiolate under mild conditions and subsequent desulfurization with sodium in liquid ammonia. Desulfurization was also achieved, but in low yield, with Raney nickel or tributyltin hydride. The nucleophilic displacement step was accompanied by little, if any, neighboring group participation.

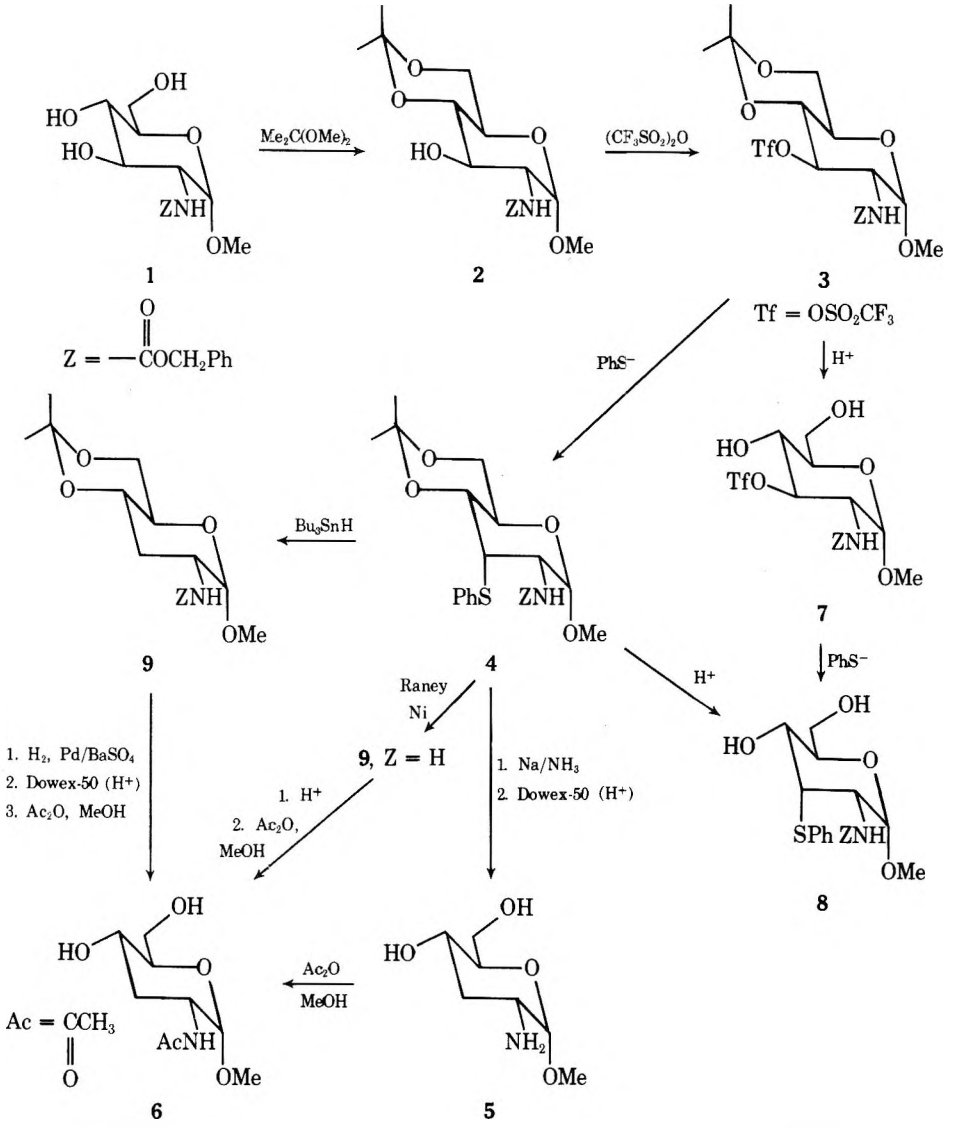
The conversion of an equatorial C-3 hydroxyl to the corresponding deoxy function in an α-linked D-hexopyranosyl glycoside, present in a number of prominent aminoglycoside antibiotics, has been of current interest because of the development of bacterial resistance by phosphorylation of this hydroxyl group.[1] Such a conversion, in several instances, was effected through the use of nucleophilic displacement as one of the key steps.[2] Recently, a reductive method proceeding through free-radical mechanism was also reported.[3] Generally speaking, nucleophilic displacement by presently available methods proceeds with difficulty, which may be accounted for by probable 1,3-diaxial interaction between the aglycone and the approaching nucleophile, as well as by complications arising from neighboring group participation. In the course of our synthetic modification studies of the antibiotic butirosin,[4] we have succeeded in such a conversion by devising a facile nucleophilic displacement. Through the combined use of the trifluoromethylsulfonyl (triflate) function, an exceedingly good leaving group,[5] and the benzenethiolate anion, one of the most powerful nucleophiles,[6] the nucleophilic displacement was achieved under extremely mild conditions. The study of this reaction in model compounds, together with subsequent desulfurization leading to the desired deoxy sugar, will be described in the present paper.

Methyl 2-deoxy-2-[[(phenylmethoxy)carbonyl]amino]-α-D-glucopyranoside (**1**) was converted to the corresponding 4,6-*O*-(1-methylethylidene) derivative (**2**) with 2,2-dimethoxypropane. Triflation of **2** with trifluoromethanesulfonic anhydride afforded the triflate (**3**) in 90% crude yield, which could be further purified by crystallization. Nucleophilic displacement of crude **3** with sodium benzenethiolate at 5 °C gave, almost exclusively (TLC evidence), the 3-(phenylthio)allopyranoside (**4**), which was subsequently isolated in crystalline form in 64% overall yield from **2**. The allo configuration of **4** was readily inferred from its 4,6-O-unsubstituted derivative **8** (cf. below). The conversion of **4** to **5** was conveniently realized by initial treatment with sodium in liquid ammonia,[8] which reductively removed both the phenylthio and the *N*-[(phenylmethoxy)carbonyl] groups, followed by hydrolytic cleavage of the 4,6-O-(1-methylethylidene) group on Dowex 50 × 4 (a strong cation exchange resin) in the hydrogen form. The product, compound **5**, was isolated by elution with aqueous ammonia and further converted to the crystalline *N*-acetyl derivative (**6**) in an overall yield of 81% from **4**. The 3-deoxy-D-ribo configuration in **6** was confirmed by NMR data, which showed a geminal coupling $J_{3a,3e}$ (ca. 11 Hz), two axial–axial couplings $J_{2a,3a}$ (ca. 12 Hz) and $J_{3a,4a}$ (ca. 11 Hz), and two axial–equatorial couplings $J_{1e,2a}$ (ca. 3.8 Hz) and $J_{2a,3e}$ (ca. 4.7 Hz each). The 4,6-di-*O*-acetate of **6** (**6**, OH = OAc) showed properties closely resembling those reported for an identical compound[9] and provided NMR data fully confirming the 3-deoxy-D-ribo configuration.

Other methods for the reductive cleavage of the phenylthio–sp^3 carbon bond in **4** were also examined. Treatment of **4** with nickel boride[10] in boiling ethanol for 12 h gave essentially unchanged starting material. Reaction of **4** with Raney nickel (previously neutralized to pH 7 with acetic acid) in boiling ethanolic solution yielded the corresponding 3-deoxy analogue, but in low yield; under these conditions the *N*-[(phenylmethoxy)carbonyl] group was preferentially hydrogenolyzed, generating the amine which was then irreversibly absorbed by the Raney nickel. Treatment of **4** with tributyltin hydride[11,12] in boiling toluene for 12 h in the presence of the radical initiator 2,2′-azobis(2-methylpropanenitrile) resulted in the isolation of the 3-deoxy compound **9** in less than 37% yield, which was characterized by eventual conversion to the crystalline compound **6**, together with ca. 12% of unreacted **4**. The side products of the reaction, showing much lower TLC mobilities, conceivably could be compounds having a free amino group at C-2 but were not further investigated.

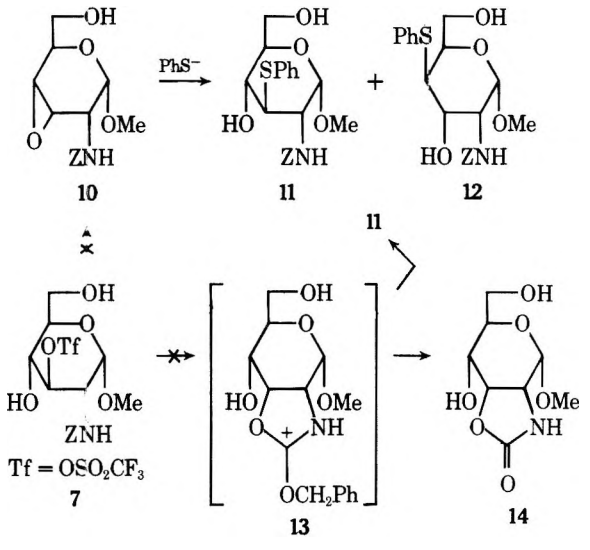
The presence of neighboring groups, such as a hydroxyl or a [(phenylmethoxy)carbonyl]amino group, in trans orientation to the triflate leaving group, may lead to possible complications in the nucleophilic displacement step. To resolve such possibilities, the attack of the benzenethiolate ion on **7**, the 4,6-dihydroxy analogue of **3**, was studied. The product, a 3-deoxy-3-phenylthio-D-allo derivative (**8**), was isolated in crystalline form in high yield (81%) and found to be identical with the product obtained by removal of the 4,6-*O*-(1-methylethylidene) group from **4**. The C-3 configuration in **8**

Scheme I



was ascertained by NMR data. The signal of H-2 in 8 and of H-3 in 8, each showing two axial–equatorial couplings ($J_{1e,2a}$ = 3.5; $J_{2a,3e}$ = 4.8; $J_{3e,4a}$ = 4.7 Hz), and the signal of H-4 in the crystalline di-*O*-acetate of 8, showing one axial–equatorial and one axial–axial couplings ($J_{3e,4a}$ = 4.5; $J_{4a,5a}$ = 8.7 Hz), all indicated the presence of an equatorial hydrogen atom, hence an axial phenylthio group at C-3. On the other hand, neighboring group participation by the C-4 hydroxyl would lead to the epoxide **10**, which would then further react with the nucleophile to give either a D-gluco derivative **11**, or a D-gulo derivative **12**, or a mixture of both, instead of the D-allo derivative 8 actually obtained in high yield. Neighboring participation by the 2-[[(phenylmethoxy)carbonyl]-amino] group would give rise to the oxazolinium intermediate **13**, which then may undergo elimination to give the oxazolone **14**, or nucleophilic attack to give the D-gluco derivative **11**, instead of 8 as actually obtained. Evidently then, under the experimental conditions used, the benzenethiolate displacement of triflate took place mostly as a straightforward S_N2 type reaction, with little, if any, neighboring group participation, thus constituting a promising reaction of synthetic utility.

Scheme II



Thus a simple reaction series for the conversion of a hydroxyl group to the deoxy function, utilizing a facile nucleophilic displacement step, has been devised. The application of this procedure to more complex systems, such as aminoglycoside antibiotics, will be the subject of further communications.[13]

Experimental Section

General. Thin layer chromatography (TLC) was performed using glass plates precoated with silica gel (Quanta Q1F, 10-cm length, Quantum Industries, Fairfield, N.J.) and aqueous solution of am-

monium molybdate containing 5% phosphoric acid and 5% sulfuric acid as spray. Column chromatography was performed using silica gel (E. Merck 60, 0.013–0.20 mm) packed by gravity as slurries in solvents. Melting points, unless otherwise specified, were determined in a silicone oil bath and were uncorrected. Nuclear magnetic resonance (NMR) spectra were determined with a Bruker WH-90 spectrometer by the pulsed Fourier transformation technique (except those for compounds **2**, **3**, **4**, and **7**, which were determined on a Varian A-60 spectrometrr). Chemical shift data are reported in δ (ppm) units relative to tetramethylsilane in the solvent chloroform-*d* and pyridine-d_5 and to sodium 3-(trimethylsilyl)propanoate-2,2,3,3-d_4 in deuterium oxide and methanol-d_4. Eu(fod$_3$)$_3$-d_{27}, i.e., tris-[6,6,7,7,8,8,8-heptafluoro-2,2-di(methyl-d_3)-3,5-octanedion-1,1,1-d_3-ate-*O*,*O*']europium(3+), was used as a shift reagent. The triflates **3** and **7** were stable at −29 °C and were generally stored at this temperature.

Methyl 2-Deoxy-4,6-*O*-(1-methylethyldiene)-2-[[(phenylmethoxy)carbonyl]amino]-α-D-glucopyranoside (2). A solution of methyl 2-deoxy-2-[[(phenylmethoxy)carbonyl]amino]-α-D-glucopyranoside (**1**, 8.67 g) in 85 mL of dry *N*,*N*-dimethylformamide containing 0.89 g of *p*-toluenesulfonic acid and 17.5 mL of 2,2-dimethoxypropane was stirred for 36 h at room temperature. The mixture was neutralized with 0.72 mL of triethylamine and evaporated to a syrup in vacuo. A mixture of the syrup and 50 mL of water was stirred at 5 °C for 1 h, the aqueous phase decanted, and the residue extracted into 500 mL of chloroform. The chloroform extract was washed with water and saturated sodium chloride solution, dried over sodium sulfate, and evaporated in vacuo to give 7.34 g of a sticky semisolid containing some tenaciously held, residual *N*,*N*-dimethylformamide. The material was homogeneous by TLC (chloroform–methanol, 75:1), and its NMR spectrum was consistent with structure **2**.

Methyl 2-Deoxy-4,6-*O*-(1-methylethylidene)-2-[[(phenylmethoxy)carbonyl]amino]-3-*O*-[(trifluoromethyl)sulfonyl]-α-D-glucopyranoside (3). To a solution of 4.1 g (11.17 mmol) of **2** in 50 mL of 1,2-dichloroethane and 12 mL of dry pyridine cooled to 0 °C was added a solution of 2.0 mL (12.5 mmol) of trifluoromethanesulfonic anhydride in 15 mL of 1,2-dichloroethane dropwise with stirring over a 30-min period. After stirring for 1 h at 0 °C the reaction was complete according to TLC (1% methanol in benzene). Following the addition of another 100 mL of 1,2-dichloroethane the reaction mixture was washed with water, dilute hydrochloric acid, aqueous sodium bicarbonate, water, and saturated sodium chloride solution and dried over sodium sulfate. Solvent removal in vacuo afforded crude **3**, which was used directly in the next step. The yield, estimated from a similar run, was about 89%. Recrystallization of a small sample from toluene–petroleum ether gave pure **3**, mp 94–95 °C.

Anal. Calcd for $C_{19}H_{24}F_3NO_9S$ (499.5): C, 45.69; H, 4.84; N, 2.80; S, 6.41. Found: C, 45.68; H, 4.80; N, 2.75; S, 6.76.

Methyl 2,3-Dideoxy-4,6-*O*-(1-methylethylidene)-2-[[(phenylmethoxy)carbonyl]amino]-3-(phenylthio)-α-D-allopyranoside (4). To a suspension of 2.4 g (50 mmol) of sodium hydride (50% in mineral oil) in 20 mL of *N*,*N*-dimethylformamide was added 7.2 mL (70 mmol) of benzenethiol dropwise with stirring and cooling in a nitrogen atmosphere. Stirring was continued at room temperature for 3 h to give a solution of sodium benzenethiolate. The solution was cooled to 0 °C, and a solution of the crude, dried triflate **3**, prepared from 4.1 g (11.2 mmol) of **2** as described above, in slightly more than 5 mL of dry *N*,*N*-dimethylformamide was added in one portion. The mixture was stirred overnight at 5 °C, and TLC (0.5% methanol in benzene) showed the complete disappearance of starting material and the almost exclusive formation of a single product, with only minute traces of side products. The mixture was neutralized by adding 2.9 mL of acetic acid and 3 mL of water. After the addition of 100 mL of benzene, the mixture was washed four times with water, then with saturated sodium chloride solution, and dried over sodium sulfate. Solvent removal in vacuo afforded an oil which was chromatographed over silica gel using 5% ethyl acetate in toluene as eluent. The fractions containing pure **4** were combined, evaporated, and recrystallized from benzene–petroleum ether to give 3.127 g (6.8 mmol) of crystals, mp 115–116 °C, $[\alpha]^{23}D$ +46.8 (c 1, chloroform).

Anal. Calcd for $C_{24}H_{29}NO_6S$ (459.5): C, 62.73; H, 6.36; N, 3.05; S, 6.98. Found: C, 63.00; H, 6.49; N, 2.97; S, 7.06.

An additional 267 mg (0.58 mmol) of **4**, mp 114–115 °C, was obtained from the tailing chromatographic fractions.

Methyl 2-Amino-2,3-dideoxy-α-D-*ribo*-hexopyranoside (5) and Methyl 2-(Acetylamino)-2,3-dideoxy-α-D-*ribo*-hexopyranoside (6). To 50 mL of liquid ammonia was added 233 mg (0.51 mmol) of finely divided **4**. Small pieces of metallic sodium was added with stirring until a blue color persisted for 1 min. The excess sodium was removed by addition of ammonium chloride crystals, and the ammonia was evaporated to give a dry residue which was then extracted with methanol. Evaporation of the methanol extract gave a residue, which was then extracted with ethanol. Subsequent evaporation of the ethanol extract gave another residue, which was mixed with water and washed three times with benzene to remove benzenethiol. The aqueous layer was passed over a 10-mL column of Dowex 50 × 4 (hydrogen form),[14] and the column was washed thoroughly with water. Elution of the resin with 1 N aqueous ammonia followed by evaporation in vacuo afforded crude **5** as a white solid. The product was N-acetylated in a methanol–water (1:1) solution at room temperature by the addition of 0.2 mL of acetic anhydride. After 3 h evaporation to dryness afforded **6** as a crystalline residue. Recrystallization from ethanol gave 90 mg (0.41 mmol) of pure **6**, mp 211–212 °C, $[\alpha]^{23}D$ +138° (c 1, water).

Anal. Calcd for $C_8H_{17}NO_5$ (219.2): C, 49.30; H, 7.82; N, 6.39. Found: C, 49.30; H, 8.08; N, 6.26.

NMR (D_2O): H-2, δ 3.98 (d of t, $J_{1,2}$ = 3.8, $J_{2,3e}$ = 4.7, $J_{2,3}$ = 12.5 Hz, *J* values obtained by spin decoupling); H-3a, δ 1.79 (q with additional fine splittings, width 34.5 Hz, $J_{3a,3e} \simeq J_{3a,4} \simeq$ 11 Hz); H-3e, δ 2.1 (m, partially hidden by $CH_3C{=}O$). NMR (pyridine-d_5): H-1, δ 5.00 (d, $J_{1,2}$ = 3.5 Hz).

Acetylation of **6** with acetic anhydride in pyridine afforded the 4,6-di-*O*-acetate of **6**, mp 138 °C, $[\alpha]^{23}D$ +112° (c 0.38, methanol) (reported[9] +90°).

Anal. Calcd for $C_{13}H_{21}NO_7$ (303.31): C, 51.48; H, 6.98; N, 4.62. Found: C, 50.80; H, 6.74; N, 4.52.

NMR ($CDCl_3$): H-1, δ 4.58 (d, $J_{1,2}$ = 3.5 Hz); H-2, δ 4.22 (d of d of q, partly hidden, $J_{2,3e}$ = 4.6, $J_{2,3a}$ = 12.5 Hz); H-3e, δ 2.2 (d of t, $J_{3a,3e}$ = 11.5 Hz); H-3a, δ 1.64 (q, $J_{3a,4}$ = 11.0 Hz); H-4, δ 4.80 (d of t, $J_{3e,4}$ = 5.0, $J_{4,5}$ = 10.2 Hz); H-5, δ 3.82 (d of q, $J_{5,6}$'s = 4.5 and 3.0 Hz); H-6, δ 4.17 (q); $-OCH_3$, δ 3.39 (s); $-OC(:O)CH_3$'s, δ 1.97 (s), 2.02 (s), and 2.08 (s); NH, δ 5.56 (d, broad, $J \sim 9.6$ Hz).

The spectrum is identical with that reported in the literature.[9]

Methyl 2-Deoxy-2-[[(phenylmethoxy)carbonyl]amino]-3-*O*-[(trifluoromethyl)sulfonyl]-α-D-glucopyranoside (7). Chromatographically pure **3**, 0.30 g, was warmed in 3 mL of moist toluene and cooled to room temperature. Needles separated, and the crystallization process was completed by gradual addition of petroleum ether. After standing overnight at 5 °C, the product was filtered from the mother liquor, which was strongly acidic to pH paper, and dried affording 0.18 g of **7**, mp 88–91 °C. The product was differentiated from the starting material **3** by the respective ^1H NMR spectra and by TLC, which showed that **7** had a much lower mobility than **3** in benzene containing 1% of methanol.

Anal. Calcd for $C_{16}H_{20}F_3NO_9S$ (543.5): C, 41.83; H, 4.38; N, 3.04; S, 6.97. Found: C, 42.24; H, 4.41; N, 3.11; S, 6.89.

Compound **7** formed a di-*O*-acetate with acetic anhydride–pyridine, needles from benzene–petroleum ether, mp 109–110 °C dec.

Anal. Calcd for $C_{20}H_{24}F_3NO_{11}S$ (543.5): C, 44.20; H, 4.45; N, 2.58; S, 5.90. Found: C, 44.12; H, 4.56; N, 2.81; S, 6.13.

Methyl 2,3-Dideoxy-2-[[(phenylmethoxy)carbonyl]amino]-3-(phenylthio)-α-D-allopyranoside (8). A. From Compound 7. A solution of sodium benzenethiolate was prepared from 240 mg (5 mmol) of sodium hydride (50% in mineral oil), 0.9 mL (9 mmol) of benzenethiol, and 5 mL of *N*,*N*-dimethylformamide (cf. preparation of **4**, above). Compound **7**, 0.30 g (0.65 mmol), was added with stirring at 5 °C. After additional stirring overnight at 5 °C, the solution was neutralized with 3 mL of 2 N acetic acid, and the solvent was removed in vacuo. The residue was dissolved in chloroform, washed with water (two times) and saturated sodium chloride, and dried over sodium sulfate. The filtered solution was passed over a column containing 9 g of silica gel. The column was washed well with chloroform and finally eluted with 5% methanol in chloroform. The fractions containing product were combined, evaporated, and crystallized from water to give 0.23 g (0.53 mmol) of **8**. Recrystallization from ethyl acetate–petroleum ether gave the analytical sample, mp 61–63 °C.

Anal. Calcd for $C_{21}H_{25}NO_6S{\cdot}H_2O$ (435.5): C, 57.65; H, 6.22; N, 3.20; S, 7.33. Found: C, 57.87; H, 5.97; N, 3.16; S, 7.39.

NMR (CD_3OD): H-1, δ 4.63 (d, $J_{1,2}$ = 3.5 Hz); H-2, δ 4.17 (t, $J_{2,3}$ = 4.8 Hz); relationship verified by spin decoupling. NMR [$CDCl_3$, 2.5% solution containing ca. 0.6% Eu(fod$_3$)d_{27}]: H-1, δ 5.02 (d, $J_{1,2}$ = 3.5 Hz); H-3, δ 4.18 (t, $J_{2,3} \simeq J_{3,4} \simeq$ 4.7 Hz).

Compound **8** formed a di-*O*-acetate with acetic anhydride in pyridine, needles from hexane, mp 96–97 °C.

Anal. Calcd for $C_{25}H_{29}NO_8S$ (503.6): C, 59.63; H, 5.81; N, 2.78; S, 6.37. Found: C, 59.89; H, 5.92; N, 2.76; S, 6.61.

NMR ($CDCl_3$): H-1, δ 4.69 (d, $J_{1,2}$ = 3.5 Hz); H-3, δ 4.12 (t, $J_{2,3} \simeq$

$J_{3,4} \simeq 4.5$ Hz); H-4, δ 4.98 (d of d, $J_{4,5} \simeq 8.7$, $J_{3,4} \simeq 4.5$ Hz; additional complex splittings at the lower field doublet, probably due to virtual coupling with H-5), H-2, H-5, and H-6, δ 4.20–4.46 (m, overlapping); all assignments verified by spin decoupling. NMR (pyridine-d_5): H-4, δ 5.4 [q, partly hidden by $-C(:O)OCH_2C_6H_5$, $J_{3,4} = 3.5$, $J_{4,5} \simeq 10$ Hz].

B. From Compound 4. Compound **4** (0.20 g) was heated on a steam bath in 10 mL of acetic acid–water (4:1) for 1 h and cooled. The solution was evaporated to dryness in vacuo. The residue was acetylated with acetic anhydride in pyridine to give needles from hexane, mp 96–97 °C, identical with the di-*O*-acetate of **8** by TLC (toluene–ethyl acetate, 8:2) and mixture melting point determination. The sample was de-*O*-acetylated with sodium methoxide in methanol at 5 °C to yield a crystalline product identified as **8** by NMR and TLC, mp 58–60 °C.

Studies on the Desulfurization of 4 by Other Methods. A. Nickel Boride. A solution of 480 mg (2.0 mmol) of nickel chloride hexahydrate in 10 mL of water was aerated for 10 min with nitrogen, then treated with a 2 N aqueous sodium borohydride solution added dropwise with stirring until the precipitation of nickel boride ceased (1.9 mL used). The precipitate was washed three times with ethanol and then heated under reflux with a solution of 20 mg (0.043 mmol) of **4** in 3.0 mL of ethanol for 12 h. TLC showed that no reaction had occurred.

B. Raney Nickel. A suspension of Raney nickel (W. R. Grace, Davison Chemical, No. 30) was neutralized with 2 N acetic acid from pH 10.8 to 7.0 with stirring. The catalyst was washed three times with water, five times with *N,N*-dimethylformamide, and finally three times with methanol and used in the following desulfurization reaction.

Compound **4** (273 mg 0.59 mmol) in 10 mL of methanol and 2.0 mL (ca. 2.4 g) of settled Raney nickel was stirred at room temperature for 2 h. TLC showed the presence of mostly the 2-amino analogue of **4**, i.e., **4** (Z = H) (R_f, 1% methanol in toluene, 0.0; 5% methanol in benzene, 0.27), in addition to some starting material (R_f, 1% methanol in toluene, 0.66) and a small amount of the 2-amino-3-deoxy analogue of **4**, i.e., **9** (Z = H) (R_f, 5% methanol in benzene, >0.06). The presence of a free amino group was detected by ninhydrin, and the presence of a phenylthio group by strong fluorescence quenching under UV at 2537 Å. The reaction mixture was filtered and evaporated to dryness giving 137 mg of residue [65% yield assuming all of the product to be **4** (Z = H)].

The above reaction product (125 mg) in 1.5 mL of methanol and 0.6 mL of settled Raney nickel was heated under reflux with stirring for 4 h. Another 0.7 mL of settled Raney nickel was added, and reflux with stirring was continued for 4 h. TLC showed that the major product was **9** (Z = H), with a minor amount of **4** (Z = H). The reaction mixture was filtered and evaporated to 75 mg of colorless oil [60% yield assuming all of the product to be **9** (Z = H)].

The 4,6-*O*-(1-methylethylidene) group was removed from crude **9** by treatment with 4.2 mL of acetic acid and 2.8 mL of water at 45 °C for 11 h. The reaction mixture was evaporated to dryness in vacuo, treated with 5 mL of methanol and 2 mL of acetic anhydride for 3 days at room temperature, and evaporated to give 72 mg of brown residue. Two recrystallization from methanol–acetone gave 16.7 mg of **6**, identified by IR, NMR, and melting point (215 °C, Fisher-Johns hot stage, uncorrected).

C. Tributyltin Hydride. To a solution of 0.28 g (0.25 mL, 0.96 mmol) of tributyltin hydride in 1.5 mL of dry toluene under an argon atmosphere was added a solution of 73.5 mg (0.156 mmol) of **4** in 2 mL of toluene. The clear solution was heated under reflux for 25 h. TLC (1% methanol in toluene) indicated the presence of largely unreacted **4** (R_f 0.50), together with minor amounts of **9** (R_f 0.33) and some decomposition products (R_f's 0.13, 0.08, 0.05, 0.00). A solution of 5.2 mg of 2,2′-azobis(2-methylpropanenitrile) (0.032 mmol) in 1 mL of toluene was then added and the reflux continued. After 2 h, TLC showed the presence of **4** and **9** in approximately equal intensities, a very weak spot at 0.28, and very small spots at R_f's less than 0.08. After an additional 7 h of reflux, the TLC spot for **9** became stronger relative to that for **4**, but the side product with R_f 0.05 had also increased. The solution was concentrated and applied to a 20 cm × 20 cm × 1000 μ silica gel plate (Quanta PQ1F), which was then developed two times with 1% methanol in benzene. Compound **9** (together with a trace of side product with R_f 0.28), 20 mg (less than 38%), was isolated, and the starting material **4**, 9.3 mg (12.7%), was recovered. The solvent front smelled very strongly of benzenethiol. Compound **9** was hydrogenolyzed for 1.5 h with a stream of hydrogen in methanol containing 2 N acetic acid and 26 mg of 20% palladium on barium sulfate catalyst. Addition of another 20 mg of catalyst and further treatment with hydrogen did not lead to any more hydrogenolysis, as evidenced by the lack of further evolution of carbon dioxide. The catalyst was filtered and washed with aqueous methanol, and solvent removal gave 17 mg of residue. An aqueous solution of the residue was percolated through a column containing 1.0 mL of Dowex 50 × 4 (hydrogen form).[12] The column was washed with water, allowed to stand for ca. 40 min, and eluted with 33 mL of 1 N aqueous ammonia. Evaporation of the eluate in vacuo gave 9.7 mg of residue. A solution of the residue in 0.35 mL of water was treated with 1.1 mL of methanol and 0.6 mL of acetic anhydride for 20 h. Evaporation gave 14 mg of residue which was recrystallized from hot ethanol to give 1.4 mg of **6**, identified by its infrared spectrum and melting point (215 °C, Fisher-Johns hot stage, uncorrected). Evaporation of the mother liquor gave an additional 4.3 mg of solid.

Acknowledgments. The authors acknowledge their appreciation to Mr. C. E. Childs and associates for microanalyses, to Dr. J. M. Vandenbelt and associates for determination of physical data (NMR by Mr. R. B. Scott, Mrs. M. D. LaBelle, and Dr. F. A. MacKellar), and to Mr. L. Hampton for technical assistance.

Registry No.—**1**, 4704-15-8; **2**, 61348-62-7; **3**, 61364-33-8; **4**, 61348-63-8; **5**, 61348-64-9; **6**, 25541-56-4; **6** di-*O*-Ac, 61348-65-0; **7**, 61348-66-1; **7** di-*O*-Ac, 61348-67-2; **8**, 61348-68-3; **8** di-*O*-Ac, 61348-69-4; 2,2-dimethoxypropane, 77-76-9; trifluoromethanesulfonic anhydride, 358-23-6; sodium benzenethiolate, 930-69-8.

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(14) A strong cation exchange resin from the Dow Chemical Co., Midland, Mich.

Preparation of *cis*- and *trans*-4-*tert*-Butyl-1-phenylphosphorinane and a Study of Reaction Stereochemistry of Its Derivatives

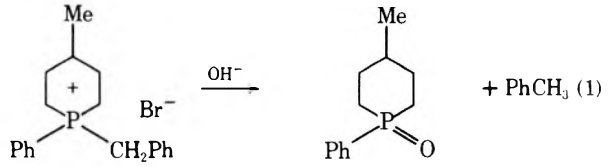
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Received October 26, 1976

Syntheses of pure cis and trans isomers of 4-*tert*-butyl-1-phenylphosphorinane and its 1-oxides (4), 1-benzyl-4-*tert*-butyl-1-phenylphosphorinanium bromide (3), and 4-*tert*-butyl-1-methyl-1-phenylphosphorinanium bromide (7) in addition to 4-*tert*-butyl-1,1-diphenylphosphorinanium bromide (10) and an isomeric mixture of 4-*tert*-butyl-1-phenylphosphorinane 1-oxide (8) are reported. Evidence for configurational assignments is discussed. It was found that hydroxide cleavage of *cis*-3 produced 66% *trans*-4 and 34% *cis*-4 while cleavage of *trans*-3 yielded 21% *trans*-4 and 79% *cis*-4. Hydroxide cleavage of *cis*-7 gave 38% *trans*-8 and 62% *cis*-8 while *trans*-7, similarly treated, gave 25% *cis*-8 and 75% *trans*-8. Treatment of 10 with aqueous sodium hydroxide yielded 60% *cis*-4 and 40% *trans*-4. The pseudo-first-order kinetics of debenzylation of the isomers of 3 and 7 were determined. Mechanistic conclusions were drawn from stereochemical and kinetic information.

As part of a series of studies designed to assess the effect of ring size on reactivity of phosphorus[1] we previously determined that the overall debenzylation of *cis*- and *trans*-1 by aqueous sodium hydroxide is not stereospecific.[2,3] Furthermore, the cis isomer (1a)[4] produces a *different* ratio of diastereomeric oxides (2) than does the trans isomer (1b). These results were explained by the operation of a dual mechanism[5] in which the balance between inversion and retention in eq 1 is obviously affected in some manner by the steric effect

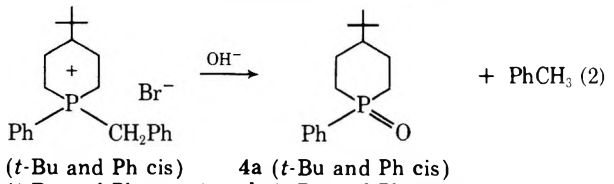


1a (Me and Ph cis) 2a (Me and Ph cis)
b (Me and Ph trans) b (Me and Ph trans)

exerted by the ring methyl. In order to elucidate more fully the role of the substituent in regulating stereochemistry of this reaction, it was deemed necessary to prepare the cis and trans isomers of 3. The *tert*-butyl group would be expected to ensure conformational homogeneity as well as provide a large steric bulk effect in position 4. Moreover, the *tert*-butyl protons offer a sensitive analytical probe for determining composition of mixtures by NMR. In addition, it was desired to gain synthetic access to the 4-*tert*-butylphosphorinane system for future conformational and configurational studies which we have planned.

Discussion of Results

Cleavage of *cis*- and *trans*-1-Benzyl-4-*tert*-butyl-1-phenylphosphorinanium Bromide. When cleavage data for 1 and 3 were compared it was found that, within experimental error, 1b and 3b gave identical results. However, for 1a and 3a the ratios of oxides produced were quite different.



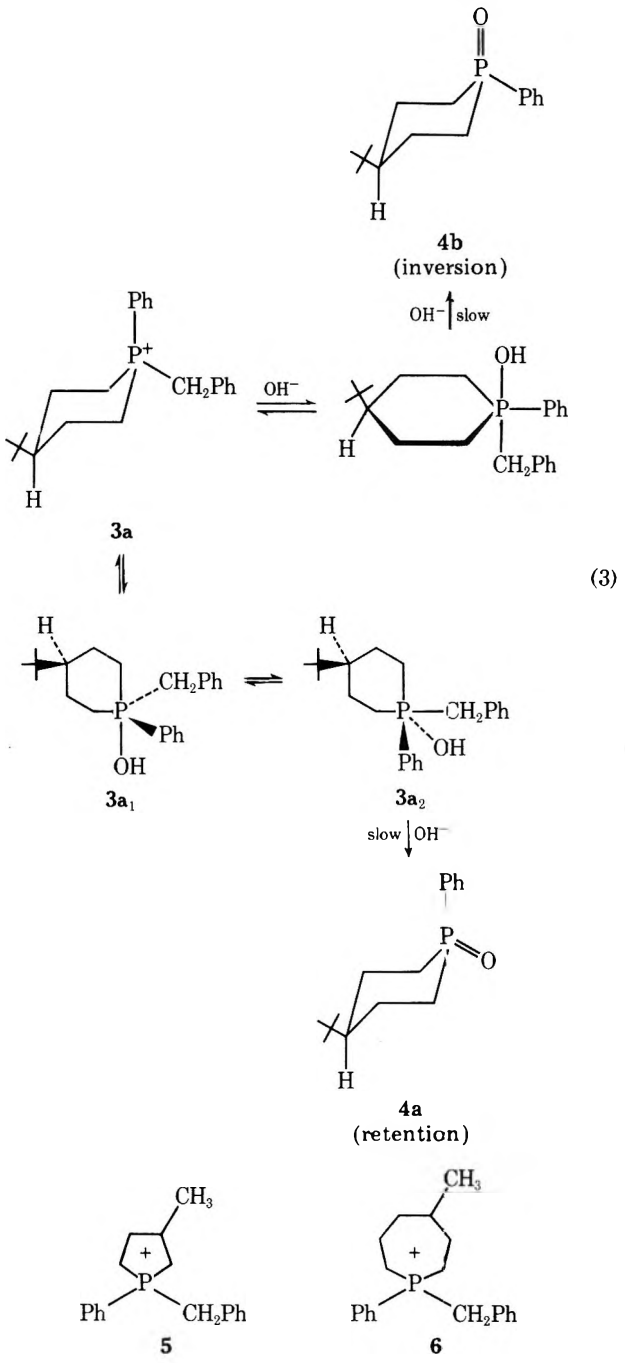
3a (*t*-Bu and Ph cis) 4a (*t*-Bu and Ph cis)
b (*t*-Bu and Ph trans) b (*t*-Bu and Ph trans)

					retention/inversion
1a	$\xrightarrow{OH^-}$	2a	+	2b	
		48%		52%	0.92
3a	$\xrightarrow{OH^-}$	4a	+	4b	
		66%		34%	1.9
1b	$\xrightarrow{OH^-}$	2a	+	2b	
		22%		78%	3.6
3b	$\xrightarrow{OH^-}$	4a	+	4b	
		21%		79%	3.8

For both isomeric salts of 1 and 3 it has been established conclusively that isomerization does not occur prior to the cleavage process. The corresponding oxides are also stereochemically stable to base. When cleavage reactions of diastereomerically pure salts are interrupted, only stereochemically unchanged salts are recovered. It seems reasonable that whatever processes are occurring for the decomposition of 1b and 3b, the 4 substituents offer minimal effect on stereochemistry because a change from methyl to *tert*-butyl produces effectively no change in isomer ratio.

It is noteworthy that retention predominates in base cleavage of 3a and 3b. We interpret this as a resistance of the six-membered ring to involvement of the two C–P ring bonds in equatorial positions in the trigonal bipyramidal intermediate leading to inversion (3a → 4b and 3b → 4a in eq 3 and 4). It is also seen that the cis isomers 1a and 3a produce more oxide of inverted configuration than 1b and 3b. We believe that the greater incidence of inversion in the former case is due to resemblance of the transition state to product oxides. In a separate experiment we have equilibrated 4a and 4b in aqueous acid and have obtained a thermodynamic mixture of oxides of 4b/4a = 3/1. Therefore, the more stabilized transition state, from the standpoint of product stability, should lead to inversion for cleavage of 3a and retention for cleavage of 3b. However, for the inversion process transition state stability would be adversely affected by the ring strain effect just mentioned. Thus, inversion accompanying cleavage of 3a, although greater than for 3b, does not predominate. If these considerations are true, it might be expected that 3b should react more rapidly with base than 3a. As discussed subsequently, this was found to be so with 3b reacting twice as rapidly as 3a.

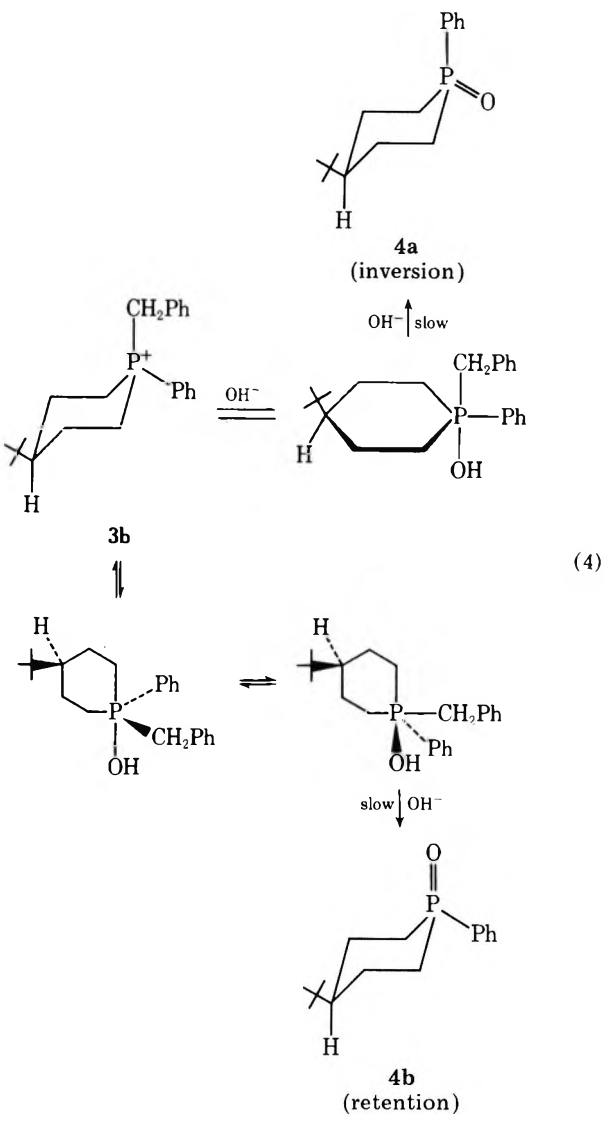
The possibility that some inversion of configuration seen for these reactions comes about through further isomerization of fluxional intermediates such as $3a_1$ and $3a_2$ (eq 5) can reasonably be dismissed. Any crossover occurring by eq 5 should result in isomerization of starting material. This is not observed for either isomer of 1 or 3. Furthermore, cleavage of 5 under similar conditions occurs completely stereospecifically (retention)[6] as does cleavage of 6 (inversion).[5] Presumably the former takes place by a retention pathway and the latter by an inversion pathway, analogous to those shown in eq 3 and 4.



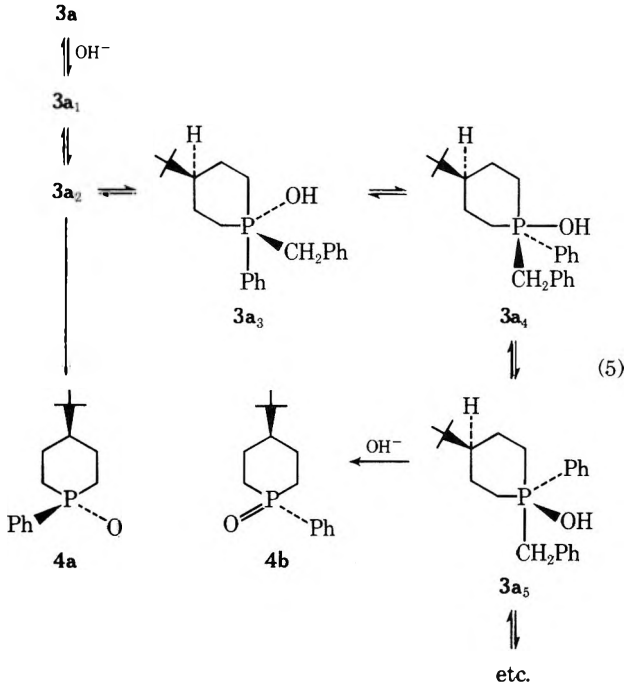
(3)

The mechanisms as discussed above assume the generally accepted apical introduction of nucleophile and apical loss of leaving group[7] and also assume expulsion of benzyl to be rate determining.[8]

The pseudo-first-order kinetics for the base cleavage of **3a** and **3b** were determined in aqueous ethanol. The solvent and conditions were initially chosen to conform to those used by Cremer et al.[8c] for studying rates of debenzylation of a variety of phosphorus heterocycles. In attempting to duplicate Cremer's kinetics for hydroxide-induced debenzylation of the unsubstituted phosphorinanium salt (eq 6), we have found that the process measured by Cremer at 25 °C is not conversion of **15** to its oxide, but some minor competing reaction (possibly reversible ylide formation). After several days at 25 °C we found no perceptible conversion of the salt to the oxide (eq 6). In fact, the spectrum of oxide, either in neutral solution or in base, shows no absorption at 307.5 nm, the wavelength used by Cremer. We have been able to duplicate the rate constant (5.64×10^{-4} L^2 mol^{-2} s^{-1} this work; 5.60×10^{-4} L^2 mol^{-2} s^{-1} Cremer et al.), but it *cannot* be associated with the appearance of the oxide.



(4)

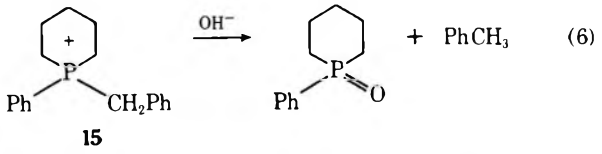


(5)

We therefore turned to pseudo-first-order conditions in 50% aqueous ethanol (1.28 N NaOH) at 80.0 °C to determine the reactivities of **3a, 3b,** and **15** which are listed in Table I.

Table I. Pseudo-First-Order Rate Constant for Debenzylation of 3a, 3b, and 15 at 80.0 °C

	λ, nm	k_1, s^{-1}	Rel rate
3a	273.5	2.81×10^{-3}	1.77
3b	273.5	5.54×10^{-3}	3.48
15	273.5	1.59×10^{-3}	1.00

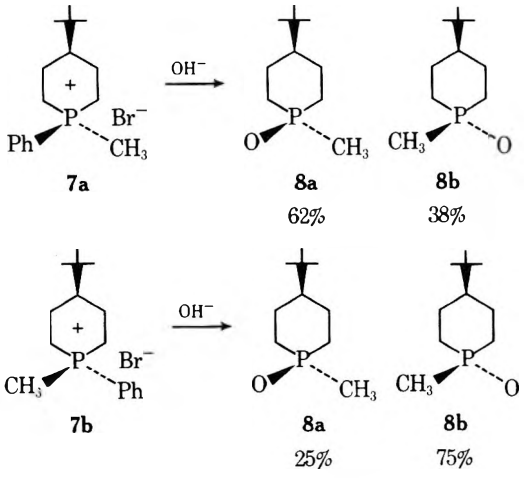


(6)

15

It is surprising to see both *tert*-butyl salts showing greater reactivity than the unsubstituted salt. However, this may be rationalized on the basis that the transition state for either **3a** and **3b** in the rate-determining step leading to the oxides shows less crowding, due to the presence of the *tert*-butyl group, than does the initial salt; i.e., the ground-state energy of **3a** or **3b** is higher than for **15**.

Cleavage of *cis*- and *trans*-4-*tert*-Butyl-1-methyl-1-phenylphosphorinanium Bromide. Hydroxide-induced displacement of phenyl from **7a** and **7b** is a much slower process (about 200 times slower) than that observed for either **3a** or **3b** because the leaving group is a poorer one. The results show both **7a** and **7b** to give predominantly *retention* of



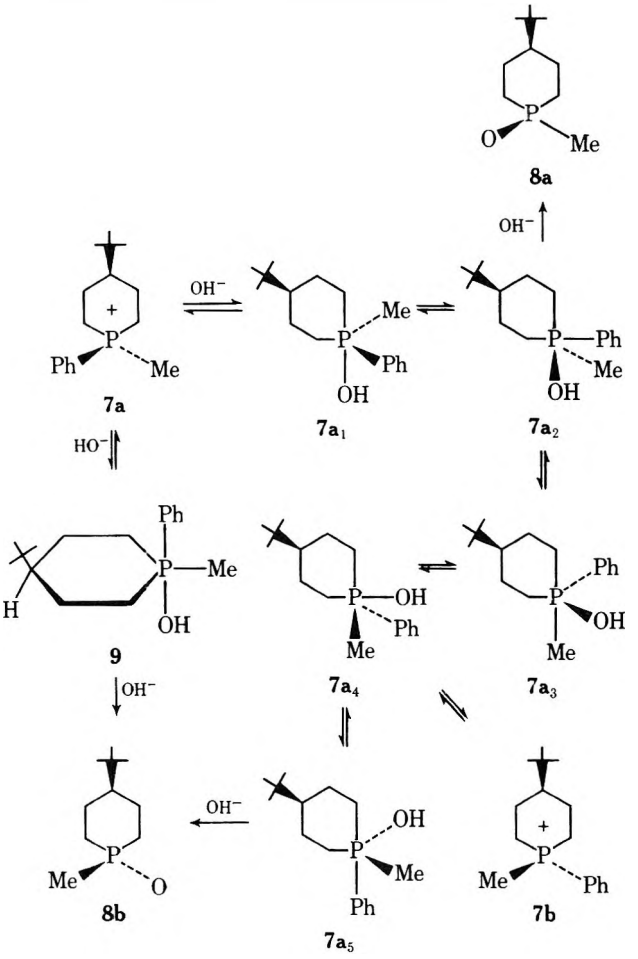
configuration. Some stereomutation of both pure phosphonium salts was observed in 1.00 N aqueous sodium hydroxide at reflux temperature for 24 h as shown in Table II. The relative rate of cleavage for **7b/7a** under these conditions is seen to be 4.5. Pseudo-first-order rate constants, determined at 75 °C in 1:1 EtOH–H_2O, also showed **7b** to be cleaved more rapidly than **7a**. The rate constants are 0.099 and 0.061 h^{-1} for the trans and cis isomers, respectively. The significance of these rate differences will be commented upon subsequently.

It will be noted from the information given in Table II that **7a** and 7b are not in complete thermodynamic equilibrium under reaction conditions, but each shows *some* stereomutation. This leads us to believe that three processes are occurring simultaneously as illustrated in Scheme I for the isomer **7a**. In addition to stereospecific processes **7a** → **8b**, **7a** → $\mathbf{7a_1}$ → $\mathbf{7a_2}$ → **8a** and **7b** → $\mathbf{7a_4}$ → $\mathbf{7a_5}$ → **8b**, a third competing process involving limited stereomutation at phosphorus must occur in order to explain **7a** ⇌ **7b**. This is represented in Scheme I for **7a** → **8a** + **8b** via the appropriate phosphorane intermediates. The low degree of inversion, which parallels closely the degree of isomerization of **7a** ⇌ **7b** (see Table II), may occur largely through stereomutation. Since neither phenyl nor

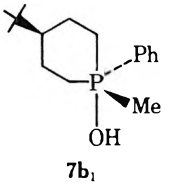
Table II. Isomerization of *cis*- and *trans*-4-*tert*-Butyl-1-methyl-1-phenylphosphorinanium Bromide (7a and 7b)

	7a	7b
% completion of cleavage	13.3	60.0
% of recovered material isomerized	16.4	22.7
Product composition		
8a/8b	3.65	0.22
% inversion	21.5	18.3

Scheme I. Pathways Available for Displacement of Phenyl from *cis*-4-*tert*-Butyl-1-methyl-1-phenylphosphorinanium Bromide (7a)

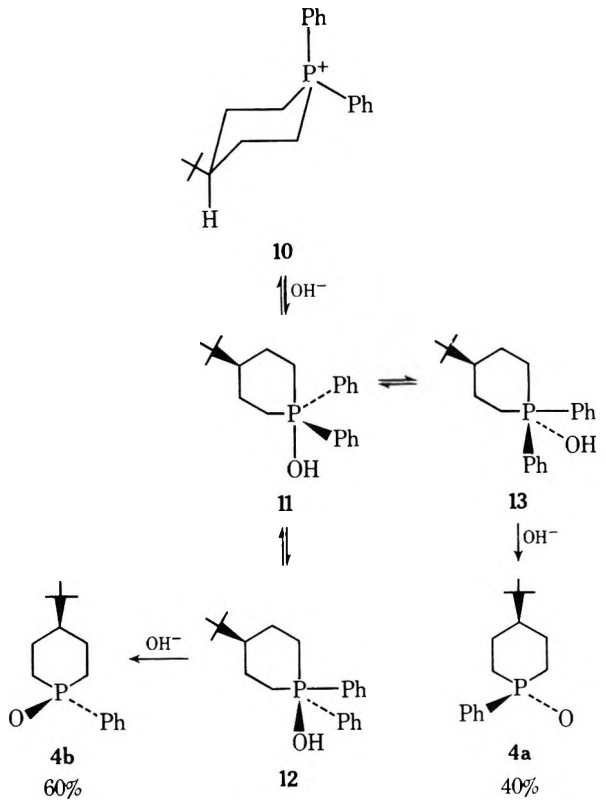


methyl is an especially good leaving group (low apicophilicity) there may be a limited tendency for inversion to occur via a phosphorane such as **9**. There would in effect be little relief of stereolectronic strain to balance ring strain introduced by diequatorial ring bonds. The more rapid decomposition of **7b** to product as compared to **7a** is probably associated with slower formation of $\mathbf{7a_1}$ in a preequilibrium step. $\mathbf{7a_1}$ exhibits sterically interacting *tert*-butyl and phenyl groups whereas $\mathbf{7b_1}$, derived from **7b**, does not.



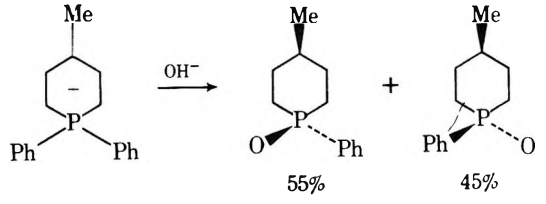
$\mathbf{7b_1}$

Cleavage of 4-*tert*-Butyl-1,1-diphenylphosphorinanium Bromide. 4-*tert*-Butyl-1,1-diphenylphosphorinanium bromide (**10**), by analogy with the previously discussed findings for **7**, probably cleaves primarily via the intermediate **11**.



The product ratio is probably the result of product-resembling transition states which could tend to favor formation of the more thermodynamically stable product **4b.**

The same argument would hold for results previously reported for the methyl analogue.[1]

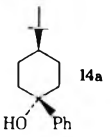
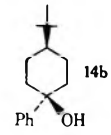


Syntheses. The key structure from which the 4-*tert*-butylphosphorinanes described in this paper are derived is **10.** This compound was obtained in good yield by cyclization of 1,5-dibromo-3-*tert*-butylpentane[9] with tetraphenyldiphosphine.[10] Base cleavage of **10** produced a mixture of *cis*- and *trans*-4-*tert*-butyl-1-phenylphosphorinane 1-oxides (**4b** and **4a,** respectively) which were cleanly separated by preparative thin layer chromatography. The oxides were stereospecifically reduced by use of phenylsilane[11] to the corresponding *cis*- and *trans*-4-*tert*-butyl-1-phenylphosphorinanes which were quaternized either by methyl bromide to yield isomerically pure **7b** and **7a,** respectively, or with benzyl bromide to furnish **3b** and **3a,** respectively.

Stereochemical Assignments. Several independent facts support the stereochemical assignments given to the isomeric oxides **4a** and **4b.** A comparison of the NMR spectra of the oxides with those of *cis*- and *trans*-4-*tert*-butyl-1-phenylcyclohexanols (**14**) of known configuration[12] show significant similarities as listed in Table III. The shapes of the doublet for **4b** and **14b** correlate nicely.

Use has been made of R_f values in assigning disposition of polar groups in six-membered rings.[13] Diastereomers with axial polar substituents are quite generally observed to have higher R_f numbers than those with equatorial polar substituents. Assignment of structure is consistent with R_f values; **4a** and **4b** exhibit values of 0.17 and 0.57, respectively, when

Table III. A Comparison of NMR Spectra for Diastereomeric Oxides (4) and *cis*- and *trans*-4-*tert*-Butyl-1-phenylcyclohexanol (14)

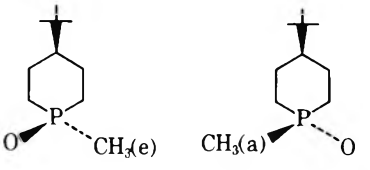
	δ, *tert*-butyl singlet, ppm	2,6 ring proton doublet
 **14a**	0.76	2.52
4a (mp 89–95 °C)	0.83	2.45
 **14b**	0.91	1.75
4b (mp 159.5–161 °C)	0.94	1.90

separated on silica gel with acetone. It might be noted that carbinol **14b** is eluted ahead of **14a** in column chromatographic (silica gel) separation.[12]

It has also been observed that for relatively simple phosphine oxides, those diastereomers containing alkyl or acyl groups in trans positions usually have higher melting points.[14] The melting points of **4a** and **4b** are respectively 88.5–95 and 159.5–161 °C, and thus in agreement with assignment of configuration. The melting range for **4a** is due to its extreme hygroscopicity.

Likewise, equilibration of either **4a** or **4b** with 6 N hydrochloric acid at 125 °C produces a mixture of 24.7% **4a** and 75.3% **4b.** Because of conformational considerations[15] **4b** would be predicted to be more thermodynamically stable than **4a.** Therefore, this finding is also in accordance with assignment of configuration.

Once the configurations of **4a** and **4b** have been established, those of the phosphines and phosphonium salts (derived from the phosphines) are also known since phenylsilane reduction of phosphine oxides[12] and quaternization of phosphines are known to take place with retention of configuration at phosphorus. However, the configurations of the diastereomeric 4-*tert*-butyl-1-methylphosphorinane 1-oxides (**8**) were uncertain because they were formed by nonstereospecific cleavage of salts **7a** and **7b.** Therefore, a mixture of oxides, **8,**



	8a	**8b**
δ_{CH_3}, ppm	1.46	1.51
J_{PCH_3}, Hz	13.2	12.7
$\delta_{t\text{-Bu}}$, ppm	0.90	0.90

composed of 28 and 72% of the two oxides of unknown configuration, was reduced with phenylsilane (retention).[11] The resulting phosphine mixture was quaternized with bromobenzene in the presence of nickel(II) bromide (retention)[16] to produce a mixture of **7a** and **7b** in the same ratio as starting oxides. Since the configurations of **7a** and **7b** are known (vide supra), and their NMR spectra determined, it was possible to assign configurations to the two oxides. This assignment is also consistent with the observation that the protons of an axial P–CH_3 exhibit smaller coupling with phosphorus than protons of an equatorial P–CH_3.[17] This phenomenon is also observed for **7a** and **7b** (J_{PCH_3} = 13.7 and 14.7 Hz, respectively).

Experimental Section

General. NMR spectra were determined with the use of a Perkin-Elmer R12-B spectrometer, and chemical shifts are reported in parts per million from Me_4Si as an internal standard. Analyses of mixtures of all *tert*-butylphosphorinane derivatives were by integration of *tert*-butyl proton signals except for mixtures of 4-*tert*-butyl-1-methylphosphorinane 1-oxides where integration of the P–CH_3 proton signal was employed. Composition of mixtures of phosphorinane oxides before and after distillation was essentially unchanged. In two cases hygroscopic oxides analyzed as fractional hydrates only because transfer operations by the analyst were not conducted in a drybox.

1,5-Dibromo-3-*tert*-butylpentane. This compound was synthesized by the method of Johnson from 4-*tert*-butylpyridine.[9] We have discovered that yields are improved significantly if the mixture of *N*-benzoyl-4-*tert*-butylpiperidine and bromine is allowed to remain at room temperature for a minimum of 2 days. We were unable to obtain satisfactory yields following the procedure of Sakurai.[18] A recent approach to the synthesis of this compound was published by Purdum and Berlin.[19]

4-*tert*-Butyl-1,1-diphenylphosphorinanium Bromide (10). Cyclization of 1,5-dibromo-3-*tert*-butylpentane with tetraphenyldiphosphine was accomplished by an adaptation[10b] of Markl's procedure:[10a] yield 43.4%; mp 316.5–318.5 °C dec; NMR (CF_3CO_2H) δ 0.95 (s, 9, *t*-Bu), 7.76 (m, 10, C_6H_5).

Anal. Calcd for $C_{21}H_{28}PBr$: C, 64.45; H, 7.21. Found: C, 64.18; H, 7.46.

***cis*- and *trans*-4-*tert*-Butyl-1-phenylphosphorinane 1-Oxide (4).** 4-*tert*-Butyl-1,1-diphenylphosphorinanium bromide (**10**, 6.00 g, 0.0153 mol) was refluxed with 75 ml of 1.00 N sodium hydroxide with magnetic stirring for 44 h. After cooling to room temperature 18 potassium hydroxide pellets were added and the resulting aqueous solution extracted with 6 × 50 mL of chloroform. The combined chloroform extracts were flash evaporated and the residue distilled to yield 3.19 g of the corresponding oxide (96.9%), bp 205° (0.15 mm) (Kugelrohr), mp 131–145 °C.

Anal. Calcd for $C_{15}H_{23}OP$: C, 71.68; H, 9.26. Found: C, 71.79; H, 9.51.

NMR integration of the separated *tert*-butyl signals showed the mixture to be composed of 40% **4a** and 60% **4b**.

Separation of *cis*- and *trans*-1-Phenyl-4-*tert*-butylphosphorinane 1-Oxide. Glass plates (8 × 8 × 0.25 in.) were coated to a thickness of 3 mm with silica gel G and heated overnight at 110 °C. An acetone solution of the mixture of isomers obtained above was then applied. The plate was placed in a chamber saturated with reagent grade acetone. The positions of the isomers were identified by development of the plate in an iodine chamber and the spots removed by scraping. The scrapings were extracted in a Soxhlet apparatus with methanol to yield a 90% total recovery of oxides by concentration and vacuum distillation of separate extracts, bp 180–200 °C (0.15 mm) (Kugelrohr).

***trans*-1-Phenyl-4-*tert*-butylphosphorinane 1-oxide (4a)** (very hygroscopic) showed the following properties: R_f 0.17; mp 88.5–95 °C; NMR ($CDCl_3$) δ 0.83 (s, 9, *t*-Bu), 7.58 (m, 5, C_6H_5) (isomerically pure).

Anal. Calcd for $C_{15}H_{23}OP \cdot \frac{1}{5}H_2O$: C, 70.94; H, 9.28. Found: C, 70.93; H, 9.05.

***cis*-4-*tert*-Butyl-1-phenylphosphorinane 1-oxide (4b)** gave R_f 0.57; mp 160–161 °C; NMR ($CDCl_3$) δ 0.96 (s, 9, *t*-Bu), 7.53 (m, 5, C_6H_5) (isomerically pure).

Anal. Calcd for $C_{15}H_{23}OP$: C, 71.97; H, 9.26. Found: C, 72.00; H, 9.41.

It is also possible to obtain the higher melting isomer (**4b**) in an isomerically pure state by fractional recrystallization of the cleavage mixture from carbon tetrachloride. The filtrates do not yield pure **4a**.

***trans*-4-*tert*-Butyl-1-phenylphosphorinane** was obtained in 100% yield by phenylsilane reduction of **4b** using the general procedure described elsewhere:[11] bp 110–120 °C (0.1 mm) (Kugelrohr); NMR ($CDCl_3$) δ 0.84 (s, 9, *t*-Bu), 7.04 (s, 5, C_6H_5).

***cis*-4-*tert*-Butyl-1-phenylphosphorinane** was obtained in 92% yield by phenylsilane reduction of **4a**:[11] bp 110–120 °C (0.1 mm) (Kugelrohr); NMR ($CDCl_3$) δ 0.72 (s, 9, *t*-Bu), 7.30 (s, 5, C_6H_5).

***trans*-1-Benzyl-4-*tert*-butyl-1-phenylphosphorinanium Bromide (3b).** The trans phosphine was quaternized with benzyl bromide in benzene[6c] to yield 95% of the bromide salt **3b**: mp 268–270 °C dec after recrystallization from ethanol–ethyl acetate; NMR ($CDCl_3$) δ 0.88 (s, 9, *t*-Bu), 4.50 (d, J_{PCH} = 14.7 Hz, 2, $CH_2C_6H_5$), 7.18 (s, 5, CC_6H_5), 7.77 (m, 5, PC_6H_5).

Anal. Calcd for $C_{22}H_{30}PBr$: C, 65.18; H, 7.46. Found: C, 65.20; H, 7.46.

***cis*-1-Benzyl-4-*tert*-butyl-1-phenylphosphorinanium Bromide (3a).** This compound was obtained as above in 87% yield from this cis phosphine: mp 224.5–226 °C dec (ethanol–ethyl acetate); NMR ($CDCl_3$) δ 0.74 (s, 9, *t*-Bu), 4.62 (d, J_{PCH_2} = 16 Hz, 2, $CH_2C_6H_5$), 7.17 (s, 5, CC_6H_5), 7.75 (m, 5, PC_6H_5).

Anal. Calcd for $C_{22}H_{30}PBr$: C, 65.18; H, 7.46. Found: C, 65.07; H, 7.51.

Base Cleavage of *cis*- and *trans*-1-Benzyl-4-*tert*-butylphosphorinanium Bromide. The pure diastereomers were cleaved under the same conditions as reported previously.[2b] Salt **3a** yielded a mixture of oxides consisting of 68% **4a** and 32% **4b**, while **3b** gave 23% **4a** and 77% **4b**. Whether or not the initial heterogeneous conditions for this reaction had an effect on the results was checked by performing the same reaction under homogeneous conditions by dissolving 0.15 g of salt in 16.4 mL of water and heating until the salt was dissolved. At that point 16.4 mL of 2 N sodium hydroxide was added and the solution refluxed for 9 h. The reaction mixture was worked up as previously described. **3a** yielded a mixture of oxides consisting of 34% **4b** and 66% **4a**, while **3b** yielded 21% **4a** and 79% **4b**. It was concluded that the difference in results between heterogeneous and homogeneous base cleavage were within experimental error.

Incomplete Base Cleavage of *cis*- and *trans*-1-Benzyl-4-*tert*-butyl-1-phenylphosphorinanium Bromide. Treatment of **3a** and **3b** under the above reaction conditions for 0.5 h and recovery of unreacted salt showed no epimerization of **3a** to **3b** or vice versa. For example, 0.15 g of **3a** after 0.5-h treatment was 51.4% cleaved, the balance of unreacted salt being unchanged configurationally. The product consisted of 32.1% **4b** and 67.9% **4a**.

***cis*- and *trans*-4-*tert*-Butyl-1-methyl-1-phenylphosphorinanium Bromide (7).** Enough methyl bromide was dissolved in 10 mL of benzene to produce a 2 M solution. 4-*tert*-Butyl-1-phenylphosphine (1.21 g, 5.18 mmol) (either cis or trans) was added and the mixture permitted to stand for 1 day. Crystals were removed by filtration, washed with benzene, and vacuum desiccated, yield 91%.

***cis*-4-*tert*-Butyl-1-methyl-1-phenylphosphorinanium Bromide (7b):** yield 91%; mp 234.5–237 °C dec (ethanol–ethyl acetate); NMR ($CDCl_3$) δ 0.83 (s, 9, *t*-Bu), 2.58 (d, J_{PCH_3} = 14.7 Hz, 3, PCH_3), 7.94 (m, 5, C_6H_5).

Anal. Calcd for $C_{16}H_{26}PBr$: C, 58.36; H, 7.96. Found: C, 58.61; H, 8.04.

***trans*-4-*tert*-Butyl-1-methyl-1-phenylphosphorinanium Bromide (7a):** yield 84%; mp 178–179 °C dec (ethanol–ethyl acetate); NMR ($CDCl_3$) δ 0.91 (s, 9, *t*-Bu), 2.50 (d, J_{PCH_3} = 13.7 Hz, 3, PCH_3), 7.96 (m, 5, C_6H_5).

Anal. Calcd for $C_{15}H_{26}PBr$: C, 58.36; H, 7.96. Found: C, 58.56; H, 8.09.

Base cleavage of *cis*- and *trans*-4-*tert*-Butyl-1-methyl-1-phenylphosphorinanium Bromide (7). The pure isomer (0.150 g, 0.455 mmol) was dissolved in 4.5 mL of 5.00 N sodium hydroxide and the mixture refluxed for 8 h. The reaction mixture was cooled and extracted with 2 × 10 mL of $CHCl_3$. The aqueous layer was saturated with 2 g of sodium chloride and extracted with 2 × 10 mL of $CHCl_3$. The extracts were combined and concentrated to 10 mL. This solution was centrifuged and the supernatant liquid evaporated to about 0.5 mL. Residual liquid was distilled: bp 155–175 °C (0.13 mm) (Kugelrohr); 80% yield. The trans salt (**7a**) gave a mixture of 25.1 and 74.9% while the cis salt (**7b**) yielded 38.1 and 41.9%.

Anal. Calcd for $C_{10}H_{21}OP \cdot \frac{1}{5}H_2O$: C, 62.60; H, 11.24. Found: C, 62.63; H, 11.14.

NMR of **8b:** δ 1.51 (d, J = 12.7 Hz, 3, PCH_3), 0.90 (s, 9, *t*-Bu). NMR of **8a:** δ 1.47 (d, J = 13.2 Hz, 3, PCH_3), 0.90 (s, 9, *t*-Bu).

Incomplete Base Cleavage of *cis*- and *trans*-4-*tert*-Butyl-1-methyl-1-phenylphosphorinanium Bromide (7). Each pure isomer was treated under conditions described immediately above, but for a period of 0.5 h with 1 N sodium hydroxide. The trans salt (**7b**) reacted to 60% completion. Recovered salt consisted of 22.7% **7a** and 77.3% **7b**. The product oxide was composed of 18.3% **8a** and 81.7% **8b**. The cis salt (**7a**) yielded 13.3% cleavage product consisting of 21.5% **8b** and 78.5% **8a** and showed 16.4% of the recovered salt to have been isomerized to **7b**. A slightly higher amount of inversion for both isomeric salts was observed for 5 N sodium hydroxide (vide supra).

Phenylation of a Mixture of *cis*- and *trans*-4-*tert*-Butyl-1-methylphosphorinane. The phosphine mixture obtained as described above (0.170 g, 0.903 mmol), 0.0987 g (0.452 mmol) of finely divided, well-dried nickel(II) bromide, and 0.19 ml of bromobenzene were heated together at 200 °C in a sealed ampule for 3 h.[16] The cooled reaction mixture was dissolved in hot water and the resulting mixture extracted with 4 × 10 mL of ether. The water layer was then extracted

with 6 × 10 mL of chloroform and an NMR spectrum ($CDCl_3$) obtained on the crystalline residue after evaporation of the solvent. The spectrum of the product corresponded to that of a mixture of **7a** and **7b** and showed the same ratio of salts (28% **7a**:72% **7b**) as the corresponding oxides from which they were derived (25% **8a**:75% **8b**) by phenylsilane reduction and phenylation.

Kinetic Procedure for Cleavage of 7a and 7b. Rate measurements were taken on a Cary 14 spectrophotometer and followed the disappearance of the salt at 2725 Å. To 2.50 mL of a 0.01 M solution of the salt in 1:1 (v:v) ethanol–water in each of 12 ampules was added 2.50 mL of 0.2 M sodium hydroxide in 1:1 (v:v) ethanol–water at 0 °C. Benzene (0.01 mL) was added to each ampule and the ampules sealed, shaken, and placed in a water bath at 75.0 ± 0.5 °C. At given time intervals the ampules were removed, cooled in ice, centrifuged to separate benzene, and opened and the contents decanted into a cuvette (leaving droplets of benzene in the ampule) and the solution scanned. A least-squares first-order plot was generated by the Finalal computer program. Molar extention coefficients at 2725 Å for **7a** and **7b** were 9.28×10^2 and 9.34×10^2, respectively.

Kinetic Procedure for Base Cleavage of 1-Benzyl-1-phenylphosphorinanium Bromide (15) and *cis*- and *trans*-1-Benzyl-4-*tert*-butyl-1-phenylphosphorinanium Bromide (3). The rate measurements were made at 273.5 nm using a Beckman Model DU ultraviolet spectrophotometer equipped with a thermostated cell compartment. A carbonate-free mixture of ethanol–water (1:1 by volume at 25 °C) was prepared and sodium hydroxide pellets were added under an inert atmosphere in making up a 1.28 N solution. Phosphonium salt was added under an inert atmosphere to this solution until a concentration of 9×10^{-4} M was obtained. The mixture was shaken and then inserted in the thermostated cell compartment. A 10-cm cell was used to follow the disappearance of unsubstituted salt at 307.5 nm. For **3a** and **3b** a 1-cm cell was employed. In order to determine wavelengths that would provide suitable absorption differences a comparison of the ultraviolet spectra of the salts and oxides was made. All the kinetic runs were followed for at least 4 half-lives, and A_∞ was measured after 10 half-lives. The rate constants were determined first graphically and then by computer.

Acknowledgments. The authors wish to thank Robert Freerks for the preparation of *cis*- and *trans*-4-*tert*-butyl-1-phenylcyclohexanol and the National Science Foundation for support of this work under Grant GP 38756X.

Registry No.—**3a**, 61332-79-4; **3b**, 61332-80-7; **4a**, 61332-81-8; **4b**, 61332-82-9; **7a**, 61332-83-0; **7b**, 61332-84-1; **8a**, 61332-71-6; **8b**, 61332-85-2; **10**, 61332-86-3; 1,5-dibromo-3-*tert*-butylpentene, 758-75-8; tetraphenyldiphosphine, 1101-41-3; benzyl bromide, 100-39-0; methyl bromide, 74-83-9; *trans*-4-*tert*-butyl-1-phenylphosphorinane, 61332-72-7; *cis*-4-*tert*-butyl-1-phenylphosphorinane, 61332-73-8.

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Reduction–Elimination of Cyclic Phosphate Derivatives as a Route to Alkenes

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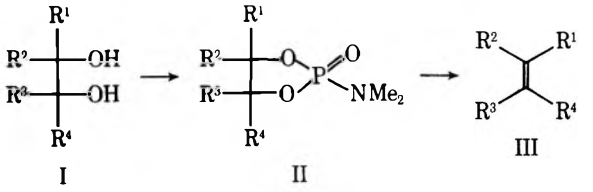
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Received September 16, 1976

The conversion of 1,2-diols to alkenes has been effected through reduction of the cyclic ethyl phosphate or *N,N*-dimethylamidophosphate derivatives with lithium in ammonia or titanium metal in THF. Accordingly, *cis*-1,2-dimethylcyclodecane-1,2-diol was converted to a 9:1 mixture of *cis*- and *trans*-1,2-dimethylcyclodecene in 81% yield through its dimethylamidophosphate derivative whereas the ethyl phosphate derivative afforded a 6.7:1 mixture of these products in 57% yield. *trans*-1,2-Dimethylcyclodecane-1,2-diol gave a 6:1 mixture of *trans*- and *cis*-1,2-dimethylcyclodecene in 24% yield via the amidophosphate and a 4.3:1 mixture of these isomers in 55% yield via the ethyl phosphate. The analogous cyclododecanediols were converted to the 1,2-dimethylcyclododecenes in 53–86% yield with syn-elimination preferences of 9:1–13.3:1. The 2,3-decanediols afforded the 2-decenes in 75% yield. The erythro diol gave 1.4:1 (phosphate) and 1.9:1 (amidophosphate) mixtures of *cis*- and *trans*-2-decenes. The threo isomer afforded a 6.7:1 mixture of trans and cis isomers from both cyclic phosphate derivatives.

We recently described a stereoselective method for the conversion of vicinal diols to alkenes via reduction–elimination of cyclic phosphoric amide derivatives with dissolving metals (I → II → III).[1] We have now completed studies which further delineate the scope and stereochemistry of the sequence and show that, in some cases, cyclic phosphoric esters offer ad-

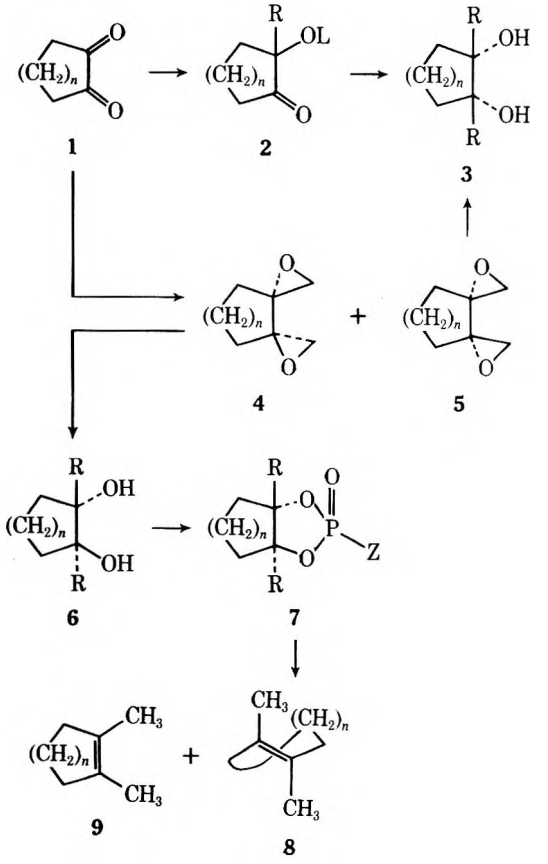
vantages over amides. We have also examined alternative reducing agents.



I II III

Our initial impetus for studying vicinal glycol eliminations arose from a need for 1,2-disubstituted *trans*-cyclodecenes and cyclododecenes as synthetic intermediates. Sharpless and Flood found that vicinal glycols could be directly deoxygenated with potassium hexachlorotungstate.[2] The reaction proceeds by syn elimination but isomerization of the starting glycol gives rise to stereochemically impure olefins. We hoped to find alternative methods of greater stereoselectivity which would be applicable to *ditertiary* glycols. For the systems of interest to us, the phosphoric amide reduction–elimination reaction (II → III)[1] gave slightly better results than the hexachlorotungstate deoxygenation.[2] In either event, since both schemes involve preferential syn elimination and since we wished to prepare trans cycloalkenes, our main problem was to find an efficient route to *trans*-1,2-dialkylcycloalkane-1,2-diols. The addition of organometallic reagents to 1,2-cyclodecanedione (**1a**) and 1,2-cyclododecanedione (**1b**) affords only the cis glycols **3a** and **3b** under a variety of reaction conditions.[2,3] We examined Grignard reagents and organolithium reagents in ether, hexane, and hexamethylphosphoric amide as solvents at temperatures ranging from −80 to 30 °C and found no indication of trans products. Presumably, the intermediate mono adducts **2** (L = MgX or Li) exist in a chelated form which favors approach leading to the cis isomer **3**.[4]

Chart I[a]



[a] **a** series, n = 6; **b** series, n = 8

In support of this hypothesis we found that derivatives of the intermediate mono adduct in which chelation could not occur, such as the trimethylsilyl ether **2** (L = $SiMe_3$), gave mixtures of trans and cis glycols **3** and **6**. Thus keto ether **2b** (L = $SiMe_3$, R = 4-pentenyl) upon treatment with 4-pentenyllithium in ether–hexane followed by removal of the silyl group in methanolic potassium carbonate afforded a 3:2 mixture of the trans and cis glycols in 22% yield. Unfortunately, the reaction proceeded with significant recovery of starting ketol **2b** (L = H, R = 4-pentenyl) and attempts to improve the yield were to no avail. The use of *tert*-butyldimethylsilyl[5] and allyl protecting groups proved even less satisfactory. Evidently, enolzation seriously interferes with addition in these cases.

A more satisfactory route to the trans diols **6** evolved from our discovery that dimethylsulfonium methylide[6] adds to diones **1a** and **1b** to yield mainly the trans diepoxides **4**. Dione **1a** gave a 7:3 ratio of trans and cis diepoxides **4a** and **5a** in over 70% yield while dione **1b** afforded a 5:3 ratio of trans and cis isomers **4b** and **5b** in comparable yield. These stereoisomers could be readily separated by chromatography. Reduction of each with lithium aluminum hydride afforded the known *trans*- and *cis*-cyclodecanediols (**4a, 5a**) and cyclododecanediols (**4b, 5b**) in high yield, thereby confirming the stereochemical assignments.[2,3] Preliminary experiments with the cyclododecane *trans*-diepoxide **4b** indicated that organolithium reagents smoothly attack the epoxides to give *trans*-1,2-dialkyl-1,2-cyclododecanediols. For example, the bisbutenyl diol **6b** (R = 3-butenyl) was obtained as a crystalline solid in 75–80% yield upon treatment of epoxide **4b** with allyllithium.

The next phase of our studies involved conversion of the trans diols **6** to the cyclic phosphoramides **7** (Z = dimethylamino) and subsequent reduction–elimination along the lines previously reported for the cis diols **3**.[1] To that end, treatment of *trans*-1,2-dimethyl-1,2-cyclodecanediol **6a** (R = CH_3) with methyllithium followed by *N,N*-dimethylamidophosphorodichloridate[7] in ether–tetrahydrofuran–hexamethylphosphoramide afforded the cyclic phosphoramide **7a** (R = CH_3; Z = dimethylamino). This reaction was significantly slower than the analogous conversion of the cis glycol **3a** (R = CH_3) and mixtures of products containing appreciable hydroxylic material were isolated in only moderate yield even after prolonged reaction time. Treatment of these crude mixtures with lithium in ammonia afforded *trans*- and *cis*-1,2-dimethycyclodecene **8a** (R = CH_3) and **9a** (R = CH_3) in an 86:14 ratio.

trans-1,2-Dimethyl-1,2-cyclododecanediol **6b** (R = CH_3) also reacted less efficiently than its cis counterpart **3b** (R = CH_3) with *N,N*-dimethylamidophosphorodichloridate. The resulting crude cyclic phosphoramide **7b** (R = CH_3, Z = dimethylamino) gave a 92:8 mixture of *trans*- and *cis*-1,2-dimethylcyclododecenes **8b** (R = CH_3) and **9b** (R = CH_3) upon reduction with lithium in ammonia. The butenyl homologue of diol **6b** (R = 3-butenyl) gave only a trace of cyclic phosphoramide **7b** (R = 3-butenyl, Z = dimethylamino) even after prolonged reaction time. The main products consisted of polyenes and acidic materials.

In view of the problems encountered in forming the cyclic phosphoramides **7** (Z = dimethylamino) we decided to examine the cyclic phosphates (Z = OEt). This decision was prompted by Ireland's finding that tertiary alcohols react more readily with diethyl phosphorochloridate than with the bis(dimethylamino) analogue.[8] The ditertiary diols **6a** and **6b** appear to follow a similar trend in their reaction with ethyl phosphorodichloridate to give the cyclic phosphates **7a** and **7b** (R = CH_3; Z = OEt). In both cases reaction times were shorter and the products contained fewer impurities. Reduction with lithium in ammonia afforded an 81:19 mixture of *trans*- and *cis*-1,2-dimethylcyclodecenes **8a** (R = CH_3) and

Table I. Net Conversion of Diols to Olefins via Reduction–Elimination of Cyclic Phosphate Derivatives Using Lithium/Ammonia

Registry no.	Diol	Reagent	Products	Yield, %[a]	Syn/anti
56491-42-0	**3a** (R = CH_3)	Cl_2PONMe_2	**9a** (90%), **8a** (10%)	81	9.0
	3a (R = CH_3)	Cl_2PO_2Et	**9a** (87%), **8a** (13%)	57	6.7
61376-38-3	**6a** (R = CH_3)	Cl_2PONMe_2	**9a** (14%), **8a** (86%)	24	6.1
	6a (R = CH_3)	Cl_2PO_2Et	**9a** (19%), **8a** (81%)	55	4.3
56499-08-2	**3b** (R = CH_3)	Cl_2PONMe_2	**9b** (90%), **8b** (10%)	86	9.0
	3b (R = CH_3)	Cl_2PO_2Et	**9b** (93%), **8b** (7%)	76	13.3
61376-39-4	**6b** (R = CH_3)	Cl_2PONMe_2	**9b** (8%), **8b** (92%)	53	11.5
	6b (R = CH_3)	Cl_2PO_2Et	**9b** (8%), **8b** (92%)	66	11.5
	n-C_7H_{15}CH(OH) | CH_3CH(OH)		n-C_7H_{15}CH=CHCH_3		
19721-82-5	Erythro (**10**)	Cl_2PONMe_2	Cis (66%), trans (34%)	40,[a] 76[b]	1.9
	Erythro (**10**)	Cl_2PO_2Et	Cis (58%), trans (42%)	23[b]	1.4
19721-81-4	Threo (**11**)	Cl_2PONMe_2	Cis (13%), trans (87%)	42,[a] 76[b]	6.7
	Threo (**11**)	Cl_2PO_2Et	Cis (13%), trans (87%)	25[b]	6.7

[a] Isolated yield based on diol. [b] Yield based on analysis by gas chromatography.

Table II. Reduction–Elimination of the Phosphoramide Derived from Diol 3b (R = CH_3)

Reagent	Yield, %[b]	Syn/anti
Li, NH_3[a]	98	9.0
Na–naphthalene[a]	73	24
Na–xylene[a]	61	>99
$TiCl_4$–Mg(Hg)	77	7.3
$TiCl_3$–K	92	7.3
Zn–HOAc	0[c]	
Al(Hg)	0[c]	
$Cr(ClO_4)_2$–$(CH_2NH_2)_2$	0[c]	

[a] See ref 1. [b] Isolated yield. [c] Recovered starting material.

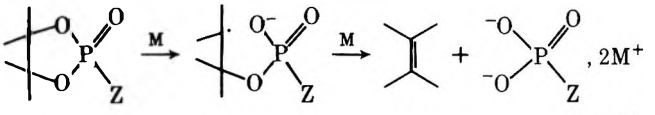
9a (R = CH_3) and a 92:8 mixture of *trans*- and *cis*-1,2-dimethylcyclododecenes **8b** (R = CH_3) and **9b** (R = CH_3).

Table I summarizes conversions of vicinal diols to alkenes via reduction–elimination of cyclic phosphoric acid amide or ester derivatives. With cyclic ditertiary trans diols **6a** and **6b** (R = CH_3) the ester derivative gives a higher overall yield than the amide with comparable stereoselectivity. The corresponding cis diols **3a** and **3b** (R = CH_3) are most efficiently converted to olefins through their cyclic phosphoramides. Both disecondary vicinal acyclic diols, *erythro*- and *threo*-2,3-decanediol,[9] behave like the cyclic cis diols. These trends suggest that the phosphoramides are more efficiently reduced than the phosphoric esters, a fact noted by Ireland[8] in his work on alcohol phosphate and phosphoramidate hydrogenolysis, but in some cases the phosphoric esters are more readily formed.

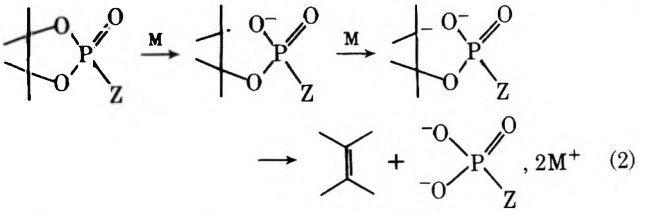
We conducted a brief survey of other reducing agents which might convert cyclic phosphate derivatives to alkenes. For these studies, summarized in Table II, we used the crystalline *N,N*-dimethyl phosphoramidate derived from *cis*-1,2-dimethylcyclododecane-1,2-diol (**3b**).[1] The titanium reagents of Corey[10] and McMurry[11] effected the reduction–elimination about as efficiently as alkali metal reagents whereas less active reducing agents such as zinc,[12] aluminum amalgam,[13] and chromous perchlorate[14] were ineffective.

In conclusion, the two-step conversion of diols to olefins via cyclic phosphates or phosphoramidates can be effected with reasonable efficiency and with a relatively high degree of stereoselectivity. The method of Sharpless and Flood[2] using potassium hexachlorotungstate accomplishes the same overall conversion in one step in comparable yield. In some cases (the *trans*-1,2-cyclodecanediol **6a**, for example) we have found that the two-step method proceeds more stereoselectively. Clearly, the preference for one or the other method will depend upon diol structure and availability of reagents.

As for mechanism, our findings suggest a two-step process for the reduction–elimination. Two possibilities are shown below. In each case rotation about the carbon–carbon bond



(1)



(2)

of the intermediate radical anion (or dianion) leads to the product of net anti elimination. Thus the syn–anti ratio will depend upon the relative timing of the first and second bond breaking steps and, possibly, the relative transition state stability for phoshate expulsion in a carbanion-type elimination reaction.

Experimental Section[15]

***cis*-1,2-Dimethylcyclodecane-1,2-diol (3a,R = Me). A. From 1,2-Cyclodecanedione (1a).** To a solution of 3.73 g of 1,2-cyclodecanedione (**1a**)[16] in 100 mL of ether at 0 °C was added 80 mL of 2.2 M ethereal methyllithium. The mixture was stirred at room temperature for 23 h, cooled to 0 °C, and 80 mL of water was carefully added. The product, isolated by extraction with ethyl acetate, showed appreciable carbonyl absorption in its infrared spectrum so the above described methyllithium addition was repeated. The product thus obtained was distilled at 115 °C (0.02 mm) to give 3.75 g of crystalline diol **3a** (R = Me), mp 44–45 °C. Recrystallization from hexane afforded material of mp 55–56 °C; IR (KBr) 3300, 2840, 1430, 1350, 1075 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 1.17 (CH_3), 1.47 (m, CH_2), 2.86 ppm (OH).

Anal. Calcd for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08. Found: C, 71.85; H, 12.15.

B. From Diepoxide 5a. A solution of 0.58 g of diepoxide **5a** in 30 mL of ether was stirred with 0.27 g of lithium aluminum hydride at room temperature for 2 h. The mixture was treated successively with 0.3 mL of water, 0.3 mL of 15% aqueous sodium hydroxide, and 0.9 mL of water and stirring was continued to granulate the resulting inorganic salts. Filtration and removal of the solvent afforded 0.62 g of diol **3a** (R = Me).

Additional confirmation of the cis stereochemistry was secured by the method of Flood[2] which involves heating the diol with dimeth-

ylformamide dimethyl acetal to obtain the cyclic formamide acetal derivative. The substance obtained from diol **3a** (R = Me) showed two equal peaks for the acetal proton in its NMR spectrum reflecting the cis, trans isomer population at this center relative to the cyclododecane substituents.

***cis*-1,2-Dimethylcyclododecane-1,2-diol (3b, R = Me). A. From 1,2-Cyclododecanedione (1b).** To a solution of 5 g of 1,2-cyclododecanedione (**1b**)[17] in 150 mL of ether at −78 °C was added 35 mL of 2.1 M ethereal methyllithium. The mixture was stirred overnight and cooled to 0 °C, and water was carefully added. Extraction with ethyl acetate afforded 6 g of crude material which was recrystallized from hexane to give 4.2 g (72%) of diol **3b** (R = Me): mp 94–95 °C (lit.[2] mp 92–95 °C); IR (KBr) 3400, 2950, 2870, 1480, 1450, 1380, 1110, 1100 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 1.15 (CH_3), 1.38 (m, CH_2), 2.25 ppm (OH).

B. From Diepoxide 5b. A solution of 1.52 g of diepoxide **5b** in 80 mL of ether was reduced as described above for epoxide **5a** to give 1.43 g of diol **3b** (R = Me).

***cis*- and *trans*-Dimethylenecyclodecane Bisepoxide (4a, 5a).**[18] A solution of dimsylsodium was prepared from 5.2 g of 57% sodium hydride in mineral oil (which was freed of the oil by three successive washings with hexane) and 50 mL of dimethyl sulfoxide.[6] Tetrahydrofuran (50 mL) was added, the solution was cooled to −10 °C, and 25 g of trimethylsulfonium iodide in 120 mL of Me_2SO was added, followed by 5.1 g of 1,2-cyclodecanedione (**1a**)[16] in 5 mL of THF. The mixture was stirred overnight, water was added, and the product was isolated by ether extraction to give 3.9 g of oil. Separation of the cis and trans diepoxides **5a** and **4a** was achieved by chromatography on silica gel. Final purification was effected by high-pressure liquid chromatography on Porasil using 5% ethyl acetate in hexane as the eluent. In this way 1.6 g of the trans diepoxide **4a** and 0.7 g of the cis isomer **5a** were obtained.

4a: bp 70 °C (0.1 mm); IR (film) 3060, 3000, 2940, 2880, 1480, 1425, 910 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 1.58 (m, CH_2), 2.73 ppm (ABq, $-CH_2O-$).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.2; H, 10.6.

5a: bp 70 °C (0.1 mm); IR (film) 3060, 2940, 2880, 1480, 1425 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 1.60 (m, CH_2), 2.72 ppm (ABq, $-CH_2O-$).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.2; H, 10.6.

***cis*- and *trans*-1,2-Dimethylenecyclododecane Bisepoxide (4b, 5b).**[18] The procedure described above for **4a** and **5a** was followed using 10.2 g of dione **1b**[17] and 42.6 g of trimethylsulfonium iodide. The crude product (11.1 g) was chromatographed on silica gel to give 5.6 g of trans isomer **4b** and 3.6 g of cis isomer **5b.**

4b: bp 85 °C (0.1 mm); IR (film) 3060, 2950, 2770, 1470, 995, 915 cm^{-1}; δ_{Me_4Si} (CCl_4) 1.40 (m, CH_2), 2.53 ppm (ABq, $-CH_2O-$).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 75.30; H, 10.84.

5b: mp 65.5–66.5 °C (hexane); IR (KBr) 3070, 3000, 2950, 2870, 1470, 970, 900 cm^{-1}; δ_{Me_4Si} (CCl_4) 1.38 (m, CH_2), 2.48 ppm (ABq, $-CH_2O-$).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 75.02; H, 10.96.

***trans*-1,2-Dimethylcyclodecane-1,2-diol (6a, R = Me).** The procedure described for the reduction of diepoxide **5a** to diol **3a** (R = Me) was employed using 1.4 g of diepoxide **4a** and 0.64 g of lithium aluminum hydride. The product thus obtained (1.47 g) was recrystallized from hexane to give 1.0 g of trans diol **6a** (R = Me): mp 84–85.5 °C; IR (KBr) 3440, 2990, 2940, 2850, 1480, 1370, 1340, 1100, 1080, 1060, 930 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 1.23 (CH_3), 1.8–1.1 (m, CH_2), 2.48 ppm (OH).

Anal. Calcd for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08. Found: C, 71.9; H, 12.0.

The cyclic formamide acetal prepared by the method of Flood[2] showed a single peak for the acetal proton in its NMR spectrum.

***trans*-1,2-Dimethylcyclododecane-1,2-diol (6b, R = Me).** The procedure described for the reduction of diepoxide **5a** was followed using 0.5 g of diepoxide **4b** and 0.23 g of lithium aluminum hydride. The product thus obtained (0.53 g), an oil, was identical with an authentic sample:[2,3] IR (film) 3450, 3000, 2950, 2870, 1470, 1370, 1100 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 1.23 (CH_3), 1.37 (m, CH_2), 2.00 ppm (OH).

***trans*-1,2-Bis(3-butenyl)cyclododecane-1,2-diol (6b, R = 3-Butenyl).** A 400-mL portion of a solution of allyllithium, prepared from 25.2 g of tetraallyltin in 550 mL of ether and 150 mL of 2.3 M phenyllithium in ether–benzene according to the procedure of Seyferth and Weiner,[19] was added to 10.3 g of diepoxide **4b** in 100 mL of ether. The mixture was stirred at room temperature overnight, then it was cooled to 0 °C and water was added. Extraction with ether afforded 30 g of oily solid which was recrystallized from hexane to give 11.9 g (84%) of diol **6b** (R = 3-butenyl): mp 112–113 °C; IR (KBr) 3460, 2950, 2870, 1640, 900 cm^{-1}; δ_{Me_4Si} ($CDCl_3$) 1.2–2.3 (m, CH_2, OH), 4.8–5.2 (m, $CH{=}CH_2$), 5.5–6.2 ppm (m, $CH{=}CH_2$).

Anal. Calcd for $C_{20}H_{36}O_2$: C, 77.87; H, 11.76. Found: C, 77.83; H, 11.82.

General Procedure for the Preparation of Cyclic *N,N*-Dimethylphosphoramidates. A solution of 1 mmol of diol in 10 mL of THF was cooled to 0 °C and 1.1 mL of 2.1 M ethereal *n*-butyllithium was added with stirring. After a few minutes 5 mL of hexamethylphosphoramide (HMPA) was added followed by 0.4 g (2.5 mmol) of *N*,N-dimethylamidophosphorodichloridate[7] in 5 mL of THF. The solution was stirred overnight (or longer with less reactive diols), water was added, and the cyclic phosphoramidate was isolated by ether extraction. The cyclic phosphoramidates derived from diols **3a** (R = Me), **6a** (R = Me), **6b** (R = Me), **10,** and **11** were oils and were used without purification. The phosphoramidate, mp 131–138 °C, derived from diol **3b** (R = Me), has been described previously.[1]

General Procedure for the Preparation of Cyclic Ethyl Phosphates. The procedure described above for the phosphoramidates was followed using ethyl phosphorodichloridate[20] save for the quantity of HMPA which was 0.5 mL. The phosphates prepared from diols **3a** (R = Me), **3b** (R = Me), **6a** (R = Me), **6b** (R = Me), **10,** and **11** were oils and were used without purification.

General Procedure for the Reduction–Elimination of Cyclic Phosphoramidates and Phosphates Using Lithium in Ammonia. A solution of ca. 1 mmol of the crude phosphoramidate or phosphate in 2–3 mL of ether was added to a solution of 40 mg (5.7 g-atoms) of lithium wire in 50 mL of liquid ammonia with stirring. After 15–30 min solid ammonium chloride was added to discharge the blue color, the ammonia was allowed to evaporate, and the product was isolated by ether extraction. The results of these reductions are summarized in Table I.

Analyses of Olefin Mixtures. The 1,2-dimethylcyclodecenes (**8a, 9a**) could not be separated by gas or liquid chromatography so the ratios were estimated from the intensity of the vinylic CH_3 signals in their NMR spectra.

An enriched sample (87%) of the *Z* isomer **9a** showed the following properties: IR (film) 3010, 2940, 2870, 1475, 1380 cm^{-1}; δ_{Me_4Si} (CCl_4) 1.37 (m, CH_2), 1.57 (87%) and 1.80 (13%) (vinylic CH_3 of *Z* and *E* isomers **9a** and **8a,** respectively), 2.23 ppm (allyl CH_2). These properties compared favorably with those of an authentic sample.[3,21]

Anal. Calcd for $C_{12}H_{22}$: C, 86.67; H, 13.33. Found: C, 86.6; H, 13.65.

An enriched sample (81%) of the *E* isomer **8a** showed the following properties: IR (film) 2940, 2870, 1460, 1375 cm^{-1}; δ_{Me_4Si} (CCl_4) 1.1–1.7 (m, CH_2), 1.57 (19%) and 1.80 (81%) (vinylic CH_3 of *Z* and *E* isomers **9a** and **8a**), 2.1–2.9 ppm (m, allylic CH_2).

Anal. Calcd for $C_{12}H_{22}$: C, 86.67; H, 13.33. Found: C, 86.5; H, 13.55.

The 1,2-dimethylcyclododecenes (**8b, 9b**) were analyzed and separated by gas chromatography on silver nitrate impregnated Carbowax 20M. The pure isomers were compared with authentic samples using IR, NMR, and GLC.[2,3]

The 2-decenes were analyzed by gas chromatography on silver nitrate impregnated 1,4-butanediol. The pure isomers were compared with authentic samples using IR, NMR, and GLC.[22] Dodecane was used as the internal standard for estimation of yields by gas chromatography (see Table I).

Reduction Elimination of the Cyclic Phosphoramidate Derived from *cis*-1,2-Dimethylcyclododecane-1,2-diol (3b, R = Me). A. Using Titanium Tetrachloride–Magnesium Amalgam. The procedure of Corey[10] was used to prepare the reagent from 0.044 g of mercuric chloride, 0.144 g of magnesium, and 0.33 mL of titanium tetrachloride. To this reagent in 5 mL of THF at room temperature was added a solution of 100 mg of phosphoramidate[1] in 5 mL of THF. The mixture was heated at reflux for 3.5 h, it was then cooled to 0 °C, and 0.5 mL of saturated aqueous potassium carbonate was added. After stirring for 0.25 h the mixture was filtered through Celite and extracted with ether to give 55 mg of an oil which was further purified by chromatography on silica gel. The resulting 47 mg (77%) of material was found to be an 88:12 mixture of (*Z*)- and (*E*)-1,2-dimethycyclododecene (**9b and 8b**) by gas chromatographic analysis and spectra comparison with authentic samples.[2,3]

B. Using Potassium–Titanium Trichloride. The procedure of McMurry was employed for the reduction of titanium trichloride.[11] To a suspension of 0.29 g of titanium trichloride in 10 mL of THF was added 0.24 g of potassium slices. The mixture was stirred at reflux for 0.5 h, 100 mg of phosphoramidate in 2–3 mL of THF was added, and reflux was maintained overnight. The mixture was cooled to 0 °C, ethanol was added, and the whole was filtered through Celite. Removal of solvent and chromatography on silica gel gave 56 mg (92%)

of an 88:12 mixture of (*Z*)- and (*E*)-1,2-dimethylcyclododecenes (**9b** and **8b**).

Acknowledgments. We are indebted to the National Science Foundation for support of this work through a research grant (MPS 75-07777). We thank Professor R. E. Ireland for unpublished procedures and advice on the preparation of phosphoramidates.

Registry No.—**1a**, 96-01-5; **1b**, 3008-41-1; **4a**, 61349-14-2; **4b**, 61349-15-3; **5a**, 61376-40-7; **5b**, 61376-41-8; **6b** (R = 3-butenyl), 61349-16-4; **7a** (R = Me; Z = NMe_2), 61376-42-9; **7a** (R = Me; Z = OEt), 61349-17-5; **7b** (R = Me; Z = NMe_2), 61376-43-0; **7b** (R = Me; Z = OEt), 61349-18-6; **7b** (R = 3-butenyl; Z = NMe_2), 61349-19-7; **8a**, 61349-20-0; **9a**, 14113-67-8.

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The Structure in Solution of the Halogen Adducts of Phosphines and Arsines

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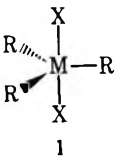
Received October 29, 1976

1-Methylphosphorinane (**4**) and 1-methylarsenane (**6**) form 1:1 and 1:2 adducts with Br_2 and I_2, but only 1:1 adducts with Cl_2, as determined by conductometric titrations and by isolation. The 1-phenyl compounds (**5**, **7**) exhibit the same behavior. These materials can have either a trigonal bipyramidal structure with As or P between the two halogen atoms, or a simple molecular complex structure with As or P at the end of the halogens. We have been able to distinguish these structural types by the conductance of the adducts in solution and by the *R* value analysis (vicinal coupling constants) of deuterated derivatives. The 1:1 arsine adducts with Cl_2 and Br_2 are nonconducting trigonal bipyramids. All the 1:1 phosphine adducts, the 1:1 adducts of the arsines with I_2, and all the 1:2 adducts of both the phosphines and the arsines are highly conducting molecular complexes with presumably little distortion in the shape of the ring.

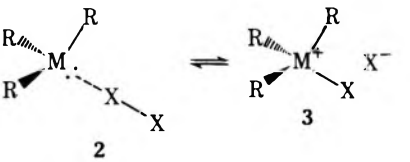
The halogen complexes of trivalent phosphines and arsines have been of interest not only because of their structural complexities but also because of their use in synthesis, as in the Wiley reaction for the preparation of alkyl halides[2a] and in the cleavage of the C–O bond of acids, acid anhydrides, esters, and lactones to form a C–Br bond under very mild conditions.[2b] A number of different structural methods have been applied to these compounds,[3] but hard structural data are particularly lacking in the solution phase. Previous work[3] has demonstrated that both 1:1 and 1:2 adducts are possible (eq 1). For the 1:1 adducts, there are at least two general

$$R_3M \xrightarrow{X_2} R_3MX_2 \xrightarrow{X_2} R_3MX_4 \qquad (1)$$

structural classes possible. The central atom M can be located between the two halogen atoms X, so that M is pentacoordinate and the overall structure is a trigonal bipyramid (TB) (**1**). Alternatively, the atom M can be at the end of the two halogens, in a simple molecular complex (MC), which can exist in hydrogen-bond-like (**2**) or ionic (**3**) forms. The problem,



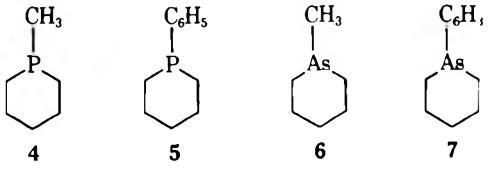
1



2 **3**

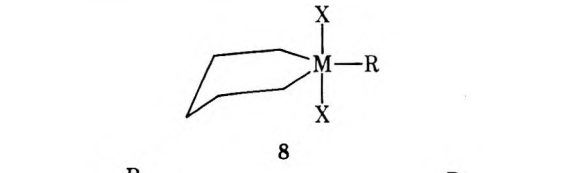
therefore, is to determine which structure (**1**–**3**) exists in solution for each of the adducts of trivalent phosphorus or arsenic with chlorine, bromine, or iodine. We hope to extend the results to antimony and fluorine by induction.

Although distinguishing the trigonal bipyramid and molecular complex would be fairly straightforward by x-ray crystallography, the problem is more difficult in solution.[3] A critical difference between the two structural types is the R–M–R valence angle, which in the molecular complex is little changed from the parent base but in the trigonal bipyramid is enlarged to about 120°. When the R groups on M take the form of a six-membered ring, the enlarged angle in the trigonal bipyramid brings about a significant flattening of the ring. On the other hand, the molecular complex would exhibit little ring deformation with respect to the shape of the parent base. Thus, to provide a general solution to the problem of the structure of these adducts in solution, we have chosen to study the conformations of the adducts of 1-methyl- and 1-phenylphosphorinane and -arsenane (**4**–**7**) with the halogens

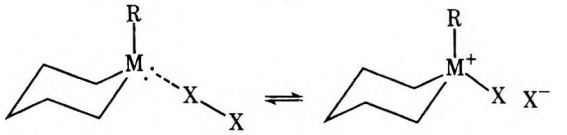


4 **5** **6** **7**

(Cl_2, Br_2, I_2). These rings should be considerably flattened in the trigonal bipyramid (**8**) and essentially undistorted in the molecular complex (**9**, **10**).

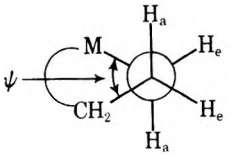


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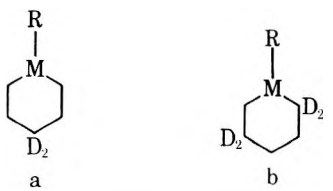
9 **10**

NMR coupling constants provide one means of determining the nature of ring deformations in solution.[4] We have previously used such an approach to study the structures of the complexes of sulfides and selenides with halogens in solution.[5] Any $-CH_2CH_2-$ fragment in a six-membered ring can yield two averaged vicinal coupling constants, $J_{trans}[\frac{1}{2}(J_{aa} + J_{ee})]$ and $J_{cis}[\frac{1}{2}(J_{ae} + J_{ea})]$, whose ratio R gives the internal torsional angle of the ring directly from eq 2.[4] Therefore, to de-



$$\cos\psi = \left(\frac{3}{2 + 4R}\right)^{1/2} \qquad (2)$$

termine the shape of the phosphorinane or arsenane ring, suitable bismethylene fragments must be isolated and their NMR spectra analyzed. Thus the two deuterated forms a and b suffice to provide a solution to the conformational problem,



provided that the four-spin spectra can be analyzed. The torsional angles of a molecular complex (**9** or **10**) should be close to that of the parent, uncomplexed ring for both the α,β (a) and the β,γ (b) segments. There are considerable distortions, however, in the trigonal bipyramid (**8**), with the α,β segment considerably flattened (Ψ decreased).[5]

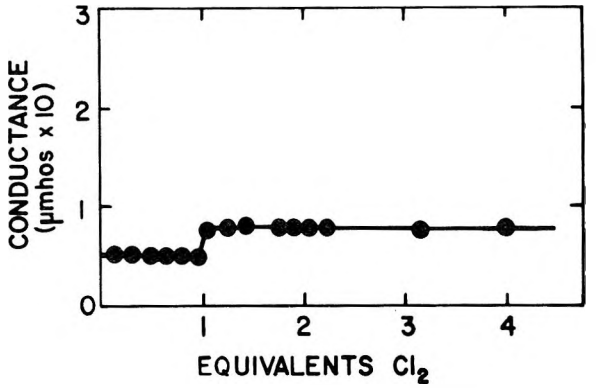


Figure 1. The conductance of 1-methylarsenane (**6**) in $ClCH_2CH_2Cl$ at 25 °C as a function of added equivalents of Cl_2 in $ClCH_2CH_2Cl$.

Following the method of Harris and co-workers,[6] we have also examined the conductance of solutions of these adducts in the same or a similar solvent as used for our NMR studies, in order to distinguish the ionized (**10**) and un-ionized (**9**) forms of the molecular complex. Addition of halogen in increments to a solution already containing the phosphine or arsine provides a titration curve that gives the stoichiometry and relative conductance of the various adducts. Thus by the combined NMR/conductance method, we can unambiguously distinguish the three structural types (**8**, **9**, **10**).

Results

Crystalline adducts could be isolated with both the 1:1 and the 1:2 stoichiometry for the Br_2 and I_2 complexes of all four substrates (**4**–**7**). Only a 1:1 adduct, however, was isolable for the Cl_2 complexes of the same materials. The conductance of the adducts was measured in two different fashions. First, the isolated, crystalline adducts were dissolved in 1,2-dichloroethane or methylene chloride and the molar conductivity measured. These values are given in Table I (designated by footnote c). Conductometric titrations were also performed by adding increments of the halogen, dissolved in 1,2-dichloroethane or methylene chloride, to a solution of the substrate (**4**–**7**) in the same solvent. The results of these titrations are illustrated in Figures 1–6 for the halogen adducts of 1-methylphosphorinane (**4**) and 1-methylarsenane (**6**).[7] Essentially identical results were obtained with the phenyl substrates (**5**, **7**). In our hands, triphenylphosphine and -arsine produced conductance titrations identical with those reported previously.[6] Molar conductivities were calculated at the 1:1 and 1:2 (substrate/halogen) points on the titration curves, and these values may also be found in Table I. All conductances in Table I were corrected for volume, although those in the figures represent raw data.

In order to have a fully ionic standard, we prepared the tetrafluoroborate derivatives of the 1-methylarsenane system ($R_3As^+X\ BF_4^-$) by reaction of the appropriate 1:1 halogen adduct (only Br_2 and I_2) with silver tetrafluoroborate. Attempts to prepare the tetrafluoroborate derivatives of 1-methylphosphorinane in this manner failed. The molar conductivities for the arsenane systems are given in Table I.

The NMR spectrum of both deuterated variants of the parent base 1-methylarsenane (**6a** and **6b**) are ABCD. The analyses have been given elsewhere.[8] In contrast, all the 1:1 and 1:2 halogen adducts of 1-methylarsenane gave AA′BB′ or AA′XX′ spectra for both variants, a and b. The spectral nonequivalence in the parent compound is caused by slow inversion about arsenic. The higher symmetry of the spectra of the adducts must be due to static higher symmetry or a

Table I. Molar Conductivities (mho cm^2 mol^{-1})[a]

Registry no		Cl_2	Br_2	I_2	$2Br_2$	$2I_2$
39763-50-3	$(CH_2)_5PCH_3$ (4)	21.0[b] 18.7[b,c]	3.1 3.3[c]	12.8[b] 13.7[b,c]	9.6 8.8[c]	25.9[b] 25.4[b,c]
3302-83-8	$(CH_2)_5PC_6H_5$ (5)	5.9	5.9	8.5	12.9	18.5
30077-31-7	$(CH_2)_5AsCH_3$ (6)	0.07 0.06[c]	0.02 0.04[c]	2.1 3.2[c]	6.2 5.6[c]	13.8 14.1[c]
30077-30-6	$(CH_2)_5AsC_6H_5$ (7)	0.18	0.27	3.6	9.7	13.2
61394-98-7	$(CH_2)_5^+As(CH_3)Br$ $^-BF_4$		23.8			
61395-00-4	$(CH_2)_5^+As(CH_3)I$ $^-BF_4$			25.0		

[a] All measurements were performed in $ClCH_2CH_2Cl$ by the titration method at concentrations in the range $4-8 \times 10^{-3}$ M, unless otherwise specified. [b] Measured in CH_2Cl_2 because of low solubility in $ClCH_2CH_2Cl$. [c] Measured by dissolving a known amount of the crystalline adduct in solution.

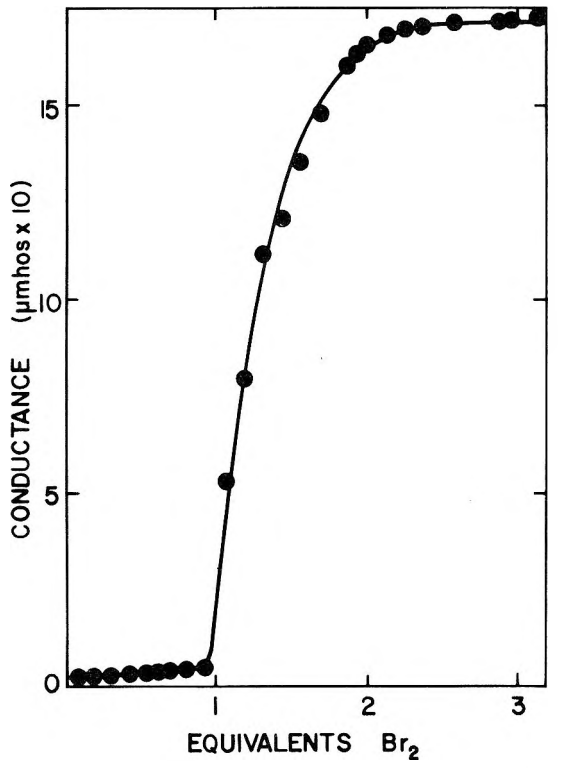


Figure 2. The conductance of 1-methylarsenane (6) in $ClCH_2CH_2Cl$ at 25 °C as a function of added equivalents of Br_2 in $ClCH_2CH_2Cl$.

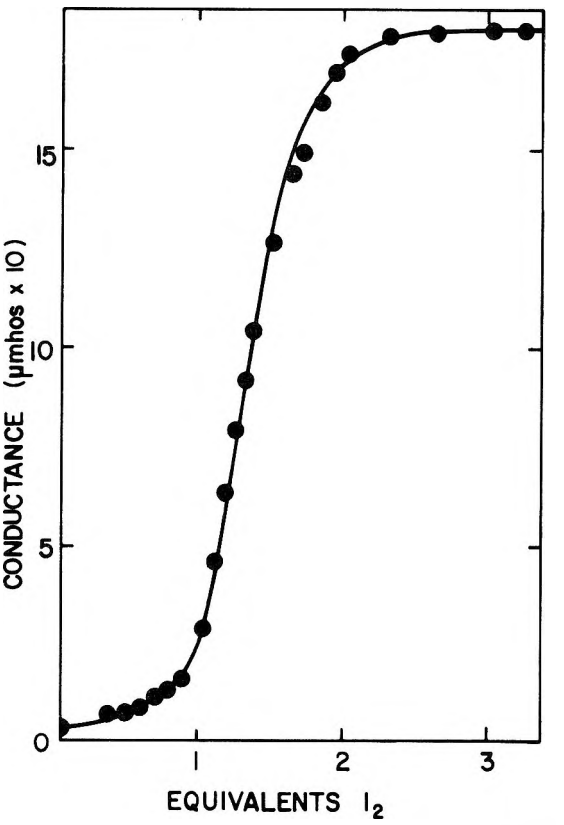


Figure 3. The conductance of 1-methylarsenane (6) in $ClCH_2CH_2Cl$ at 25 °C as a function of added equivalents of I_2 in $ClCH_2CH_2Cl$.

dynamic process that averages spectral lines. This point will be examined again in the Discussion. The observed spectra for **6a**-X_2 (Cl_2, Br_2) and **6b**-X_2 (Br_2) are given in Figures 7–9.[7] The spectrum of **6b**-Cl_2 has been presented elsewhere.[9] The spectra for **6a**-Br_4 and **6b**-Br_4 are given in Figures 10 and 11.[7] The iodine complexes were insufficiently soluble to give acceptable spectra. The 1-phenylarsenane adducts (**7**-X_2) were not examined by the NMR methods.

Initial values of coupling constants and chemical shifts for the complexes of 1-methylarsenane were estimated, and final values were obtained by standard iterative procedures.[10] The calculated spectra are given in the figures, along with the experimental spectra. In the case of the γ-deuterated compounds (**6a**), analyses were carried out on both 60- and 270-MHz spectra, but 60-MHz analyses were sufficient for the α,β′ compounds (**6b**), which were obtained with irradiation at the deuterium frequency. Deuterium irradiation was not available at 270 MHz. Analyses of 1-methylphosphorinane and all its halogen derivatives were also attempted, and approximate solutions have been obtained.[10] These data, however, could not be refined and will not be reported here, because of the added complications of coupling to phosphorus-31. Arsenic has a spin of ⅜, but coupling constants to As are not resolved because of rapid quadrupole relaxation. The coupling constants, R values, and torsional angles Ψ are listed in Table II. The details of the analysis of each individual case have been discussed elsewhere.[10] In certain cases, the geminal (AA′ and BB′) couplings could not be measured. This result is characteristic of bismethylene AA′BB′ spectra with very large or very

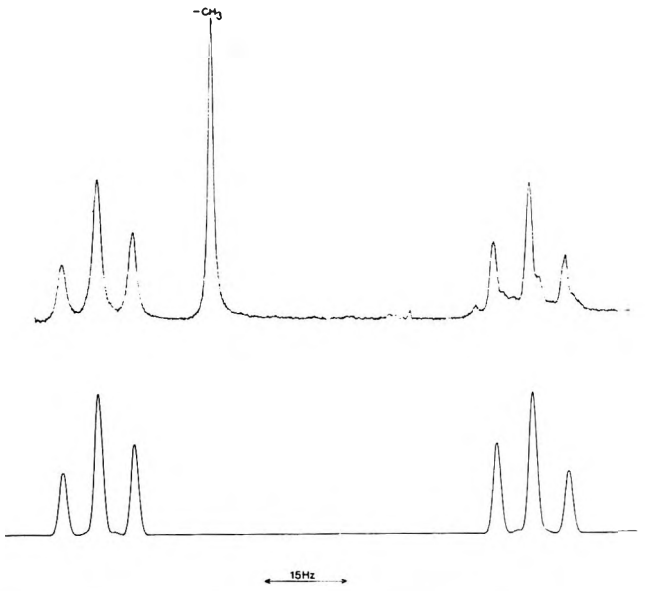


Figure 8. The observed and calculated 60-MHz proton spectra of 1-methylarsenane-*4,4-d*$_2$ 1,1-dibromide (**6a**-Br_2) with deuterium decoupling.

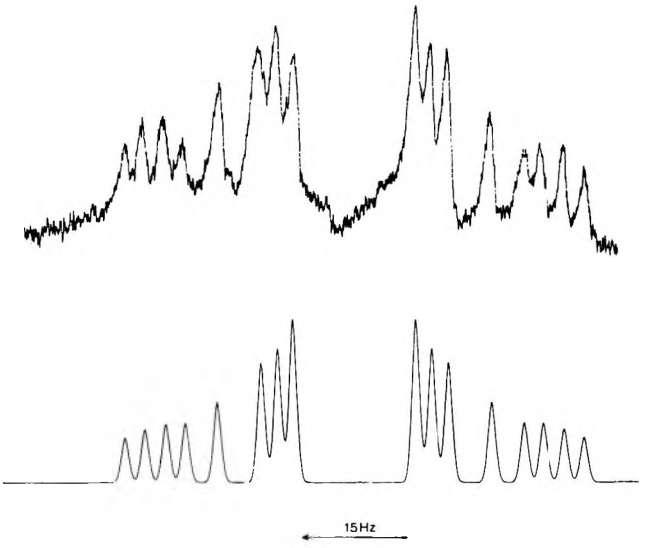


Figure 9. The observed and calculated 60-MHz proton spectra of 1-methylarsenane-*2,2,5,5-d*$_4$ 1,1-dibromide (**6b**-Br_2) with deuterium decoupling. The α-proton and methyl singlets are omitted.

small chemical shift differences ($\Delta\nu_{AB}$) and has been discussed in detail elsewhere.[9]

Although coupling constants provide the most important structural information from the NMR spectrum, we have also recorded the proton and carbon-13 chemical shifts for 1-methylarsenane and its halogen adducts (Table III).[11]

Discussion

Conductance. The conductance curves clearly show the existence of both 1:1 and 1:2 adducts of Br_2 and I_2 but only 1:1 adducts of Cl_2 (Figures 1–6)[7] for both the phosphine and the arsine systems. The respective adducts with appropriate stoichiometries subsequently were isolated. All of the 1:2 adducts have very high ionic character (Table I). This statement is true no matter what the halogen (Br, I), central atom (P, As), or substituent (CH_3, C_6H_5) is. Our UV studies showed the presence of Br_3^- or I_3^- in these solutions. Therefore, the best structure for the 1:2 adducts appears to be the ionized

Table II. Coupling Constants and Torsional Parameters for 1-Methylarsenane (6) and Its Halogen Adducts

		J_{trans}, Hz	J_{cis}, Hz	ΔJ_{gem}, Hz	R	Ψ, deg
Parent[a]	$\alpha\beta$	10.0, 8.6	3.3, 3.5	0.7	2.7	61
	$\beta\gamma$	8.0, 7.6	3.1, 2.7	0.9	2.7	61
Cl_2[b]	$\alpha\beta$	7.0	7.0	2.5	1.0	45
	$\beta\gamma$	9.3	2.2	0.0	4.2	66.5
Br_2[c]	$\alpha\beta$	7.5	6.1	2.5	1.2	49
	$\beta\gamma$	9.2	2.1	0.0	4.3	67
Br_4[d]	$\alpha\beta$	8.6	4.0	3.0	2.2	58
	$\beta\gamma$	8.8	2.7	0.0	3.3	63

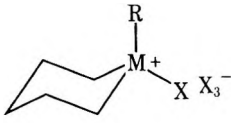
[a] Taken from ref 8; there are two J_{trans} and two J_{cis} couplings because the spectra are ABCD or AA'CD; all spectra of the adducts are AA'BB' or AA'XX'. [b] Taken in CCl_4; all others were taken in CH_2Cl_2. Registry no., 60958-64-7. [c] Registry no., 60958-65-8. [d] Registry no., 61395-01-5.

Table III. Chemical Shifts of 1-Methylarsenane and Its Halogen Adducts

		Parent[a]	Cl_2[b]	Br_2[c]	$2Br_2$[c]
^1H[d]	α	1.27, 1.64	3.30	3.60	3.43
	β	1.63, 1.78	2.30	2.25	2.10
	γ	1.45, 1.45	1.90	1.92	1.90
	CH_3	0.90	2.94	3.24	3.07
^{13}C[d,e]	α	22.4	51.1	47.2	51.9
	β	23.9	23.9	24.2	24.0
	γ	29.3	52.0	47.2	43.5
	CH_3	5.1	22.4	22.2	23.0

[a] ^1H spectrum in CCl_4; ^{13}C spectrum neat. [b] ^1H and ^{13}C spectra in CCl_4. [c] ^1H spectrum in CH_2Cl_2; ^{13}C spectrum in $CDCl_3$. [d] In parts per million downfield from Me_4Si. [e] Some of these ^{13}C data are reported in ref 11.

form **11**. Our results in this matter only serve to corroborate the observations of others in similar systems.[3,6]



11

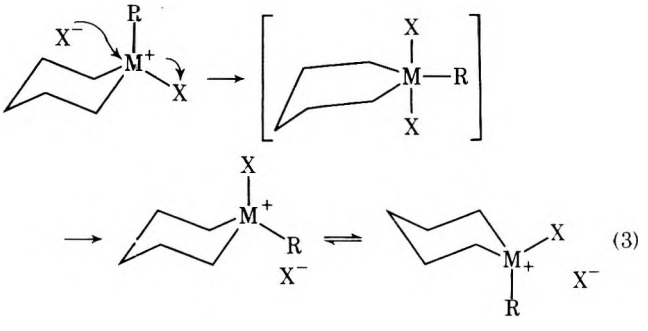
The 1:1 adducts give somewhat different results for the phosphines and arsines. All the phosphine adducts exhibit high conductance (Table I). We therefore consider that these materials most likely have the structure of the ionized molecular complex (**10**), although there may be some contribution from **9**. In contrast, the 1:1 arsine complexes with Cl_2 and Br_2 are essentially nonconducting. These results are consistent either with the nonionic molecular complex **9** or the trigonal bipyramid **8**. Past experience[5] has indicated that the nonconducting condition is usually a property only of the trigonal bipyramid. The arsine complex with I_2, however, is conducting and presumably of the form **10** (possibly with some **9**). The fully ionic tetrafluoroborates substantiate these conclusions. The bromoarsenanium tetrafluoroborate is two orders of magnitude more conducting than the simple 1:1 complex, whereas the iodoarsenanium tetrafluoroborate is only four times more conducting than the simple complex. It is unwise to attempt to calculate the ionic character of the iodine complex from these figures (% **9** vs. % **10**), because individual ionic conductances are not known and the anion is different in the two cases (I^- and BF_4^-). That the 1:1 iodine complex must be nearly fully ionized (mostly **10**) is indicated by its yellow color, i.e., the I–I bond must be substantially broken. In contrast,

the 1:1 molecular complex of I_2 with thiane (the analogous sulfur heterocycle) is deep violet at room temperature (significant contribution from **9**).[5]

The qualitative conclusions from the conductance data are that the 1:2 adducts possess the ionic, trihalide structure **11**, the 1:1 phosphine adducts possess the ionic molecular complex structure **10** (with possibly some contribution from **9**), the 1:1 I_2 adduct of the arsine also has the structure **10** (possibly with some **9**), and the 1:1 Cl_2 and Br_2 adducts of the arsine have the nonionic trigonal bipyramidal structure **8**.

Magnetic Resonance. The *R* value analysis of 1-methylarsenane (**6**) indicates that the entire molecule is slightly puckered with respect to the shape of cyclohexane (Table II, $\Psi = 61°$ for both α,β and β,γ segments).[8] This puckering is the distortion expected for the smaller C–As–C bond angle. Our preliminary analysis indicates that 1-methylphosphorinane is similarly puckered.[10] These conclusions refer to the average shape of the two conformations present.[8,12] The equatorial conformation actually may be puckered more and the axial conformation less (or even flattened).

Although ring reversal interconverts the axial and equatorial conformations of the arsenanes and phosphorinanes, it does not alter the cis/trans relationship of the ring protons with the 1 substituent, because atomic inversion is slow about phosphorus and arsine.[13] As a result, the spectrum of the α,β protons of **6a**, for example, is ABCD.[8] In contrast, all of the spectra of the halogen adducts are AA′BB or AA′XX′. Before examining the value of the coupling constants, we would like to comment briefly on this higher spectral symmetry, which can arise from a number of causes. (1) The trigonal bipyramid should give AA′BB′ spectra, provided that the rear end of the ring (**8**) is flipping rapidly above and below the plane of the C–As–C segments. (2) For the molecular complex **9**, rapid dissociation of halogen or methyl halide, atomic inversion, and association from the opposite side would render the spectrum AA′BB′. Normally, a halo substituent raises the barrier to inversion, so that this explanation seems unlikely in light of the known height of arsenic and phosphorus inversion barriers.[13] (3) Rapid nucleophilic attack by the anion X^- or X_3^- on the tetravalent central atom of the ionic molecular complex **10** (eq 3) would render the spectrum AA′BB′, since ring reversal is rapid at room temperature. Such a process requires no assumption as to whether the substituent R is axial or equatorial or a mixture. For the molecular complex, we favor the third rather than the second explanation for the AA′BB′ symmetry of the spectra, since it does not have to invoke rapid inversion about the central atom. The transition state for this process (eq 3) would in fact be the trigonal bipyramid (**8**). Alternatively, **8** could be an actual intermediate between the two molecular complexes of eq 3. The observed symmetry for the MC adducts therefore might only reflect the fact that they are in equilibrium with an unobservable TB. The main point to be emphasized, however, is that some dynamic process must be operating within the molecular complex, since the symmetry of the free base is such as to give an ABCD spectrum, and complexation alone does not alter this symmetry.



(3)

Table IV. Structural Classification of 1:1 Halogen Complexes[a]

	Cl_2	Br_2	I_2
P	MC[b]	MC[b]	MC[b]
As	TB[c]	TB[c]	MC[b]
Sb	(TB)	(TB)	(TB)
S	(TB)(?)	MC[c]	MC[c]
Se	(TB)	TB[c]	MC[c]
Te	(TB)	TB[c]	(TB)

[a] Structures in parentheses are inferred. [b] Based on conductance only. [c] Based on conductance and NMR.

The spectra (Figures 7, 8)[7] of the α,β protons of the 1:1 Cl_2 and Br_2 complexes of **6** have the deceptively simple triplet structure that we have found to be characteristic of a low *R* value[5] and hence of an extremely flattened ring ($\Psi = 45–49°$) (Table II).[14] Furthermore, the *R* value of the β,γ portion of the ring (Figure 9)[9] indicates considerable puckering ($\Psi = 66–67°$), and this type of distortion is a common response to flattening at the opposite end of a six-membered ring.[5] These torsional angles are exactly what is expected of a trigonal bipyramid **8**, in agreement with the observation of extremely small conductance. Insolubility of the 1:1 I_2 complex prevented analysis of its NMR spectra. The conductance results indicate that the 1:1 I_2 complex should not be appreciably distorted in the molecular complex **10** from the shape of the parent arsenane.

The 1:2 Br_2 adduct (Figures 10 and 11)[7] gave *R* values and torsional angles ($\Psi = 58–63°$) (Table II) that are characteristic of the relatively undistorted (slightly puckered) ring expected for a molecular complex (**11**), in agreement with the conductance results.

Thus the NMR results prove conclusively that the 1:1 Cl_2 and Br_2 complexes of 1-methylarsenane are trigonal bipyramids (**8**), and confirm that the 1:2 Br_2 adduct has the molecular complex structure (**11**).

A few comments are in order on the magnetic resonance parameters listed in Table III. The α protons are shifted downfield by about 2 ppm, and the α carbons are shifted downfield about 30 ppm on complexation with halogen. Some of the shift must be due to the electron-withdrawing nature of the halogen substituent. The positive charge in the ionic molecular complex should also cause a downfield shift. Furthermore, in the trigonal bipyramid, the equatorial bonds from P or As to carbon are sp^2–sp^3. The sp^2 character of the orbitals from M to C would have a downfield effect. Electric field effects also might be important. The effect of halogen here is probably a complex function of several factors. One important feature of the ^{13}C spectrum of 1-phenylarsenane (**7**) is the extremely high-field resonance of the ipso carbon, 97 ppm (compared to 138 ppm for the ipso carbon of toluene). This upfield shift is another example of the heavy atom effect observed in bromo and iodo compounds. In fact, the chemical shift of the ipso carbon is almost the same in the arsenic compound **7** as it is in iodobenzene (95 ppm).

Comparison with the Group 6 Halogen Adducts. The results of these studies on the group 5 adducts are summarized in Table IV, together with our earlier results[5] on group 6 adducts, which did not include Cl_2. For the 1:1 Br_2 and I_2 adducts, the results for group 5 precisely parallel those for group 6. Our previous inference that all the group 6 Cl_2 adducts are trigonal bipyramids rather than molecular complexes may be in error, since we have now observed that the phosphine adduct is indeed a molecular complex. It would be worthwhile to examine the Cl_2 adducts of the group 6 compounds to determine whether any are simple molecular complexes, in

particular the sulfide. To the extent that the experimental data go, however, at present there is complete structural parallelism between the two groups.

The group 5 bases form stable isolable 1:2 adducts with Br_2 and I_2. The conductance clearly levels off after 2 equiv of halogen has been added (Figures 2, 3, 5, 6).[7] There is no evidence for higher order adducts. In contrast, the group 6 bases show a sharp leveling off only at the 1:1 ratio, and the conductance then continues to increase slowly after many equivalents of halogen have been added. We interpreted these results in terms of the presence of higher order adducts (1:2, 1:3, 1:4, etc.) that are favored by the addition of excess halogen.[5] The group 5 results are cleaner, since only two adducts need to be considered.

Conclusions

The method of coupling constant ratios shows that the 1:1 Cl_2 and Br_2 adducts of 1-methylarsenane have the extremely flattened chair that is characteristic of the trigonal bipyramid **8**. In addition, these complexes are almost nonconducting. The conductance titrations indicate that the 1:1 I_2 adduct with 1-methyl- or 1-phenylarsenane and the 1:1 adducts of all three halogens with 1-methyl- or 1-phenylphosphorinane are ionic molecular complexes of the type **10**, although there may be an equilibrium with the nonionic form **9**. The *R* value, conductance, and ultraviolet experiments indicate that the 1:2 Br_2 and I_2 adducts with these substrates are all halo-onium trihalides of the type **11**, with a relatively undistorted ring. These results parallel most but not all of the characteristics of group 6 (sulfide, selenide, telluride) adducts with halogen.[5] The AA′BB′ nature of the proton spectra of all the group 5 complexes indicates in some cases that the trigonal bipyramid is favored and in others that the favored molecular complex must be in rapid equilibrium with an unobserved trigonal bipyramid through nucleophilic attack of the anion on the positively charged P or As. As is normally the case, strongly electronegative substituents (Cl) favor an apical position and hence the trigonal bipyramidal structure. Increased electropositive nature of the central atom (P to Sb) has the same effect. In reverse, the lower electronegativity substituents (I) and higher electronegativity central atoms (P) favor the molecular complex.[5]

Experimental Section

^1H NMR spectra were recorded at 60 MHz on Varian T-60 and Perkin-Elmer R-20B spectrometers, at 90 MHz on a Bruker HFX-90 spectrometer, and at 270 MHz on a Bruker HX-270 spectrometer (at the University of Chicago). The HFX-90, HX-270, and R-20B spectrometers were equipped with variable temperature units. The HFX-90 and R-20B spectrometers were also equipped with heteronuclear broad-band noise decouplers for deuterium decoupling. Carbon-13 chemical shifts were obtained on the HFX-90 spectrometer, operating at 22.628 MHz as described elsewhere.[11]

Conductance measurements were obtained on an Industrial Instrument Inc. conductance bridge, Model 16B2. Conductance titrations were carried out by placing a solution (1,2-dichloroethane or dichloromethane) of the phosphine or arsine in the conductance cell at room temperature under N_2. Volumetrically calibrated amounts of halogen in the same solvent were then added in a stepwise fashion, and the conductance was measured after each addition. The conductance of the solutions did not vary with time. Conductances were corrected for volume. The cell constant was found to be 0.246 cm^{-1} from measurements on a 0.010 M aqueous solution of KCl at 25 °C. UV spectra were recorded on a Cary Model 14 spectrometer. IR spectra were obtained on Beckman IR-5, IR-9, and IR-10 spectrometers. A Control Data Corp. Model 6400 digital computer equipped with a Calcomp plotting accessory Model 1136 was used for NMR spectral analysis and plotting. Programs ENIT and NMRPLOT were used for the analyses. Melting points (uncorrected) were determined in a Thiele tube apparatus. Elemental analyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill., and by H. Beck of the Analytical Services Laboratory, Department of Chemistry, Northwestern University. All reactions were carried out under dry N_2. Solvents were distilled from appropriate drying agents and stored over molecular sieves. Ethyl ether was distilled from $LiAlH_4$ prior to use. All other commercially available reagents were used without further purification.

1-Methylphosphorinane (4) was prepared by the method of Featherman and Quin.[12] Details may also be found elsewhere.[10] From 0.18 mol of methyldichlorophosphine (a gift from Ethyl Corp.) and 0.2 mol of the di-Grignard reagent from 1,5-dibromopentane was obtained 8.0 g (35%) of the product, bp 146–148 °C (lit.[12] 144–147 °C). Deuteration followed the procedures of our earlier work.[5]

1-Phenylphosphorinane (5) was prepared by a procedure analogous to that for 1-methylphosphorinane above.[10] Phenyldichlorophosphine (Eastman, 18.0 g, 0.1 mol) and 0.12 mol of the di-Grignard reagent from 1,5-dibromopentane were used to give 6.6 g (37%) of the desired product, bp 104–110 °C (12 mm) [lit.[15] 143–144 °C (16–18 mm)].

1-Methylarsenane (6) and its deuterated derivatives **(6a, 6b)** were prepared as described before.[8]

1-Phenylarsenane (7) was prepared by the same procedure as used for 1-methylarsenane (**6**). Phenyldichloroarsine (15.6 g, 0.07 mol) and 0.1 mol of the di-Grignard reagent from 1,5-dibromopentane were used to give a 31% yield of the desired product, bp 155–158 °C (20 mm) [lit.[16] 84 °C (0.5 mm)].

1-Methylarsenane 1,1-Dichloride (1:1 Adduct). Dry Cl_2 was bubbled through a 25-mL CCl_4 solution containing 0.176 g (1.1 mmol) of 1-methylarsenane (**6**) until the solution became slightly yellow. Solvent and excess Cl_2 were removed immediately at reduced pressure to leave a white solid. The yield was quantitative (>95%), mp 163 °C dec (sealed tube) (lit.[17] 166 °C). Anal. Calcd for $C_6H_{13}AsCl_2$: C, 31.20; H, 5.67. Found: C, 31.31; H, 5.67.

1-Methylarsenane 1,1-Dibromide (1:1 Adduct). 1-Methylarsenane (**6**, 0.16 g, 0.001 mol) was dissolved in 25 mL of CH_2Cl_2, and Br_2 (0.001 mol) in 15 mL of CH_2Cl_2 was added dropwise with ice cooling. After all the Br_2 had been added, the solvent was removed at reduced pressure to give white, hygroscopic, flaky crystals. The yield was quantitative (>97%), mp 62 ° C dec (sealed tube) (lit.[18] 60 °C). Anal. Calcd for $C_6H_{13}AsBr_2$: C, 22.53; H, 4.10. Found: C, 22.55; H, 4.35.

1-Methylarsenane $2Br_2$ (1:2 adduct) was prepared by dissolving 0.16 g (0.001 mol) of 1-methylarsenane (**6**) in 50 mL of $ClCH_2CH_2Cl$. To this solution was added quickly an excess of Br_2 (0.0025 mol) in 25 mL of the same solvent. After all the Br_2 had been added, the solution was stirred at room temperature for 1 h. The solvent and excess Br_2 were removed at reduced pressure to leave bright orange-red crystals. The yield was quantitative (>97%), mp 91–92 °C dec (sealed tube). The UV spectrum in $ClCH_2CH_2Cl$ gave two characteristic Br_3^- bands at λ_{max} 275 (ϵ 13 300) and 390 nm (1700). This compound is thermochromic. When cooled to −78 °C, the color becomes much lighter. Anal. Calcd for $C_6H_{13}AsBr_4$: C, 15.02; H, 2.73. Found: C, 15.15; H, 2.79.

1-Methylarsenane I_2 (1:1 Adduct). To a solution containing 0.16 g (0.001 mol) of 1-methylarsenane (**6**) and 50 mL of dry CCl_4 was added dropwise 0.25 g (0.001 mol) of I_2 in 50 mL of CCl_4 with ice cooling and vigorous stirring. A yellow solid precipitated out immediately. After all the I_2 had been added, the solvent was removed at reduced pressure. The yield was quantitative (>97%), mp 120 °C dec (sealed tube). This compound is slightly soluble in 1,2-dichloroethane (5.8×10^{-3} mol/L), 1,1,2,2-tetrabromoethane, and CH_2Cl_2. The 1,1,2,2-tetrabromoethane solution, however, gave a brown color that was different from the crystal color.

1-Methylarsenane $2I_2$ (1:2 Adduct). To a solution containing 0.16 g (0.001 mol) of 1-methylarsenane (**6**) and 150 mL of $ClCH_2CH_2Cl$ was added slowly 0.51 g (0.002 mol) of I_2 in 100 mL of the same solvent with vigorous stirring. A deep violet solution was formed. The solvent was removed to give a quantitative yield of a deep red-violet powder of the desired product in quantitative yield (>97%), mp 110–114 °C dec (sealed tube). The UV spectrum in 1,2-dichloroethane revealed two absorption maxima characteristic of I_3^- ions: λ_{max} 295 (ϵ 30 000) and 365 nm (17 000).

1-Bromo-1-methylarsenanium Tetrafluoroborate. To an oven-dried 150 × 16 mm test tube was added 0.0371 g (0.192 mmol) of $AgBF_4$. The tube was sealed with a rubber septum. These operations were carried out in a drybox. A solution of 1-methylarsenane 1,1-dibromide was prepared by treating a $ClCH_2CH_2Cl$ solution containing 0.18 mmol of the arsine with 0.18 mmol of Br_2 in the same solvent. The resulting solution was transferred to the previously prepared tube of $AgBF_4$. The tube was shaken vigorously to ensure complete mixing. The tube then was centrifuged to compact the AgBr, and the sample was stored at −11 °C for 72 h. The supernatant was

then removed via syringe to the conductance cell. The reaction tube was washed with 3 × 10 mL of $ClCH_2CH_2Cl$, followed each time by centrifugation, with the supernatant added to the conductance cell.

1-Iodo-1-methylarsenanium Tetrafluoroborate. The procedure paralleled the method given above for the bromine compound.

1-Methylphosphorinane Cl_2 (1:1 adduct), 1-methylphosphorinane Br_2 (1:1 adduct), 1-methylphosphorinane $2Br_2$ (1:2 adduct), 1-methylphosphorinane I_2 (1:1 adduct), and **1-methylphosphorinane $2I_2$ (1:2 adduct)** were prepared from 1-methylphosphorinane (5) in the same fashion as the corresponding arsenic adducts described above.

Registry No.—Cl_2, 7782-50-5; Br_2, 7726-95-6; I_2, 7553-56-2; 1-methylarsenane I_2, 61395-02-6; 1-methylarsenane $2I_2$, 61395-03-7; 1-methylphosphorinane Cl_2, 61395-04-8; 1-methylphosphorinane Br_2, 61395-05-9; 1-methylphosphorinane I_2, 61395-06-0.

Supplementary Material Available. Figures 4–7, 10, and 11 (6 pages). Ordering information is given on any current masthead page.

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(1) This work was supported by the National Science Foundation, Grant CHE-75-05006.
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(14) Deceptively simple AA'XX' spectra of this type can be analyzed either by observation of the low intensity antisymmetric transitions that must be in a mirror image relationship in the AA' and XX' portions (as is possible with **6a**-Br_2) or by examining the ratio of the width of the inner peak to the outer peaks of the triplet (as is possible with **6a**-Br_4). Once a value of ΔJ_{gem} is settled on, the other parameters fall into place rapidly. A second possible solution for **6a**-Br_4 ($\Delta J_{gem} = 0$) was discarded because a large ΔJ_{gem} is expected on the basis of electronegativity differences between the 1 and 4 atoms. It was not, however, eliminated on experimental grounds.
(15) G. Grüttner and M. Wiernik, *Chem. Ber.*, **48**, 1473 (1915).
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Photochemical 1,3-Addition of Anisole to Olefins. Synthetic Aspects

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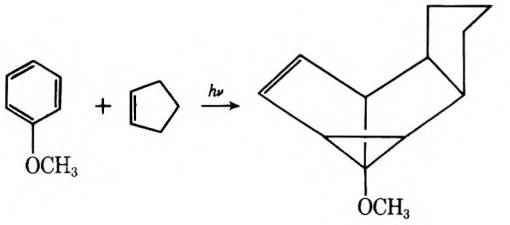
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Received June 14, 1976

Anisole undergoes photochemical 1,3-addition to a variety of olefins with about the quantum efficiency of benzene but in considerably greater chemical yield. The latter feature may result from the stability of the adducts to continued irradiation. A 1,3 photoadduct of an aromatic compound (anisole) to cyclohexene has been isolated for the first time. All of the 1,3 adducts rearrange readily on treatment with acid to derivatives of bicyclo[3.2.1]oct-2-en-8-one.

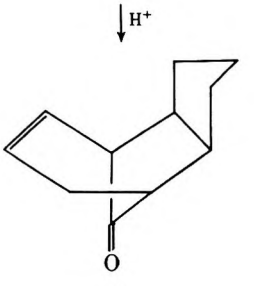
The photochemical 1,3-addition of benzene to olefins has been the subject of numerous investigations over the past 10 years.[1] Although both 1,2- and 1,4-additions occur concurrently to various extents, 1,3-addition is usually the dominant process when olefins lacking powerful substituent groups are used. The synthetic potential of this reaction has been limited by the difficulty in the isolation of the products and the susceptibility of the photoadducts to secondary photolysis.

It has been shown[2] that the 1,3-addition of anisole to cyclopentene under the influence of light proceeds in high chemical yield and that the reaction shows a great degree of locospecificity. Since the product 1 underwent rearrangement readily with acid (often even without a preliminary separation) to a bicyclo[3.2.1]octen-8-one, the synthetic potential of this reaction merited further investigation. These results are reported here. A few data on the mechanistic aspects of this reaction are also included but the bulk of the studies on the mechanism are published elsewhere.[3]



(1)

1



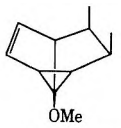
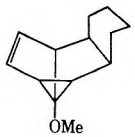
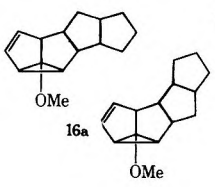
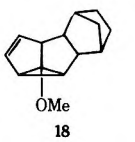
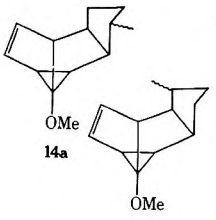
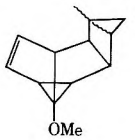
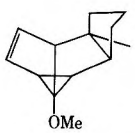
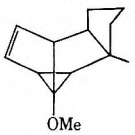
(2)

2

Results

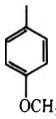
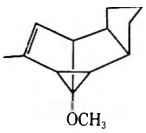
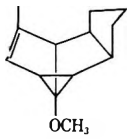
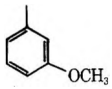
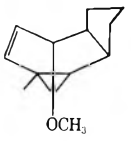
Exactly the same procedure was followed in all of the photoaddition reactions. A solution of the olefin (2 M) and anisole (2 M) in cyclohexane was irradiated at 254 nm without degassing the solution until product formation (as monitored by GLC) slowed down to a negligible rate. The isolated yields of the products, product composition, and the quantum yields in the initial stages of the reaction are given in Table IA and IB. The former lists the addition of anisole to various olefins and the latter the addition of alkyl-substituted anisoles to cyclopentene. *o*-Methylanisole did not undergo addition under these conditions. The structures of the 1,3 adducts have been established by (1) elemental analyses and/or high-resolution mass spectrometry which showed that they were 1:1

Table IA. Addition of Anisole to Olefins

Olefin	Products	Chem yield	Quantum yield[d]	Mass spectrum, m/e	Infrared spectrum,[a] cm^{-1}	Ultraviolet[b] spectrum, nm (log ε)	NMR spectrum, δ (H)
		22	0.09	164 (P) 108 (base)	3010, 2950 2850, 1640 1450, 1370 1220, 1140 1050, 785, 700	220 (3.34)	5.65 (2); 3.75 (3); 3.0 (1); 2.8–1.2 (4); 1.0–0.7 (6)
	 1	85	0.17	176 (P) 144, 129, 116 108 (base)	3050, 2950 2875, 1600 1450, 1390 1240, 1210, 1145 1090, 1030, 880	220 (3.40)	6.64 (2); 3.30 (3); 3.1–3.0 (3); 2.08 (2); 1.56 (6)
	 5	20	0.02	190 (P) 158, 143, 129, 115 108 (base), 91, 78 65, 32, 28	3005, 2950 2850, 1630 1450, 1400, 1150 1100, 1020, 830 775	220 (3.42)	5.57 (2); 3.25 (3); 2.95 (2); 2.60 (1); 2.39 (1); 2.10 (1); J = 7; 1.96 (1), J = 8; 1.59–1.39 (8)
	 10	62	0.21	204 (P) 172, 129, 108 (base), 28	3005, 2950 2890, 1600 1450, 1390 1150, 1130 1100, 1020 805, 690	221 (3.47)	3.0 (1), 2.7–2.3 (2); 5.6 (2), 3.3 (3), 2.15 (2); 1.9–0.8 (10)
	 16a 16b	64	0.08	216 (P) 184, 169, 155 141, 128, 115 108 (base), 91 79, 28	3005, 2950 2900, 1650 1440, 1390 1230, 1130 1100, 790 770	218 (3.4)	5.65 (2); 3.25 (3); 3.05 (1); 2.6 (2); 2.3–1.8 (2); 1.4 (10)
	 18	59	0.05	202 (P) 188, 170, 159 129, 108 (base) 91	3005, 2950 2900, 1600 1460, 1400 1150, 1030 715, 680	220 (3.35)	5.5 (2); 3.25 (3); 2.95 (1); 1.9–2.3 (5); 1.8–2.8 (7)
	 14a 14b	60	0.11	190 (P) 158, 129 108 (base), 91 78, 41, 40, 39 32, 28	3050, 2950 2880, 1600 1455, 1400 1240, 1220 1150, 1100, 1030	220 (3.52)	5.64 (2); 3.25 (3); 3.1 (1); 3.0–2.6 (2); 1.90 (2); 1.9–1.2 (5); 1.0–0.8 (3) (pattern indicative of mixture of isomers).
 cis:trans 3:2	 20	24	0.08	204 (P) 108 (base)	3005, 2950, 2900 1600, 1450, 1400 1380, 1240, 1225, 1150, 1100, 1040 855, 820, 725	220 (3.38)	5.64 (2); 3.25 (3); 3.1 (1); 2.95–2.20 (2); 0.9 (6); 1.9 (2); 1.7 (4)
	 21	35	0.02	190 (P) 176, 133, 108 (base) 105, 98, 97, 96 94	3050, 2950, 2880 1740, 1600, 1450 1400, 1250, 1225 1140, 1125, 1100, 1010, 745		5.67 (2); 3.26 (3); 3.1–2.8 (2); 2.2–1.6 (8); 1.18 (3)
	 22	30			3050, 2950, 2875 1590, 1450, 1395 1250, 1200, 1130 1100, 755		5.64 (2); 3.23 (3); 2.75 (1); 2.6–1.4 (9); 1.26 (3)

[a] Liquid film. [b] Solvent: cyclohexane. [c] From ref 2. [d] Quantum yield values reported based on olefin 1 M.

Table IB. Addition of Methylanisoles to Cyclopentene

Anisole	Products	Chem yield	Quantum yield	Mass spectrum, m/e	Infrared spectrum, cm^{-1}	Ultraviolet spectrum, nm (log ϵ)	NMR spectrum, δ (H)
	 27	45	0.01	190 (P), 175, 158 147, 143, 130, 128 122, (base), 115, 91 79, 77, 65, 63, 39 32, 28	3050, 2950 2850, 1650 1450, 1400 1250, 1205 1140, 1130 1090, 1030 890, 820	Solvent: cyclohexane 220 (3.48)	5.2 (1); 3.25 (3); 3.2–2.2 (3); 1.8 (3); 1.8–0.8 (8)
	 24	26	<0.01	190 (P), 150 122 (base), 92 81, 79	3100, 3000, 2900 1640, 1600, 1490 1470, 1460, 1400 1390, 1360, 1260 1210, 1130, 1035 920, 790, 760		5.6 (2); 3.27 (3); 3.2–2.6 (3); 2.0–1.4 (7); 1.22 (3)
	 25	33			3005, 2950, 2900 1720, 1630, 1460 1450, 1390, 1240 1210, 1125, 1090 1035, 875, 840 820, 780		5.23 (1); 3.23 (3); 3.2–2.2 (3); 1.8 (3); 2.0–0.1 (8)

[a] Liquid film. [b] Solvent CCl_4, Me_4Si as internal reference.

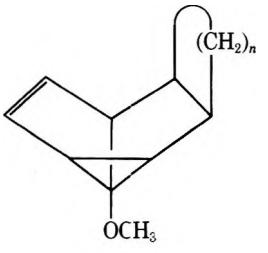
adducts; (2) infrared spectra which indicated the presence of a cyclopentenyl double bond at ca. 1600–1640 cm^{-1} (weak); (3) ultraviolet spectra which showed an absorption maximum or shoulder at 220–241 nm (ϵ_{max} ~2000) indicating a vinylcyclopropane chromophore; (4) proton magnetic resonance spectra which are highly characteristic of these adducts.[4] These NMR spectra will be discussed in detail for individual cases.

In many instances, partially deuterated 1,3 adducts were synthesized from anisole-d_5 and appropriate olefins in order to corroborate the assignments in the NMR spectrum.

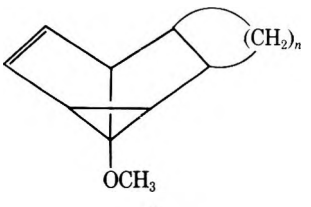
1,4 and 1,2 adducts, if formed, were no more than a small fraction of the yield of 1,3 adducts in all of these instances. 1,2-Dimethylcyclopentene did not undergo addition under the experimental conditions. Dimerization of the olefin which was presumably photosensitized by anisole was observed to take place in a few instances.

The acid-catalyzed rearrangements of these adducts was a facile process in nearly all of the instances, the isolated yields of the ketones ranging from 50 to 80%. The spectral properties of these products are listed in Table II.

The orientation of the olefinic moiety with respect to the anisole part of the adduct can be as in **3** (endo) or **4** (exo).



3

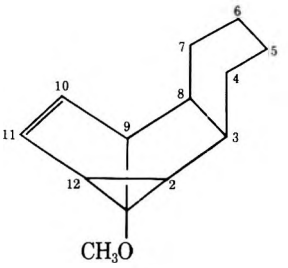


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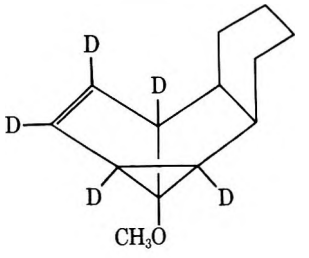
Earlier studies[1] on the 1,3-addition of benzene have shown that benzene itself gives varying mixtures of endo and exo adducts depending on the olefin that is used. With a small-ring olefin, such as cyclobutene, the endo isomer was the major product.[5] When alkyl-substituted benzenes were used endo adducts were formed exclusively.[4] A model which would explain this has been proposed[4] and will be discussed in the context of anisole addition in the next section.

In the case of anisole, with simple olefins such as cyclopentene, only one adduct was realized.[2] That this was the endo isomer was rigorously established by x-ray analysis of a derivative in the case in which the olefin was 3,4-dichlorocyclobutene.[6,7] Indirect evidence has been presented to show that the anisole:cyclopentene adduct (**1**) is also endo oriented.[2] In the present work, the adducts of anisole to various monocyclic olefins are represented as endo fused by extrapolation of the above results. It is emphasized that this is based on a model (see Discussion) and therefore tentative. NMR data cannot be used to assign the stereochemistry at the points of addition.

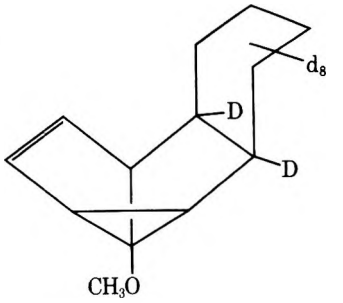
Cyclohexene. The addition of anisole to this olefin is the first reported instance of 1,3-addition of a benzene derivative to cyclohexene. A comparison of the NMR spectra (220 MHz) of the partially deuterated derivatives **6** and **7** to **5** showed that



5



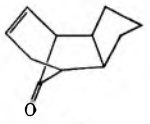
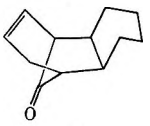
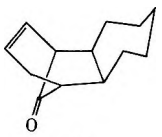
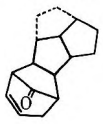
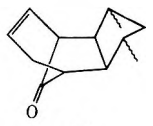
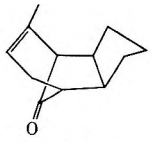
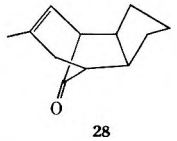
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7

the chemical shifts of protons which belonged originally to anisole were at δ 5.55 (H_{10}, H_{11}), 3.23 (–OCH_3), 2.94 (H_9), 2.08 (H_{12}), and 1.93 (H_2). The chemical shifts for the ring protons agree very well with the assignments made for the 1,3 adducts

Table II. Ketones Obtained from Acid Cleavage of 1,3 Photoadducts

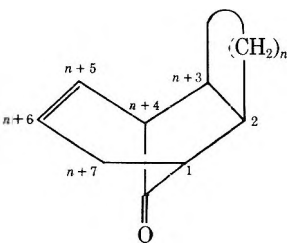
Precursor	Ketone product	Yield, %, from 1,3 adduct	Mass spectrum	Infrared[b] spectrum, cm^{-1}	NMR spectrum, δ(H)[c]	Remarks
1[a]	 2	80	See ref 2	3050, 2950, 2900 1760, 1650, 1460 1445, 1335, 1200 1110, 1010, 790, 720 685	5.62 (2), 2.65 (2); 2.4 (4); 1.7 (6)	Ultraviolet absorption: λ_{max} (pentane) 294 nm (ε 42)
5	 9	50	176 (parent) 148, 147, 105 92, 91, 81, 80 79, 40	3005, 2950, 2900 1770, 1640, 1450 1115, 805, 715, 685	5.64 (2), 2.7 (2); 2.3 (4); 2.0–1.2 (8)	2,4-DNP mp 161–163 °C
10	 12	86	190 (parent) 162, 161, 116 105, 91, 78, 41	3005, 2950, 2900 1770, 1450, 1120 780, 690	5.6 (2); 2.65 (2); 2.3 (3); 2.0 (1); 1.9–0.8 (10)	Product homogenous by GLC
16	 17a,b	47	202 (base) 162, 161, 116	3005, 2950, 2900 1760, 1450, 1190 1110, 790, 690	5.63 (2), 2.68 (2); 2.1–2.6 (4); 1.6 (10)	Two isomers; not easily separated by GLC
14 (a+b)	 15a,b	83	176 (p, base) 148, 134 93, 81, 79 77	3050, 3000, 2950 2900, 1760, 1620 1455, 1400, 1380 1225, 1110, 1010, 685	5.6 (2); 2.6 (2); 2.36 (4), 1.7 (5); 1.0 (3)	Product consisted of two isomers in the ratio 1:1.5 with retention times 28.1 and 27.0 min
22	 23	68	decomposed mass spect	2960, 2900, 1750 1450, 1370, 780 690	5.6 (2); 2.6 (2); 2.4 (1) 1.7 (8); 1.0 (3)	
24 + 25	 26	60	176 (P) decomposed mass spect sample	3005, 2950, 2900 1755, 1605, 1510 1440, 1250, 1160	5.8–5.8 (1); 2.6 (7); 2.3 (3); 1.65 (3); 1.6 (6)	
27	 28	80	176 (p, base) 133, 119 104, 93, 78 68, 44, 42	3005, 2940, 2900 1760, 1450, 1380 1195, 1150, 1135 810	5.3 (1); 2.55 (3); 2.28 (3), 1.65 (d, 3); 1.60 (6)	

[a] From ref 2. [b] Liquid film. [c] CCl_4 solution with Me_4Si as internal reference.

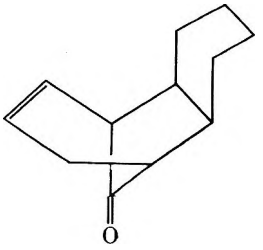
derived from benzene and alkylbenzenes.[4] The large coupling between H_{12} and H_2 (7–8 Hz) and the absence of any other strong coupling (since C_1 is substituted by the $-OCH_3$ group) confirm this observation. In contrast to both cyclopentene[5] and cycloheptene (see below), the addition to cyclohexene was inefficient in terms of both the chemical yield (20%) and rate.[3]

Ketones derived by the acid cleavage of the photoadducts had the general structure 8.[2,7]

The stereochemistry has been assigned in two cases[6,7] as mentioned already. In all of the ketones that were isolated both in this study and in earlier ones, the characteristic chemical shifts of protons on the bicyclo[3.2.1]octen-8-one system were δ 2.2–2.5 (H_2, H_{n+3}), 2.6–2.7 (H_{n+2}, two protons), 5.6–5.7 (H_{n+5}, H_{n+6}). The ketone 9 derived from 5 fully conformed to this pattern.

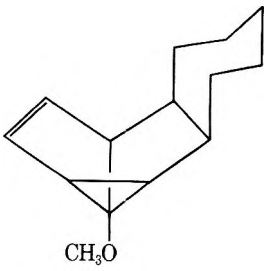


8

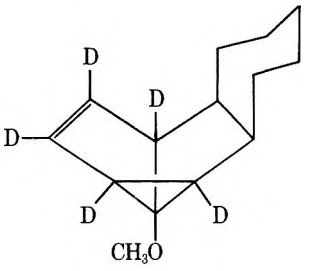


9

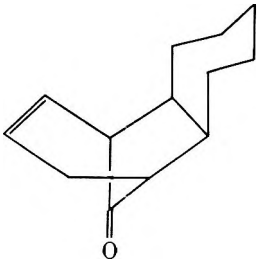
Cycloheptene. The evidence on which the structures 10 for adduct and 11 for its partially deuterated derivative were based was unexceptional. Ketones 12 and 13 were prepared from these adducts. In quantitative terms cycloheptene gave a high yield of product and, most surprisingly, the maximum



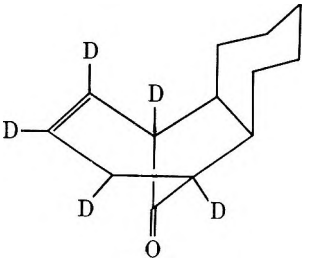
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11



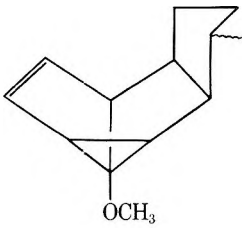
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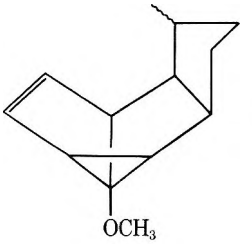
13

rate of addition[3] of any olefin.

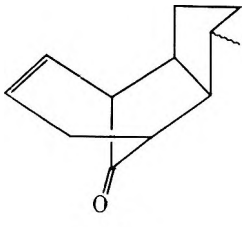
Substituted Cyclopentenes. 3-Methylcyclopentene. Gas chromatographic analysis of the product mixture showed the presence of two major products in approximately equal amounts and constituting ~80% of the products that were formed. However, they could not be isolated separately in quantity. Spectroscopic data indicated that both major products were 1,3 adducts. The NMR spectra of these adducts (as well as their partially deuterated analogues derived from anisole-d_5), when analyzed as a mixture, showed an absorption pattern for the $-CH_3$ group that consisted of two superimposed doublets which, as in the parent olefin, had a coupling of 6 Hz to the vicinal proton. The two doublets were 2–3 Hz apart and had the same chemical shift as the methyl group in the olefin. It is very likely that the cyclopentane ring was fused endo to the rest of the molecule as this was consistently true in the addition of cyclopentenes to all of the benzene and alkylbenzenes that have been studied.[4,5,8] Even so, there are four isomers possible depending on the location and orientation of the methyl group (**14a** and **14b**). The identification of only two products (according to the NMR patterns) suggest that only two of the isomers are favored. The ketones **15a** and **15b**



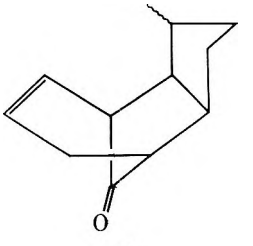
14a



14b



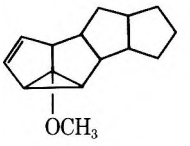
15a



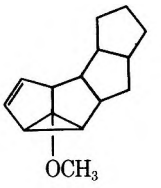
15b

derived from these adducts also seemed to consist of only two isomeric products.

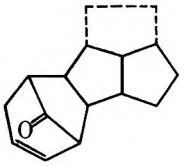
Bicyclo[3.3.0]octene. As in the preceding case, gas chromatographic analysis showed the presence of two isomeric adducts in the ratio 3:2 which together represented approximately 70% of all products formed. Comparison of the NMR spectra of the normal vs. deuterated (**16**-d_5) adduct mixture and conversion to **17** showed the typical features of the 1,3-addition products. The proposed structures **16a** and **16b** make



16a



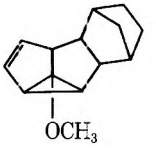
16b



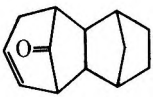
17a, b

no attempt at stereochemical assignment. Separating the isomeric products proved unsuccessful.

Norbornene. Formation of the desired 1,3 adduct of norbornene with anisole was accompanied by dimerization of the olefin to produce the exo-trans-endo dimer exactly as in the photocycloaddition reaction with benzene.[9] Dimer formation decreased at high olefin concentration again as observed in the benzene:norbornene system.[9] Gas chromatographic analysis of the adduct showed the presence of only one 1:1 adduct (**18**) in 60% yield and other unidentified products in



18



19

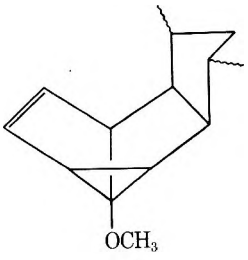
less than 10% yield. The spectroscopic characteristics of the major product (Table IA) paralleled the main features of the 1,3 adducts. Treatment with acid yielded a ketone of formula $C_{13}H_{16}O$ as the sole product (85%) whose NMR spectrum exhibited a very complex olefinic (2 H) pattern (two distinct groups: 1 H, δ 5.9 consisting of a complex triplet and 1 H, δ 5.4 consisting of two coupled triplets). The appearance of the spectrum suggested that it was not the expected ketone **19.** A deep-seated rearrangement must have occurred. The structure of the product is under investigation.

3,5-Dimethylcyclopentene. This reaction was carried out on a 60:40 mixture of the cis:trans isomers of this olefin (composition according to manufacturer). Separation of the product mixture showed that dimeric products as well as a 1:1 adduct were formed. Spectral data indicated the characteristic features of the 1,3 adduct (**20**). The broad peak in the GLC trace may be indicative of isomeric products being present, but attempts to resolve the peak were unsuccessful. No attempt was made to determine the stereochemistry of the products.

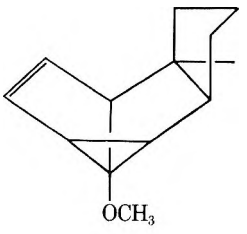
1-Methylcyclopentene. Addition of this olefin to anisole yielded (GLC analysis) four isomeric addition products of which three were isolated as pure materials. Two that were identified spectroscopically to be the 1,3 adducts are shown in Table IA. Their yields were **21** (35%), **22** (30%). Of these, one showed a more complex structure for H_8 and it was therefore identified as **22** in which H_7 provides an additional coupling. The ketone **23** was formed from **22** in the usual manner.

Addition of Methylanisoles to Olefins. The addition of o-methylanisole to cyclopentene was too slow to be detected.

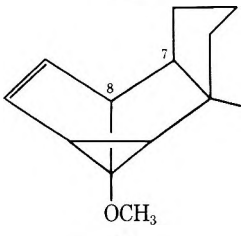
The addition of *m*-methylanisole to cyclopentene gave two adducts in good yield. The quantum yield was one of the lowest observed. In both adducts, orientational specificity was evident in the location of the $-OCH_3$ group (and not the methyl) at the 1 position. The structures of the compounds could be readily distinguished by the absence of one olefinic



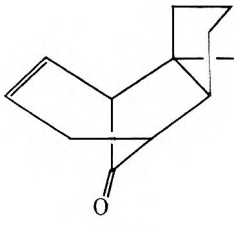
20



21

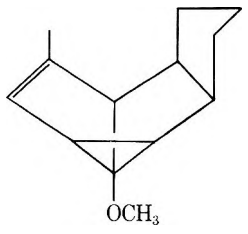


22

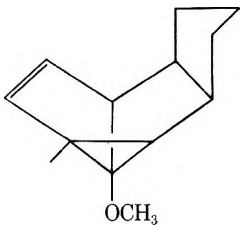


23

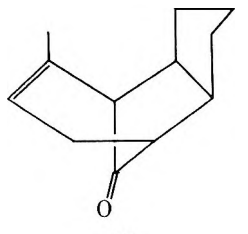
proton and the presence of an allylic methyl group in **24** but not in **25**. The formation of both products in nearly equal



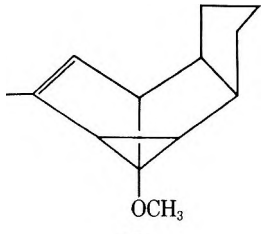
24



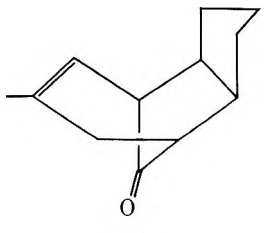
25



26



27



28

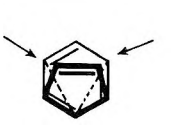
amounts parallels the observation made earlier[4] on the addition of *m*-xylene to olefins. Both adducts **24** and **25** were treated with acid as a mixture. Only one ketone was isolated from this solution in good yield. It was assigned the structure **26** since its NMR spectrum indicated the presence of only a single olefinic proton at δ 5.3 and the position of the methyl group at δ 1.65 (doublet, $J \sim 2$ Hz) suggested an allylic position. The addition of *p*-methylanisole to cyclopentene was slow and the yield of the adduct **27** was only 45%. It was converted to the ketone **28** efficiently.

Solvent Effects. The photocycloaddition reaction between anisole and cyclopentene was carried out in a variety of solvents. Results showed no significant change in the types of products formed. The solvents used were cyclohexane, diethyl ether, tetrahydrofuran, and methanol. In none of the cases was the solvent found to be incorporated in the addition product. The same results were obtained when mixed solvents were used, i.e., cyclohexane–methanol.

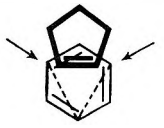
Effect of Conversion. The substantially larger yields that were obtained in the reaction of anisole with a small-ring olefin such as cyclopentene in contrast to the addition of benzene to the same olefin suggested that the effect may be due to increased photostability of the product in the first instance. The 1,3 adducts of both anisole to cyclopentene (**1**) and benzene to cyclopentene were separately dissolved in cyclohexane, benzene was added as a sensitizer, and the solutions were irradiated at 254 nm. The benzene adduct (as monitored by VPC) disappeared completed within 14 h leaving only a deep-yellow, high molecular weight material. The anisole adduct was diminished by less than 10% in the same time duration.

Discussion

It is best to discuss the present results in terms of the model which has been proposed earlier[4] to explain the photochemical 1,3-addition of benzene and alkylbenzenes to olefins. This model has considerable predictive value particularly in regard to the stereochemistry of the reaction. It is suggested that benzene in its B_{2u} state (which has the hexagonal symmetry of its ground state) reversibly forms an open sandwich-type exciplex (**29a** or **b**) which first adds 1,3 to the double bond at



29a



29b



29c

the points indicated by the arrows. The last bond to close is the cyclopropane ring which seems to form in either way as indicated by the dotted lines. The chief point of interest in this model for the 1,3-addition of anisole to olefins is that a substituent on the ring plays a major part in determining the stereochemistry. For reasons which are not clear, the exciplex seems to prefer the structure **a** (which leads to endo addition) over **b** in the case of benzene and small rings. When a substituent is present, this preference is augmented by the steric hindrance to the alternative configuration (**29c**) that is needed for exo addition. The anisole adducts to cyclobutene and to cyclopentene have been shown to be endo oriented. Similar reasoning would serve to explain the failure of o-methylanisole to add to cyclopentene and the greatly decreased rate of addition of anisole to cyclopentenes with an alkyl group at the doube bond or to bicyclic cyclopentenes. It has been acknowledged elsewhere[3] that these explanations are strictly qualitative. In particular, the reasons for the wide variations in the rates of addition of cyclopentene, cyclohexene, and cylcoheptene to anisole are obscure at present.

The scope of the 1,3-addition as a synthetic reaction has been amply demonstrated here. The presence of the methoxy group on the adduct which causes it to rearrange to the keto system **8** lends additional merit to this reaction in synthesis. We have described elsewhere[2] one method to cleave the ketone **8** further to a bicyclic derivative. Other chemistry of the ketones has also been investigated.[11,12]

Experimental Section

Infrared spectra were determined on a Perkin-Elmer Model 137B spectrometer. NMR spectra were obtained at 60 MHz on a Varian T60-1 A machine or at 220 MHz on a Varian HR-220 spectrometer. The latter was operated by the consortium at Rockefeller University, New York, N.Y. Samples were dissolved in CCl_4 with Me_4Si as internal reference. Mass spectra were determined on a J.M.S. Model D-100 high-resolution mass spectrometer.

Olefins were obtained from Chemical Samples Co. Columbus, Ohio, and used as obtained. Anisole-d_5 was synthesized by Miss Laura Garwin from benzene-d_6. The solvents used were of spectroquality. Gas chromatographic separations were carried out on a Hewlett-Packard Model 5750. The GLC columns used during the isolation and

purification of the products are as follows: (A) UCON-550X-20%-50LB, 12 ft × 0.75 in. (o.d.); (B) 10% Carbowax 20M, 6 ft × 0.75 in. (o.d.); (C) 10% Carbowax 20M, 6 ft × 0.75 in. (o.d.); (D) SE-30, 12 ft × 0.75 in. (o.d.).

General Photoaddition Procedure. A solution of the aromatic ether and olefin in cyclohexane (2 M in each solute) was introduced into a cylindrical quartz irradiation tube. The tube was placed in a Rayonet RPR-208 reactor equipped with four 253.7-nm lamps (Hg), and sealed with a rubber serum cap to allow removal of samples with a syringe. The part of the tube void of solution was covered with Al foil to prevent reactions in the gas phase.

After irradiation, the solution was transferred to a round-bottom flask and the volatile materials removed at reduced pressure while heating on a water bath (<80 °C). The residue was distilled bulb-to-bulb using a liquid N_2 trap to separate the adducts from polymeric materials. The neat products were stored in a freezer to avoid polymerization. The mixture of products appeared as a very viscous yellow oil and was further separated and purified by GLC.

General Rearrangement Procedure. The procedure has been described elsewhere.[10] To a solution of the adduct mixture described above in 80% acetone was added a small amount of concentrated HCl (1–2 mL) and the mixture was refluxed for a period of approximately 6 h. After reflux, an equal amount of H_2O was added and the reactants allowed to cool. The mixture was extracted with CH_2Cl_2 and the organic layer washed with 10% HCl, saturated $NaHCO_3$, and water and allowed to dry over anhydrous $MgSO_4$. On a scale of 0.1–1.0 g, the mixture was distilled via a short-path column. The ketone(s) appeared as viscous yellow oil(s). The latter were further isolated and purified by GLC for spectroscopic analysis.

The spectroscopic features of some of the partially deuterated adducts and ketones that were prepared are given here:

***d*$_5$-1-Methoxy-4(6)-methyltetracyclo[6.3.0.0^{2,11}.0^{3,7}]undec-9-ene (14).** GLC purified (A), ^{1}H NMR spectrum (60 MHz) δ 3.25 (3 H), 3.0–2.8 (2 H), 2.1–1.1 (5 H), 1.0–0.8 (3 H).

***d*$_5$-1-Methoxytetracyclo[8.3.0.0^{2,13}0.^{3,9}]tridec-11-ene (11).** Purification by GLC (C); IR spectrum (film) 2950, 2900, 1560, 1450, 1370, 1350, 1220, 1165, 1087, 1030, 1015, 1000, 785, 715, 680 cm^{-1}; ^{1}H NMR spectrum (60 MHz) δ 3.25 (3 H), 3.0–2.2 (2 H), 2.0–0.6 (10 H).

***d*$_5$-Tricyclo[7.3.1.0^{2,8}]tridecen-10-one (13).** Purification was effected by GLC (C); IR spectrum (film) 2940, 2860, 1750, 1450, 1205, cm^{-1}; ^{1}H NMR spectrum (60 MHz) δ 2.6 (1 H), 2.25 (2 H), 2.1–0.7 (10 H); mass spectrum, parent peak (base) *m/e* 195, other major peaks, 167, 91, 84.

***d*$_5$-Methoxypentacyclo[9.3.0.0^{3,10}.0^{2,14}.0^{5,9}]tetradec-12-ene (16).** Purification by GLC (C); IR spectrum (film) 2950, 2850, 1610, 1475, 1450, 1225, 1180, 1070, 700 cm^{-1}; ^{1}H NMR spectrum (60 MHz) δ 3.21 (3 H), 2.5 (2 H), 2.2–1.8 (2 H), 1.4 (8 H).

Registry No.—**1**, 55265-10-6; **2**, 55306-29-1; **5**, 61394-01-2; **9**, 61394-02-3; **10**, 61394-03-4; **11**, 61394-04-5; **12**, 61394-05-6; **13**, 61394-06-7; **14a**, 61394-07-8; **14a**-d_5, 61394-09-0; **14b**, 61394-08-9; **14b**-d_5, 61394-10-3; **15a**, 61394-11-4; **15b**, 61394-12-5; **16a**, 61394-13-6; **16a**-d_5, 61394-14-7; **16b**, 61394-15-8; **16b**-d_5, 61436-68-8; **17**, 61394-16-9; **18**, 61394-17-0; **20**, 61394-18-1; **21**, 61394-19-2; **22**, 61394-20-5; **23**, 61394-21-6; **24**, 61394-22-7; **25**, 61394-23-8; **26**, 61394-24-9; **27**, 61394-25-0; **28**, 61394-26-1; anisole, 100-66-3; 2-butene, 590-18-1; cyclopentene, 142-29-0; cyclohexene, 110-83-8; cycloheptene, 628-92-2; bicyclo[3.3.0]octene, 5549-09-7; norbornene, 498-66-8; 3-methylcyclopentene, 1120-62-3; *cis*-3,5-dimethylcyclopentene, 30213-29-7; *trans*-3,5-dimethylcyclopentene, 61394-27-2; 1-methylcyclopentene, 693-89-0; 1,2,2a,2b,4a,4b-hexahydro-4b-methoxy-1,2-dimethylcyclopenta[*cd*]pentalene, 61394-28-3; *p*-methylanisole, 104-93-8; *m*-methylanisole, 100-84-5; anisole-d_5, 50629-14-6.

Acknowledgment. The authors wish to thank the Air Force Office of Scientific Research (AFSC), U.S. Air Force, for Contract F 44620-72-C-0024 under which this work was carried out. The technical assistance of Ms. Laura Garwin in synthesizing anisole-d_5 and studying some of its reactions is acknowledged with pleasure.

References and Notes

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(4) J. Cornelisse, V. Y. Merritt, and R. Srinivasan, *J. Am. Chem. Soc.*, **95**, 6197 (1973).
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(11) G. Subrahmanyam and R. Srinivasan, *Indian J. Chem.*, **14**, 462 (1976).
(12) G. Subrahmanyam, *Indian J. Chem.*, **14**, 365 (1976).

Formation of 3-Cyclopentene-1-acetaldehydes on Photolysis of Substituted Norcamphors

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Received November 29, 1976

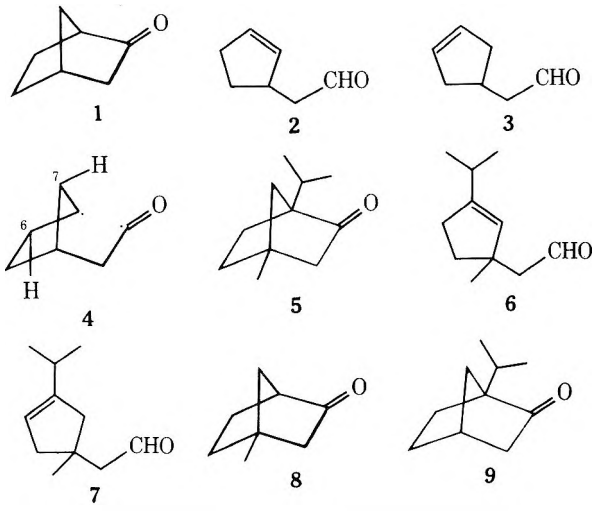
In contrast to the behavior of norcamphor (1) and various of its derivatives previously investigated, photolysis of 1-isopropyl-4-methylnorcamphor (**5**), 4-methylnorcamphor (**8**), and 1-isopropylnorcamphor (**9**) leads in each case to both 2- and 3-cyclopentene-1-acetaldehydes. Quantum yields for these isomerizations are reported, and the results are explained in terms of conformational and stereochemical effects in the biradical intermediates.

A recent review has called attention to the fact that photolysis of norcamphor (1) leads specifically to the Δ^2 aldehyde **2** and not to the Δ^3 isomer **3**, although in principle the presumed intermediate biradical **4** could disproportionate to both **2** and **3**.[1] Various 1- and/or 3-substituted norcamphors also have been examined in the past and found to behave similarly.[1] These facts have been available for some time, and with them in mind we took particular notice of the photochemical behavior of 1-isopropyl-4-methylnorcamphor (**5**), a new ketone which had arisen unexpectedly in a rearrangement reaction.[2] In the course of securing the structure of this compound we investigated its photochemistry and found that photolysis furnished both the Δ^2 and the Δ^3 aldehydes, **6** and **7**, respectively, in the ratio 62:38.[2] This result suggested more careful study of **5**, along with examination of the two simpler ketones 4-methylnorcamphor (**8**) and 1-isopropylnorcamphor (**9**). An additional reason for our interest was that this problem appeared related to our earlier investigation of the photochemical behavior of various substituted bicyclo[3.2.1]-octan-6-ones (**10**). In this latter series we had demonstrated

Table I. Quantum Yields for Products from Norcamphors

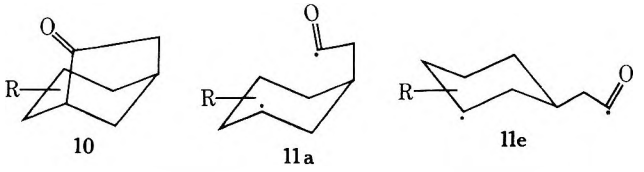
Norcamphor	Quantum yield[a] Δ^2 aldehyde	Δ^3 aldehyde	Total
1	2, 0.28[b]	0	0.28
5	6, 0.16	7, 0.10	0.26
8	12, 0.19	13, 0.13	0.32
9	14, 0.29	15, 0.04	0.33

[a] Estimated error ±~10%. [b] From ref 6.



1 2 3 4 5 6 7 8 9

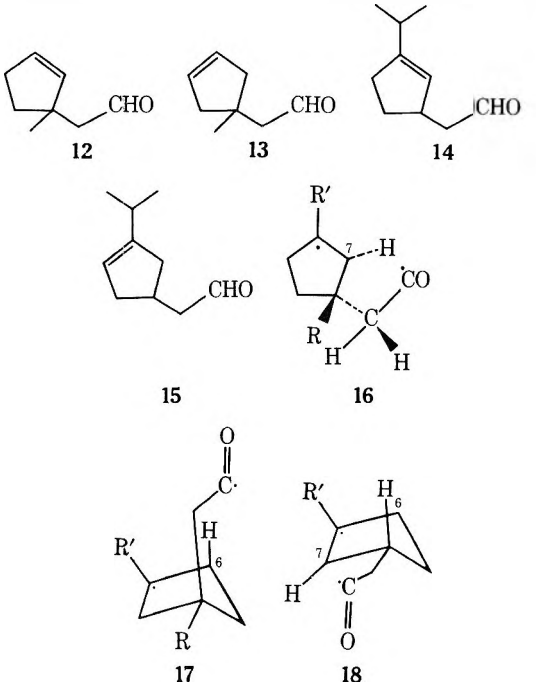
that the lifetime and energy content of the biradical **11** formed on photolysis permit this species to undergo conformational relaxation of the six-membered ring before disproportionation, so that the photoproducts arise specifically from the stable conformer **11a** or **11e**.[3] From the results described below similar behavior appears to play a role in the photochemistry of norcamphor and its derivatives.



10 11a 11e

Irradiation of 8[4] in benzene through Pyrex as previously described for 5[2] gave both the Δ^2 and Δ^3 aldehydes **12** and **13** in the ratio of 59:41. Similar photolysis of 9[2] also yielded both products **14** and **15**, but now in the ratio of 88:12.[5] No other products were found in significant amount. Structures of these new aldehydes were assigned from IR and NMR spectroscopic and vapor phase chromatographic (VPC) properties and comparison of these data with those previously found for **6** and **7**.[2] In particular the difference in double bond position in the Δ^2 and Δ^3 aldehydes leads to two fewer allylic hydrogens in the Δ^2 compounds **6**, **12**, and **14** than in their respective Δ^3 isomers **7**, **13**, and **15**. As a result the ^{1}H NMR spectra (220 MHz) of **6**, **12**, and **14** all show an upfield signal for these two protons ($\delta \sim 1.6$ ppm) that is absent in the spectra of the three Δ^3 aldehydes. Also in all three cases the Δ^2 aldehyde has a shorter retention time than its Δ^3 isomer under standardized VPC conditions. Quantum yields for these products were determined in benzene solution at low conversion (4–5%) by calibrated VPC analysis and using a merry-go-round apparatus. Norcamphor (**1**), for which the quantum yield for formation of **2** under these conditions is known,[6] served as a convenient actinometer. The results are collected in Table I.

From these data it is apparent that alkyl substitution affects the distribution of products with only minor changes in overall quantum yield. While there is a small, as yet unexplained, effect due to the isopropyl substitutent, it is clear from the chemical and quantum yield data that the presence or absence of the methyl group at C(4) largely controls product distribution in these four isomerizations. Examination of molecular models suggests two ways in which this can occur. The geometry of the biradical (see **16**) leading to abstraction from C(7) and formation of Δ^2 aldehyde involves an unavoidable eclipsing nonbonded interaction between the C(4) substituent and hydrogen of the adjacent side chain methylene group. This is true regardless of the specific conformation adopted by the five-membered ring (see below). Substitution of methyl for hydrogen at C(4) will disfavor **16** and should then decrease



12 13 14 15 16 17 18

R = CH_3 or H
R′ = $CH(CH_3)_2$ or H

abstraction at C(7). Steric effects of this sort have been recognized as important in ketone photochemistry for some years.[7] A second effect of the methyl group is to favor the geometry (see **17**) leading to abstraction from C(6) with formation of Δ^3 aldehyde, which requires an axial-like orientation of both the acyl side chain and the C(6) hydrogen atom. This conformation will be favored by substitution of methyl for hydrogen at C(4), since in this case either this methyl group or the acyl side chain must adopt an axial-like position. With hydrogen at C(4) the preferred conformation (such as **18**) is expected to have the acyl side chain in an equatorial-like position, from which abstraction at C(7) but not C(6) is possible. This second effect appears directly analogous to the conformational relaxation of biradical **11** referred to above. The failure of the bulky isopropyl group to exert an important conformational effect is understandable, since it is directly attached to the effectively planar radical center in the biradical intermediate. A close analogy exists in the bicyclo[3.2.1]-octan-6-ones, where replacement of hydrogen by methyl at the cyclohexyl radical center of **11** has little effect.[3]

From these results we conclude that the regiospecific photochemical conversion of norcamphor (**1**) into the Δ^2 aldehyde **2** is satisfactorily explained by a combination of stereochemical and conformational factors which are already recognized as significant determinants of the course of related transformations. The unusual product specificity observed on photolysis of **1** and its previously examined derivatives led several years ago to the proposal that the particular geometry of

norcamphor favored concerted transfer of the syn C(7) hydrogen to the carbonyl carbon as α-cleavage occurred, and that this process was faster than the common biradical disproportionation pathway.[8] This suggestion would be difficult to reconcile with our present findings, which would require that remote alkyl substitution on the rigid norbornane skeleton strongly influence the rate of the proposed concerted transfer of hydrogen. While further studies with various stereospecifically substituted norcamphors are certainly desirable to support this conclusion, it seems clear from our results that no special mechanism is necessary to account for the product specificity observed with norcamphor.

Experimental Section

Materials and Equipment. Unless noted otherwise below, these were the same as we have described previously.[3] NMR spectra were obtained at 60 MHz unless otherwise indicated.

Photolysis of 4-Methylnorcamphor (8). A 120-mg sample of 8[4] in 40 mL of benzene containing 1.2 mL of methanol was degassed for 15 min with N_2 and then irradiated through Pyrex for 8 h. Most of the solvent was removed by distillation through a Vigreux column and the products were isolated by preparative VPC on a 25 ft × 0.25 in. 25% DEGS column to give, in order of elution, 1-methylcyclopent-2-en-1-acetaldehyde (12) and 1-methylcyclopent-3-en-1-acetaldehyde (13) in the ratio 3:1.

Characterization data for **12:** IR 3040 (w), 2940 (s), 2850 (m), 2720 (m), 1725 (s), 1450 cm^{-1} (m); NMR δ 1.17 (s, 3 H), 1.48–1.97 (m, 2 H), 2.10–2.60 with d, J = 3 Hz, at 2.37 (m, 4 H), 5.63 (s, 2 H), 9.70 (t, J = 3 Hz, 1 H).

Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.62; H, 9.73.

Characterization data for **13:** IR 3045 (m), 2945 (s), 2830 (s), 2720 (m), 1725 (s), 1615 (w), 1435 (w), 1375 (w), 670 cm^{-1} (m); NMR δ 1.12 (s, 3 H), 2.1–2.5 with s at 2.30 and d, J = 3 Hz, at 2.38 (m, 6 H), 5.60 (s, 2 H), 9.72 (t, J = 3 Hz, 1 H).

Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.39; H, 9.66.

Photolysis of 1-Isopropylnorcamphor (9). Irradiation of 77 mg of 9[2] for 7 h and workup under conditions described above for photolysis of 8 gave these products, isolated by preparative VPC on an 9 ft × 0.25 in. 15% DEGS column, in order of elution: 3-isopropylcyclopent-2-en-1-acetaldehyde (14) and 3-isopropylcyclopent-3-en-1-acetaldehyde (15) in the ratio 13:1.

Characterization data for **14:** IR 3035 (w), 2955 (s), 2860 (m), 2700 (m), 1725 (s), 1640 (w), 1470 (m), 1380 (m), 1365 cm^{-1} (m); NMR δ 1.03 (d, J = 7 Hz, 6 H), 1.18–2.58 (m, 7 H), 3.05 (m, 1 H), 5.22 (m, 1 H), 9.67 (t, J = 2 Hz, 1 H).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 79.08; H, 10.67.

Characterization data for **15:** IR 3035 (w), 2955 (s), 2700 (m), 1725 (s), 1650 (w), 1470 (m), 1380 (m), 1375 cm^{-1} (m); NMR (220 MHz) δ 1.00 (d, J = 7 Hz, 6 H), 1.80–2.82 (m, 8 H), 5.18 (m, 1 H), 9.64 (t, J = 3 Hz, 1 H).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 79.11; H, 10.48.

Determination of Quantum Yields. Benzene solutions of the VPC purified norcamphor derivatives were prepared to give an absorbance at 313 nm of 0.502–0.553 (0.035–0.037 M). Aliquots (4 mL) of these solutions were degassed in three freeze–thaw cycles, sealed in identical Pyrex tubes, and irradiated with a Hanovia Model L 450-W mercury lamp in a merry-go-round apparatus for 15 min (4–5% conversion). The product yields were determined by calibrated VPC on an 8 ft × 0.25 in. 3% DEGS column.

Acknowledgements. We thank Mr. S. T. Bella for microanalyses and both the National Science Foundation (Grant CHE74-21436) and The Rockefeller Foundation (Grant RF 70095) for support of this research. NMR spectra at 220 MHz were obtained on an instrument at The Rockefeller University and operated by a consortium supported in part by NSF Grant PCM74-12247.

Registry No.—**8,** 49664-72-4; **9,** 59247-60-8; **12,** 61436-67-7; **13,** 61394-30-7; **14,** 61394-31-8; **15,** 61394-32-9.

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(3) W. C. Agosta and S. Wolff, *J. Am. Chem. Soc.*, **97,** 456 (1975); **98,** 4182 (1976).
(4) R. L. Cargill, D. F. Bushey, P. D. Ellis, S. Wolff, and W. C. Agosta, *J. Org. Chem.*, **39,** 573 (1974).
(5) We have confirmed that under these conditions norcamphor (**1**) yields only **2.** Product ratios are for low conversion. Minor aldehydes **13** and **15** are selectively destroyed on prolonged irradiation.
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(8) T. Matsui, *Tetrahedron Lett.*, 3761 (1967).

Synthesis of Isocoumarins, Dihydroisocoumarins, and Isoquinolones via π-Allylnickel Halide and π-Olefin–Palladium Complexes

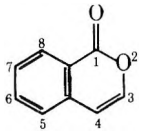
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Received October 18, 1976

2-Bromobenzoic esters were treated with π-(2-methoxyallyl)nickel bromide to produce 2-acetonylbenzoic esters. These were cyclized to isocoumarins by treatment with NaH/*tert*-butyl alcohol, or to dihydroisocoumarins by treatment with $NaBH_4$. The sodium salts of 2-bromobenzoic acids were reacted with a variety of π-allylnickel halide complexes to produce 2-allylbenzoic acids. These were cyclized to isocoumarins by treatment with palladium chloride. In a similar fashion isoquinolones were prepared from 2-allylbenzamides. This cyclization is thought to proceed by a palladium-assisted nucleophilic attack on the olefin of the allyl group.

Isocoumarins[1] (1*H*-2-benzopyran-1-one, **1**) are a class of naturally occurring lactones which display a wide range of biological activity.[2] They have been prepared by cyclization of homophthalic acid derivatives,[3] 2-vinylbenzoic acid derivatives,[4] 2-carboxybenzyl ketones[5] (available primarily from the Hurtley reaction),[6] by the ortholithiation of *N*-methyl-



1

Table I. Reaction of π-(2-Methoxyallyl)nickel Bromide with 2-Haloaromatic Esters

Substrate	Time, h	Temp, °C	Product	Yield, %[a]
Methyl ester of				
2-Bromobenzoic acid	16	50	Methyl 2-acetonylbenzoate (**2a**)	93
2-Bromo-4,5-dimethoxybenzoic acid	42	55	Methyl 2-acetonyl-4,5-dimethoxybenzoate (**2b**)	97
2-Iodo-4-chlorobenzoic acid	40	0–25	Methyl 2-acetonyl-4-chlorobenzoate (**2c**)	68
2-Bromo-3-pyridinecarboxylic acid	100	50	Methyl 2-acetonyl-3-pyridinecarboxylate (**6**)	78

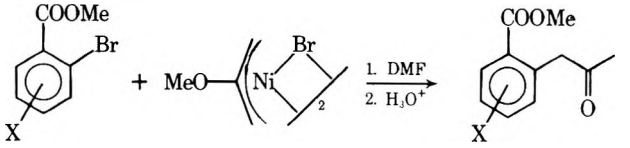
[a] Yields are of isolated, purified product.

Table II. Reaction of π-Allylnickel Bromide Complexes with Aromatic Halides[a]

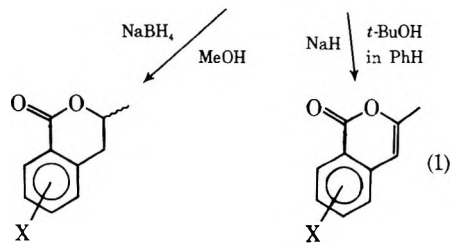
Substrate	Nickel complex	Time, h	Product	Yield,[b] %
Sodium salt of				
2-Bromobenzoic acid	π-Allylnickel bromide	96	2-(2-Propenyl)benzoic acid (**4a**)	76
2-Bromobenzoic acid	π-Crotylnickel bromide	96	2-(2-Butenyl)benzoic acid (**4b**)	91
2-Bromobenzoic acid	π-(1,1-Dimethylallyl)nickel bromide	90	2-(3-Methyl-2-butenyl)benzoic acid (**4c**)	87
2-Bromobenzoic acid	π-(2-Methallyl)nickel bromide	120	2-(2-Methyl-2-propenyl)benzoic acid	71
2-Iodo-4-chlorobenzoic acid	π-Allylnickel bromide	120	2-(2-Propenyl)-4-chlorobenzoic acid (**4d**)	c
2-Iodo-4-chlorobenzoic acid	π-Crotylnickel bromide	96	2-(2-Butenyl)-4-chlorobenzoic acid (**4e**)	c
2-Bromo-5-methoxybenzoic acid	π-Allylnickel bromide	96	2-(2-Propenyl)-5-methoxybenzoic acid (**4f**)	c
2-Bromobenzamide	π-Allylnickel bromide	90	2-(2-Propenyl)benzamide	59
2-Bromo-*N*-methylbenzamide	π-Allylnickel bromide	70	2-(2-Propenyl)-*N*-methylbenzamide	70

[a] All reactions were carried out at 50 °C using 1.5 mmol of nickel complex/mmol of substrate in DMF. [b] Reported yields are of isolated products purified by preparative layer chromatography. [c] These compounds were not isolated. Cyclization to the isocoumarin was carried out on the crude reaction mixture (see Table V).

benzamides,[7] and by the oxidation of isochromans.[8] These methods frequently suffer from requiring difficult to prepare starting materials and/or severe conditions for cyclization. We have recently developed methods, using π-allylnickel halide complexes[9] for the facile introduction of the acetonyl group into aromatic substrates,[10] and for palladium assisted cyclization of 2-allylanilines to 2-alkylindoles.[11] Herein we report the extension of the newly developed methods to the synthesis of isocoumarins, dihydroisocoumarins, and isoquinolones. The approaches are summarized in eq 1 and 2.

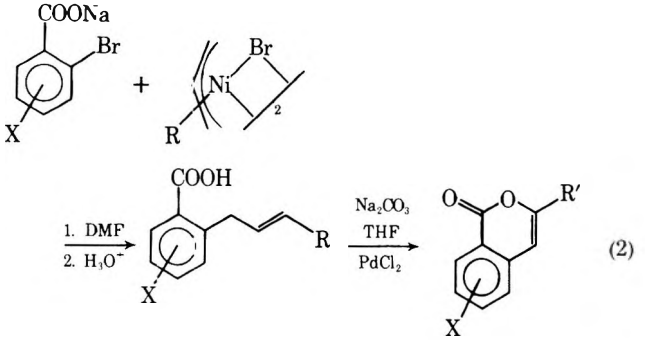


2a, X = H
b, X = 4,5-di-OMe
c, X = 4-Cl



3'a, X = H
b, X = 6,7-diOMe
c, X = 6-Cl

3a, X = H
b, X = 6,7-di-OMe
c, X = 6-Cl



4a, X = R = H
b, X = H; R = Me
c, X = H; R = $(Me)_2$
d, X = 4-Cl; R = H
e, X = 4-Cl; R = Me
f, X = 5-OMe; R = H

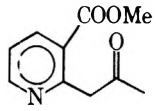
5a, X = H; R' = Me
b, X = H; R' = Et
c, X = H; R' = *i*-Pr
d, X = 6-Cl; R' = Me
e, X = 6-Cl; R' = Et
f, X = 7-OMe; R' = Me

Results

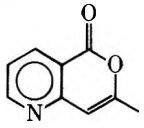
Preparation of Substrates for Cyclization. Treatment of several substituted methyl 2-bromobenzoates with π-(2-methoxyallyl)nickel bromide produced the corresponding methyl 2-acetonylbenzoates in good yield (Table I). The reaction proceeded under mild conditions (50 °C, DMF) and displayed the specificity typical for π-allylnickel halide complexes.[10,11] With methyl 2-iodo-4-chlorobenzoate, reaction took place exclusively at the iodide, leaving the chloride untouched. The heteroaromatic bromo ester methyl 2-bromo-3-pyridinecarboxylate also reacted cleanly. Thus, this procedure provides a mild and specific synthetic approach to

Table III. Preparation of 3-Methylisocoumarins from 2-Acetonyl Esters

Substrate	Product	Yield, %[a]
Methyl 2-acetonylbenzoate	3-Methylisocoumarin (**3a**)	81
Methyl 2-acetonyl-4,5-dimethoxybenzoate	3-Methyl-6,7-dimethoxyisocoumarin (**3b**)	67
Methyl 2-acetonyl-4-chlorobenzoate	3-Methyl-6-chloroisocoumarin (**3c**)	71
Methyl 2-acetonyl-3-pyridinecarboxylate (**6**)	7-Methyl-5*H*-pyrano[4,3-*b*]pyridin-5-one (**7**)	61



6



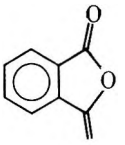
7

[a] Reported yields are for pure, isolated products.

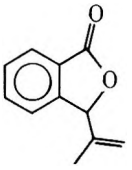
Table IV. Preparation of Dihydroisocoumarins from Methyl 2-Acetonylbenzoates

Substrate	Product	Yield, %[a]
Methyl 2-acetonylbenzoate	(±)-3-Methyl-3,4-dihydroisocoumarin (**3'a**)	75
Methyl 2-acetonyl-4,5-dimethoxybenzoate	(±)-3-Methyl-3,4-dihydro-6,7-dimethoxyisocoumarin (**3'b**)	81
Methyl 2-acetonyl-4-chlorobenzoate	(±)-3-Methyl-6-chloro-3,4-dihydroisocoumarin (**3'c**)	94

[a] Reported yields are for pure, isolated products.



8



9

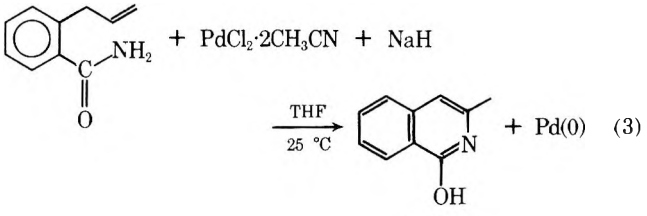
2-acetonylbenzoic esters from readily available starting materials.

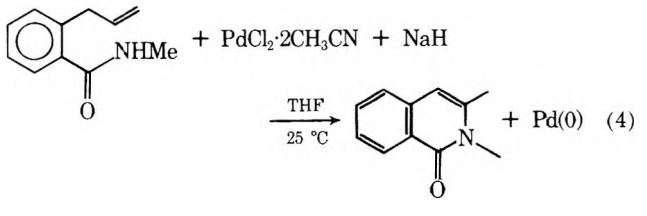
Attempts to prepare 2-allylbenzoic acids, for conversion to isocoumarins as in eq 2, by the reaction of 2-bromobenzoic acids with π-allylnickel halides met with limited success. While 2-bromobenzoic acid reacted with π-allylnickel bromide to give a fair (49%) yield of 2-(2-propenyl)benzoic acid, π-crotyl-, π-cyclohexenyl-, and π-(1,1-dimethylallyl)nickel bromide produced primarily benzoic acid from 2-bromobenzoic acid, with little allyl transfer being observed. In contrast, 4-bromobenzoic acid reacted cleanly with π-crotylnickel bromide to produce 4-(2-butenyl)benzoic acid in good yield. To circumvent this problem, the 2-bromobenzoic acids were converted to their sodium salts prior to reaction with the π-allylnickel bromide complexes. In this fashion high yields of 2-allylbenzoic acids were obtained (Table II) for later conversion to isocoumarins. In several cases these allyl acids were not purified. Rather cyclization was carried out on crude reaction mixtures to give a high-yield, one-pot conversion of 2-bromobenzoic acids to isocoumarins. The conversion of 2-bromobenzamide to 2-(2-propenyl)benzamide, for cyclization to an isoquinolone, was carried out in a similar fashion.

Cyclization Studies. The optimum conditions for the cyclization of 2-acetonylbenzoates to 3-methylisocoumarins (eq 1) was treatment with 2 equiv of NaH in refluxing benzene (16 h) with a catalytic amount of *tert*-butyl alcohol (Table III). The presence of halogen, methoxy, or heterocyclic nitrogen did not interfere with the cyclization. Treatment of methyl 2-acetonylbenzoate with 4 equiv of NaH in refluxing benzene (2 h) produced a 1:1 mixture of 3-methylisocoumarin and 1,3-dihydroxynaphthalene, resulting from C-acylation rather than O-acylation. Reductive cyclization of several methyl 2-acetonylbenzoates using excess $NaBH_4$ in methanol[5] produced racemic 3-methyl-3,4-dihydroisocoumarins in good yield (Table IV). Again, methoxy or halogen substituents did not interfere.

Isocoumarins were also synthesized from 2-alkenylbenzoic acids, using a palladium assisted cyclization reaction (eq 2) involving nucleophilic attack of carboxylate on the Pd-complexed olefin (vide infra). These results are summarized in Table V. With two exceptions, isocoumarins were the sole cyclic products. With 2-vinylbenzoic acid, a small amount of the five-membered-ring lactone **8** was obtained in addition to the major product, isocoumarin. In contrast the five-membered-ring lactone **9** was the sole cyclic product from the reaction of 2-(2-methyl-2-propenyl)benzoic acid. The presence of chloride or methoxide groups in the benzene ring did not interfere with cyclization. Purification of the alkenylbenzoic acids prior to cyclization was not necessary, since contaminants from the allylation reaction did not interfere with the cyclization. The cyclization could be made *catalytic* with regard to palladium by the addition of cupric acetate and O_2 to provide a means for oxidation of the Pd(0) produced in the cyclization step.

Dihydroisocoumarins were available by the above procedure by simply exposing the cyclization reaction mixture to an atmosphere of H_2 after cyclization was complete, utilizing the Pd metal precipitate present as catalyst. In this fashion 3,4-dihydroisocoumarin was produced from 2-vinylbenzoic acid in 65% yield, as was 3-methyl-3,4-dihydroisocoumarin from 2-(2-propenyl)benzoic acid in 68% yield. Finally 2-(2-propenyl)benzamide was converted to 3-methylisocarbostyril (eq 3) and 2-(2-propenyl)-*N*-methylbenzamide to 3-methyl-*N*-methylisoquinolone (eq 4) by treatment with $PdCl_2$ and NaH in THF.





Discussion

The reaction of π-(2-methoxyallyl)nickel bromide with 2-bromobenzoic esters to produce 2-acetonylbenzoic esters proceeded without complication, and displayed the reactivity and selectivity common to other π-allylnickel halide complexes.[9,10] The success of this reaction with methyl 2-bromo-3-pyridinecarboxylate is of note because the behavior of bromopyridines, with their ability to strongly coordinate to nickel during the course of the reaction, toward these nickel complexes was previously unknown. Although coordination

Table V. Preparation of Isocoumarins from 2-Alkenylbenzoic Acids[a]

Substrate	Time, h	Product	Yield,[b] %
2-(2-Propenyl)benzoic acid (4a)	3	3-Methylisoccumarin (5a)	86
2-(2-Propenyl)benzoic acid[b]	119	3-Methylisoccumarin (5a)	41 (1900)[c]
2-(2-Butenyl)benzoic acid (4b)	3	3-Ethylisocoumarin (5b)	86
2-(3-Methyl-2-butenyl)benzoic acid (4c)	4	3-Isopropylisccoumarin (5c)	96
2-(2-Propenyl)-4-chlorobenzoic acid (4d)[d]	4	3-Methyl-6-chloroisocoumarin (5d)	63[c]
2-(2-Butenyl)-4-chlorobenzoic acid (4e)[d]	4	3-Ethyl-6-chloroisocoumarin (5e)	54[e]
2-(2-Propenyl)-5-methoxybenzoic acid (4f)[d]	3	3-Methyl-7-methoxyisocoumarin (5f)	65[f]
2-Vinylbenzoic acid	3	Isocoumarin (1)	62
		3-Methylene phthalide (8)	21
2-(2-Methyl-2-propenyl) benzoic acid	5	9	31

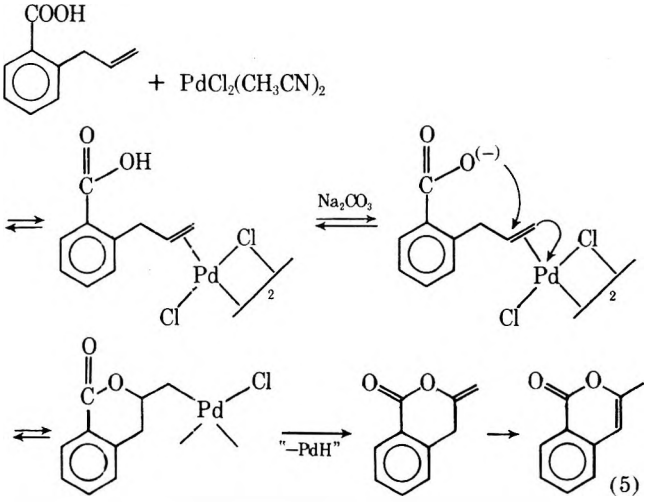
[a] Unless otherwise noted, all reactions were run using a stoichiometric amount of $PdCl_2{\cdot}2CH_3CN$. [b] Reported yields are of isolated, purified products. [c] Yield based on $PdCl_2{\cdot}2CH_3CN$, present in catalytic amounts. [d] This material was used without purification as obtained in Table II. [e] Yield is based on sodium 2-iodo-4-chlorobenzoate. [f] Yield is based on sodium 2-bromo-5-methoxybenzoate.

of the pyridine to the π-allylnickel halide complex, as evidenced by an immediate color change upon addition of substrate, apparently does occur, this coordination does not interfere with the allyl transfer. The yield of methyl 2-acetonyl-3-pyridinecarboxylate is probably somewhat higher than reported, since this product is quite water soluble and some difficulty in isolation was experienced. Both the base-catalyzed cyclization of these substrates to 3-methylisocoumarins (Table III) and the reductive cyclization to 3-methyl-3,4-dihydroisocoumarins (Table IV) were carried out in a routine fashion and require little comment. Both procedures resulted in high-yield production of the desired products.

Although aliphatic bromo acids, such as bromoacetic acid and 11-bromoundecanoic acid, react cleanly with π-allylnickel halide complexes to produce the corresponding allyl acids,[13] 2-bromobenzoic acid underwent primarily reductive debromination to produce benzoic acid upon reaction with a variety of π-allylnickel halide complexes. That benzoic acid is *not* produced in the reaction of 4-bromobenzoic acid with π-crotylnickel bromide suggests that the debromination of 2-bromobenzoic acid results from an intramolecular proton transfer from the carboxylic acid to the 2 position of the aromatic ring during reaction. Since radical anions are thought to be intermediates in the reaction of π-allylnickel halides with organic halides,[14] this is not unlikely. The problem of debromination was surmounted by converting the 2-bromobenzoic acids to their sodium salts prior to reaction with the nickel complexes. In this fashion, a number of substituted 2-allylbenzoic acids were prepared in high yield (Table II).

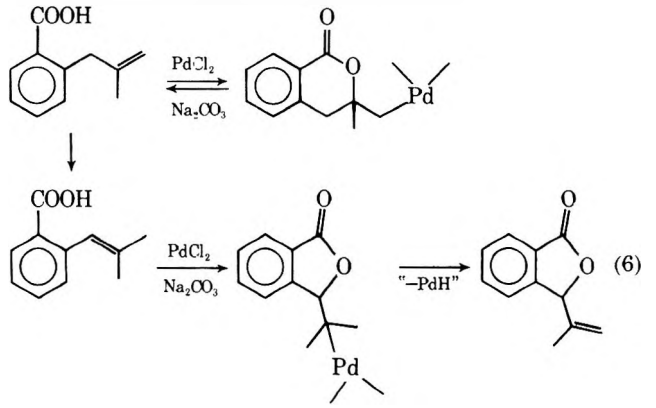
Palladium(II) has frequently been used to activate simple carbon–carbon double bonds to undergo attack by a variety of nucleophiles. The well-known Wacker process for the conversion of ethylene to acetaldehyde has as a key step the nucleophilic attack of palladium complexed ethylene by water. Other nucleophiles including acetate, chloride, and alkoxide as well as alcohols[15] and amines[16] react with Pd(II) complexed olefins. Several intramolecular versions of this reaction have also been developed. Thus 2-allylphenols were converted to benzofurans,[17] 2-allylanilines to indoles,[11] α,β-unsaturated ketoximes to isoxazoles,[18] *o*-hydroxychalcones to flavones,[19] and $\alpha,\beta,\gamma,\delta$-unsaturated carboxylic acids to α-pyrones,[20] by treatment with some form of Pd(II) and some base to generate a nucleophilic heteroatom.

Treatment of a number of 2-allylbenzoic acids with $PdCl_2(CH_3CN)_2$ and sodium carbonate in THF (eq 2) led to production of 2-alkylisocoumarins in high yield (Table V). The reaction is thought to proceed as in eq 5, involving coordination of the olefin to Pd(II), generation of free carboxylate by sodium carbonate, attack of carboxylate on this Pd(II) complex olefin to produce the ring closure and a σ-alkyl palladium



(5)

complex, followed by elimination of PdH and rearrangement to the observed isocoumarin. This mechanism is similar to that proposed for formation of indoles from 2-allylanilines,[11] and benzofurans from 2-allylphenols.[17] The stereochemistry of the ring closure and the state of coordination of the carboxylate group prior to attack are not known. Amines[21] and methoxide[22] have been shown to add to Pd(II) complexed olefins in a trans fashion, without prior coordination, while hydride[23] adds cis and is coordinated prior to attack. Chloride is known to attack by either mechanism, depending on concentration.[24] With all substrates but 2-vinylbenzoic acid, six-membered-ring lactones are the sole cyclized products when β-elimination is possible. It thus appears that the degree of substitution of the carbon atom to which palladium is bonded prior to β-elimination is of little consequence in determining the ring size of the product. With 2-(2-methyl-2-propenyl)benzoic acid, cyclization to the six-membered-ring lactone would result in a complex lacking β hydrogens, making β-elimination to product impossible (eq 6). The observed



(6)

product apparently results from an initial double bond rearrangement followed by ring closure. Since Pd(II) assisted additions to olefins are often reversible,[25] and since Pd(II) catalyzed double bond migrations are well known,[26] this is a reasonable assumption. Closure to a seven-membered ring would produce a σ-alkylpalladium complex which could β-eliminate. However, this was not observed.

As with other systems involving Pd(II) which produce materials that are not easily oxidized, the conversion of 2-allylbenzoic acids to 3-methylisocoumarins can be made catalytic in Pd(II) by providing a means of reoxidizing the Pd(0) produced in the elimination step. In this case cupric acetate and oxygen were used. Although using 2% $PdCl_2$ catalyst led to 1900% yield of isocoumarin (based on catalyst), the reaction was rather slow, and the yield of isocoumarin based on 2-allylbenzoic acid was rather low (41%). However, no attempt to optimize this catalytic reaction was made. Only the feasibility of developing a catalytic system was demonstrated.

Summary

The synthetic approaches to isocoumarins, dihydroisocoumarins, and isoquinolones presented above are among the mildest and most tolerant of functionality yet developed. The reaction of π-(2-methoxyallyl)nickel bromide with 2-haloaromatic esters provides direct access to 2-acetonylaromatic esters from readily available starting materials, for subsequent conversion to isocoumarins and dihydroisocoumarins by standard methods. The Pd(II) cyclization of 2-allyl aromatic acid derivatives to isocoumarins, dihydroisocoumarins, and isoquinolones is also very mild, tolerant of functionality, and of general utility. In most instances these new methods are a marked improvement over existing methods, and should find application in the synthesis of complex molecules.

Experimental Section

General. All melting points are uncorrected. Nuclear magnetic resonance (NMR) spectra were taken on either Varian Associates Model A-60A or T-60 60 MHz spectrometers or a JEOL MH 100 spectrometer. Me_4Si was used as the internal standard and absorptions are expressed in parts per million (δ). Infrared (IR) spectra were recorded on a Perkin-Elmer Model 337 or Model 267 spectrometer. Absorptions are reported in microns. Analytical thin layer chromatography (TLC) was performed using Brinkmann precoated silica gel F-254 plates (0.25 mm). Preparative layer chromatography was carried out using 20 × 20 cm plates coated with Brinkmann silica gel PF-254 (2.0 mm). Products were visualized with ultraviolet light. Elemental analyses were performed by Midwest Microlab Ltd., Indianapolis, Ind.

Materials. All solvents were freshly distilled and stored under an argon atmosphere. Immediately prior to use they were degassed and saturated with argon. DMF (Mallinckrodt) was distilled from CaH_2 under reduced pressure at 15–20 mmHg. Benzene (thiophene-free) was distilled at atmospheric pressure and stored over Linde type 4A molecular sieves. THF was refluxed over $LiAlH_4$ and distilled at atmospheric pressure under nitrogen. 2-Iodo-4-chlorobenzoic acid was prepared by diazotization of 4-chloroanthranilic acid.[27] 2-Bromo-5-methoxybenzoic acid was prepared by bromination of 3-methoxybenzoic acid.[28] 2-Bromo-3-pyridinecarboxylic acid was prepared via diazotization,[29] followed by oxidation[30] of 2-amino-3-picoline. 2-Bromo-4,5-dimethoxybenzoic acid was prepared by the bromination and oxidation[31] of veratraldehyde. Conversion of these acids to the corresponding salts was accomplished by reaction with an equimolar amount of sodium methoxide in methanol, followed by precipitation with ether or hexane–ether. Esterifications were performed via the method of Brewster and Ciotti.[32] 2-Vinylbenzoic acid was prepared from 2-bromostyrene (Columbia Chemical Co.) by treatment of the corresponding Grignard reagent with carbon dioxide.[33] 2-Bromobenzamide and 2-bromo-*N*-methylbenzamide were prepared by treatment of 2-bromobenzoyl chloride[34] with aqueous ammonia and methylamine, respectively, by the method of Vogel.[35] Sodium hydride and potassium hydride were purchased as oil dispersions from Alfa Inorganics Nickel carbonyl was purchased from Matheson in 1-lb lecture bottles. π-(2-Methoxyallyl)nickel bromide was prepared by the method of Hegedus and Stiverson.[10] All other nickel complexes were prepared by the method of Semmelhack and Helquist,[36] except that in the case of π-(1,1-dimethylallyl)nickel bromide, the reaction was carried out at reflux rather than at 70 °C. All of the nickel complexes were stored under argon at −20 °C until just prior to use. Transfers of the complexes were performed in a nitrogen-filled glove bag.

General Procedure for the Reaction of 2-Haloaromatic Acid Derivatives with π-Allylnickel Bromide Complexes. Reactions were carried out in a 50-mL one-neck flask with side arm containing a magnetic stirring bar and fitted with a serum cap and stopcock. The reaction flask was flushed several times with argon and placed in a nitrogen-filled glove bag containing the nickel complex. The desired amount of the complex was transferred to the reaction flask and dissolved in argon-saturated DMF (10 mL solvent/mmol complex), producing a deep red solution. The substrate (1.5 mmol/mmol nickel complex) was weighed out in a separate 50-mL one-neck flask with side arm. The flask was then fitted with a serum cap and stopcock and flushed with argon. Argon-saturated DMF was added via syringe to dissolve the substrate and the resulting solution added via syringe to the nickel complex. With substrates which were not very soluble in DMF, the flask containing the substrate was fitted with a stir bar prior to addition of solvent, and the solution of nickel complex added to the slurry of substrate. In all cases the reaction mixture was stirred at ca. 50 °C until the red color of the nickel complex disappeared. The resulting dark green solution was poured into a separatory funnel containing 50 mL of 1.2 N HCl, saturated with NaCl, and extracted with 4 × 50 mL of ether. The combined ether extracts were washed with 6 × 25 mL of saturated aqueous NaCl to ensure removal of DMF. The ether layer was then dried with anhydrous $MgSO_4$ and solvent removed by rotary evaporator. The resulting crude product was purified by preparative layer chromatography.

Reaction of 2-Haloaromatic Esters with π-(2-Methoxyallyl)nickel Bromide. A. Methyl 2-Acetonylbenzoate (2a). To a solution of the nickel complex (0.46 g, 1.10 mmol, in 10 mL of DMF) was added methyl 2-bromobenzoate (0.35 g, 1.64 mmol, in 10 mL of DMF) and the mixture stirred at 52 °C for 16 h. After routine isolation the material was purified by preparative layer chromatography (1:1 hexane–ether).

The R_f 0.24 band contained 0.26 g (81%) of pale yellow oil: NMR ($CDCl_3$) δ 2.17 (s, 3, $COCH_3$), 3.90 (s, 3, $COOCH_3$), 4.10 (s, 2, $-CH_2-$), 7.40 (m, 1 H, ArH), 8.10 (m, 1 H, ArH); IR (neat) 3.23–3.50 (m, C–H), 5.80 (vs, aromatic ester), 5.83 (vs, saturated acyclic ketone), 5.99 (m), 6.21 (m, aromatic C=C), 6.21 (m, aromatic C=C), 6.33 (m, aromatic C=C), 6.67 (m), 6.90 (s), 6.94 (s), 7.35 (s), 7.52 (s), 7.69 (sh), 7.87 (s), 8.40 (m), 8.62 (s, methyl ester), 8.77 (s), 9.26 (s), 9.52 (m), 10.42 (m), 12.50 (m), 13.51 (s, 4 adjacent ArH), 14.29 (s), 15.25 (m), 15.87 μ (m). A portion was molecularly distilled at 0.05 mmHg and submitted for analysis. Anal. ($C_{11}H_{12}O_3$): C, H.

B. Methyl 2-Acetonyl-4,5-dimethoxybenzoate (2b). To a solution of the nickel complex (0.34 g, 0.84 mmol, in 10 mL of DMF) was added methyl 2-bromo-4,5-dimethoxybenzoate (0.32 g, 1.15 mmol, in 10 mL of DMF) and the mixture stirred at 55 °C for 42 h. After routine isolation and purification by preparative layer chromatography (1:10 hexane–ether, two developments, R_f 0.28) 0.29 g (97%) of white solid was obtained: 100-MHz NMR (acetone-d_6) δ 2.12 (s, 3, $-COCH_3$), 3.76 (s, 3, $-COOCH_3$), 3.80 (s, 3, $-OCH_3$), 3.82 (s, 3, $-OCH_3$), 4.04 (s, 2, $-CH_2-$), 6.82 (s, 1, ArH), 7.50 (s, 1, ArH); IR (paraffin oil) 5.81 (vs, aromatic ester carbonyl), 5.85 (vs, saturated acyclic ketone), 6.21 (m, aromatic C=C), 6.33 (m, aromatic C=C), 6.54 (s), 6.92 (m), 7.35 (s), 7.58 (m), 7.72 (m), 7.81 (s, aromatic ester C–O), 8.16 (s), 8.44 (m), 8.55 (s), 8.62 (sh, methyl ester), 10.00 (m), 11.24 (m), 12.82 μ (m). A portion was recrystallized from ether (white needles, mp 118–119 °C) and submitted for analysis. Anal. ($C_{13}H_{16}O_5$): C, H.

C. Methyl 2-Acetonyl-4-chlorobenzoate (2c). To a solution of the nickel complex (0.78 g, 1.86 mmol, in 15 mL of DMF) was added methyl 2-iodo-4-chlorobenzoate (0.71 g, 2.40 mmol, in 15 mL of DMF) and the mixture stirred at 0 °C for 40 h, slowly warming to room temperature in the process. After routine isolation and purification by preparative layer chromatography (1:1 hexane–ether, R_f 0.44), 0.37 g (68%) of pale yellow oil was obtained: NMR ($CDCl_3$) δ 2.25 (s, 3, $-COCH_3$), 3.84 (s, 3, $-COOCH_3$), 4.08 (s, 2, $-CH_2-$), 7.25 (m, 2, ArH), 8.00 (d, J = 4 Hz, 1, ArH); IR (neat) 3.13–3.50 (br, C–H), 5.81 (br, vs, aromatic ester, acyclic saturated ketone carbonyls), 6.25 (s, aromatic C=C), 6.37 (s, aromatic C=C), 6.73 (m), 6.99 (s), 7.38 (s), 7.52 (m), 7.69 (sh), 7.94 (vs), 8.40 (m), 8.62 (s), 9.05 (vs), 9.26 (s), 11.24 (s, isolated ArH), 11.90 (m, 2 adjacent ArH), 12.99 μ (s). Anal. ($C_{11}H_{11}ClO_3$): C, H, Cl.

D. Methyl 2-Acetonyl-3-pyridinecarboxylate (6). To a solution of the nickel complex (0.46 g, 1.10 mmol, in 12 mL of DMF) was added

methyl 2-bromo-3-pyridinecarboxylate (0.36 g, 1.65 mmol, in 12 mL of DMF) and the reaction mixture stirred at 50 °C for 100 h. After this time, 15 mL of 1.2 N HCl was added and the mixture stirred for about 1 h to hydrolyze the enol ether. After neutralization with Na_2CO_3, the organics were extracted with 3 × 75 mL of chloroform and dried over $MgSO_4$. Chloroform was removed by rotary evaporator and the DMF removed at 0.05 mmHg to leave an oily residue.

Purification of this crude product by preparative layer chromatography (1:5 hexane–ether, two developments, R_f 0.27) gave 0.24 g (78%) of **6**, a bright yellow oil: NMR ($CDCl_3$) δ 2.32 (s, 3, $COCH_3$), 3.90 (s, 3, $COOCH_3$), 4.45 (s, 2, $-CH_2-$), 7.38, 8.40, 8.80 (AMX, 3, ArH); IR (neat) 2.70–3.13 (w), 3.23–3.51 (m, C–H), 5.80 (vs, aromatic ester carbonyl), 6.02 (m, acyclic saturated ketone carbonyl), 6.10 (m), 6.29 (s), 6.35 (s), 6.90 (s), 6.97 (s), 7.35 (s), 7.55 (m), 7.84 (vs, aromatic ester C–O), 8.62 (s, methyl ester), 8.81 (s), 9.26 (vs), 9.39 (m), 10.36 (m), 12.25 (m), 12.50 (m), 13.33 μ (s). A portion was molecularly distilled at 0.05 mmHg. Anal. ($C_{10}H_{11}NO_3$): C, H, N.

Reaction of 2-Haloaromatic Acid Salts with π-Allylnickel Complexes. A. 2-(2-Propenyl)benzoic Acid (4a). To a solution of π-allylnickel bromide (0.56 g, 1.6 mmol, in 15 mL of DMF) was added sodium 2-bromobenzoate (0.52 g, 2.3 mmol, in 15 mL of DMF) and the mixture stirred at 50 °C for 96 h. After routine isolation and purification by preparative layer chromatography (28:12:1 hexane–ether–formic acid, R_f 0.38), 0.28 g (76%) of white solid (mp 83–84 °C) was obtained: NMR ($CDCl_3$) δ 3.86 (d, J = 6 Hz, 2, $-CH_2-$), 5.07 (m, 2, $-C=CH_2$), 6.09 (m, 1, $-C=CH-$), 7.40 (m. 3, ArH), 8.00 (m. 1, ArH), 13.61 (s, 1, –COOH); IR (paraffin oil) 3.72–3.98 (br, OH), 5.92 (vs, aromatic –COOH carbonyl), 6.25 (s, aromatic C=C), 6.35 (m, aromatic C=C), 6.76 (m), 7.14 (m), 7.69 (m), 7.87 (s), 9.30 (m), 10.20 (m), 11.11 (s), 13.07 (s), 15.18 (m), 15.38 μ (m). Anal. ($C_{10}H_{10}O_2$): C, H.

B. *cis,trans*-2-(2-Butenyl)benzoic Acid (4b). To a solution of π-crotyl nickel bromide (0.55 g, 1.43 mmol, in 15 mL of DMF) was added sodium 2-bromobenzoate (0.48 g, 2.14 mmol, in 15 mL of DMF) and the mixture stirred at 50 °C for 96 h. After routine isolation and purification by preparative layer chromatography (28:12:1 hexane–ether–formic acid, R_f 0.52) 0.34 g (91%) of white solid (mp 89–90 °C) was obtained: NMR ($CDCl_3$) δ 1.68 (d, J = 4 Hz, 3, $C=CCH_3$), 3.78 (d, J = 5 Hz, 2, $C=CCH_2$), 5.60 (m, 2, HC=CH), 7.39 (m, 3, ArH), 8.10 (m, 1, ArH), 12.87 (s, 1, –COOH); IR (paraffin oil) 3.74–3.94 (br, OH), 5.93 (vs, aromatic –COOH carbonyl), 6.37 (m, aromatic C=C), 6.73 (w), 6.87 (m), 7.09 (m), 7.63 (m), 7.87 (m), 9.26 (w), 10.31 (m), 10.93 (m), 13.79 μ (m). Anal. ($C_{11}H_{12}O_2$): C, H.

C. 2-(3-Methyl-2-butenyl)benzoic Acid (4c). To a solution of π-(1,1-dimethylallyl)nickel bromide (0.45 g, 1.09 mmol, in 10 mL of DMF) was added sodium 2-bromobeenzoate (0.36 g, 1.62 mmol, in 10 mL of DMF) and the mixture stirred at 50 °C for 90 h. After isolation and purification as in B, the R_f 0.41 band contained 0.27 g (87%) of the desired product as a white solid: NMR ($CDCl_3$) δ 1.95 (s, 6, $-CH_3$), 3.82 (d, J = 7 Hz, 2, $-CH_2-$), 5.40 (m, 1, C=CH), 7.40 (m, 3, ArH), 8.15 (m, 1, ArH), 12.70 (s, 1, –COOH); IR (paraffin oil) 3.70–3.95 (br, OH), 5.95 (vs, aromatic –COOH carbonyl), 6.33 (m), 6.71 (w), 6.90 (m), 7.09 (m), 7.66 (m), 7.84 (m), 9.26 (m), 10.75 (m), 13.51 μ (m).

D. 2-(2-Methyl-2-propenyl)benzoic Acid. To a solution of π-(2-methylallyl)nickel bromide (0.56 g, 1.43 mmol, in 15 mL of DMF) was added sodium 2-bromobenzoate (0.47 g, 2.13 mmol, in 15 mL of DMF) and the mixture stirred at 50 °C for 120 h. After routine isolation and purification by preparative layer chromatography (28:12:1 hexane–ether–formic acid, R_f 0.42) 0.27 g (71%) of white solid (mp 66–67 °C) was obtained: NMR ($CDCl_3$) δ 1.80 (s, 3, $-CH_3$), 3.84 (s, 2, $-CH_2-$), 4.94 (m, 2, $C=CH_2$), 7.40 (m, 3, ArH), 8.15 (m, 1, ArH), 11.70 (s, 1, –COOH); IR (paraffin oil) 3.70–4.17 (br, OH), 5.90 (vs, aromatic –COOH carbonyl), 6.35 (s, aromatic C=C), 6.71 (s), 6.90 (s), 7.09 (s), 7.27 (m), 7.63 (s), 7.84 (s), 7.94 (m), 9.26 (m), 11.11 (s), 12.66 (m), 13.70 μ s). Anal. ($C_{11}H_{12}O_2$): C, H.

E. 2-(2-Propenyl)-4-Chlorobenzoic Acid (4d). To a solution of π-allylnickel bromide (0.43 g, 1.20 mmol, in 10 mL of DMF) was added sodium 2-iodo-4-chlorobenzoate (0.54 g, 1.79 mmol, in 10 mL of DMF) and the mixture stirred at 50 °C for 120 h. The crude product (0.38 g), a mixture of the desired compound and a small amount of unreacted starting material, was not readily separated by preparative layer chromatography. This mixture was used below.

F. 2-(2-Butenyl)-4-chlorobenzoic Acid (4e). To a solution of π-(crotyl)nickel bromide (0.58 g, 1.50 mmol, in 15 mL of DMF) was added sodium 2-iodo-4-chlorobenzoate (0.68 g, 2.24 mmol, in 15 mL of DMF) and the mixture stirred at 50 °C for 111 h. The crude product (0.48 g), a mixture of the desired compound and a small amount of unreacted starting material, was not readily separable by preparative layer chromatography. This mixture was used below.

G. 2-(2-Propenyl)-5-methoxybenzoic Acid (4f). To a slurry of sodium 2-bromo-5-methoxybenzoate (0.67 g, 2.64 mmol, in 15 mL of DMF) was added π-allylnickel bromide (0.64 g, 1.77 mmol, in 15 mL of DMF) and the mixture stirred at 50 °C for 96 h. The crude product (0.48 g), a mixture of the desired compound and a small amount of unreacted starting material, was not readily separable by preparative layer chromatography. This mixture was used below.

Reaction of 2-Bromobenzamides with π-Allylnickel Bromide. A. 2-(2-Propenyl)benzamide. To a solution of the nickel complex (0.68 g, 1.90 mmol, in 15 mL of DMF) was added 2-bromobenzamide (0.57 g, 2.83 mmol, in 15 mL of DMF) and the mixture stirred at 50 °C for 90 h. The reaction mixture was then mixed with 30 mL of 1.2 N HCl and extracted with 4 × 50 mL of chloroform. The combined chloroform extracts were dried with $MgSO_4$ and volatiles removed via rotary evaporator. Most of the DMF was removed by evaporation at 0.05 mmHg. The residue was dissolved in 50 mL of ether, washed with 3 × 10 mL of saturated aqueous NaCl, and dried with $MgSO_4$. Upon removal of solvent the resulting crude product was purified by preparative layer chromatography (5:5:1 hexane–ether–formic acid, R_f 0.49) to give 0.27 g (59%) of a white solid (mp 122–123 °C): NMR ($CDCl_3$) δ 3.58 (d, J = 6 Hz, 2, $-CH_2-$), 5.02 (m, 2, $C=CH_2$), 6.08 (m, 1, $-CH=C-$), 6.08 (br, 2, $-NH_2$), 7.31 (m, 4, ArH); IR (paraffin oil) 2.94 (vs, $-NH_2$), 3.25 (w, monosubstituted alkene), 3.33 (w, monosubstituted alkene), 6.06 (vs, primary amide carbonyl, amide I), 6.15 (s, primary amide N–H bend, amide II), 6.25 (m, aromatic C=C), 6.33 (m, aromatic C=C) 6.99 (m), 7.17 (s), 8.77 (m), 10.00 (m), 10.99 (m), 12.99 (m, 4 adjacent ArH), 15.38 μ (m). Anal. ($C_{10}H_{11}NO$): C, H, N.

B. 2-(2-Propenyl)-*N*-methylbenzamide. To a solution of π-allylnickel bromide (0.42 g, 1.17 mmol, in 15 mL of DMF) was added 2-bromo-*N*-methylbenzamide (0.37 g, 1.73 mmol, in 15 mL of DMF) and the mixture stirred at 50 °C for 70 h. After routine isolation and purification by preparative layer chromatography (5:5:1 hexane–ether–formic acid, two developments, R_f 0.52) 0.21 g (70%) of a white solid (mp 55–57 °C) was obtained: NMR ($CDCl_3$) δ 2.84 (d. 3, NCH_3), 3.61 (d, J = 6 Hz, 2, $-CH_2-$), 5.00 (m, 2, $-C=CH_2$), 5.95 (m, 1, $-CH=C-$), 6.98 (br, 1, NH), 7.08 (m, 4, ArH); IR (neat) 3.03 (s, N–H), 3.24 (w, monosubstituted alkene), 3.36 (w, C–H), 6.10 (s, secondary amide carbonyl, amide I), 6.23 (m), 6.45 (s, secondary amide N–H bend, amide II), 7.07 (m), 7.52 (m), 7.87 (m), 8.47 (w), 9.09 (m), 9.76 (m), 10.99 (m), 12.50 (m), 13.33 (m, 4 adjacent ArH), 14.29 μ (m).

General Procedure for the Preparation of 3-Methylisocoumarins from 2-Acetonylaromatic Esters. A twofold excess of NaH (as a 50% dispersion) was weighed out in a 50-mL three-neck flask. After addition of a magnetic stirring bar, the flask was fitted with a serum cap, stopper, and stopcock, and the system flushed with argon. The NaH dispersion was washed twice with argon-saturated hexane and the residue pumped to dryness. The system was then filled with argon and the desired amount of argon-saturated benzene added. Under a slow stream of argon, the serum cap was replaced by a reflux condensor and the substrate, followed by 3–4 drops of *tert*-butyl alcohol, added via syringe through the condensor. The resulting mixture was then refluxed overnight, cooled to room temperature, and poured into 50 mL of 1.2 N HCl which was previously saturated with NaCl. The aqueous layer was separated and extracted with 3 × 50 mL of ether and the combined organic extracts dried over anhydrous $MgSO_4$. After removal of solvent via rotary evaporator, the crude product was purified by preparative layer chromatography.

A. 3-Methylisocoumarin (3a). Using the procedure described above, methyl 2-acetonylbenzoate (0.19 g, 1.0 mmol), NaH (0.05 g, 2.0 mmol), and 2 drops of *tert*-butyl alcohol in 30 mL of benzene were refluxed for 19 h. After routine isolation and purification by preparative layer chromatography (5:1 benzene–ether, R_f 0.56), 0.13 g (81%) of a white, crystalline solid (mp 71–71.5 °C)[3a] was obtained with NMR and IR spectra identical with those reported for this compound prepared by a different route.[38]

B. 3-Methyl-6,7-dimethoxyisocoumarin (3b). Methyl 2-acetonyl-4,5-dimethoxybenzoate (0.26 g, 1.02 mmol), NaH (0.05 g, 2.04 mmol), and 2 drops of *tert*-butyl alcohol in 27 mL of benzene was refluxed for 79 h. After routine isolation and purification by preparative layer chromatography (20:1 chloroform–methanol, R_f 0.67) 0.15 g (67%) of a pale yellow solid (mp 134–135 °C)[5] was obtained: NMR (acetone-d_6) δ 2.22 (s, 3, $-CH_3$), 3.93 (s, 3, $-OCH_3$), 3.96 (s, 3, $-OCH_3$), 6.34 (s, 1, CH=C), 6 92 (s, 1, ArH), 7.50 (s, 1, ArH); IR (paraffin oil) 5.88 (vs, α,β-unsaturated δ-lactone carbonyl), 6.02 (m, cyclic six-membered vinyl ether C=C stretch), 6.21 (m), 6.37 (m), 6.64 (s), 7.22 (m), 7.38 (m), 7.91 (s), 8.06 (m, asymmetric C–O–C stretch), 8.26 (m), 8.58 (m), 8.77 (m), 9.35 (s, symmetric C–O–C stretch), 9.90 (m), 10.20 (w), 11.36 (m), 10.90 (w), 12.82 (w), 13.07 μ (m).

C. 3-Methyl-6-chloroisocoumarin (3c). Methyl 2-acetonyl-4-chlorobenzoate (0.30 g, 1.34 mmol), NaH (0.07 g, 2.68 mmol), and 2 drops of *tert*-butyl alcohol in 30 mL of benzene were refluxed for 24 h. After routine isolation and purification by preparative layer

chromatography (20:1 benzene–ether, R_f 0.42) 0.19 g (71%) of colorless needles (mp 154–155 °C) was obtained. This compound was identical in all respects with that prepared from 2-(2-propenyl)-4-chlorobenzoic acid (see below).

D. 7-Methyl-5*H*-pyrano[4,3-*b*]pyridin-5-one (7). Methyl 2-acetonyl-3-pyridinecarboxylate (0.12 g, 0.63 mmol), NaH (0.03 g, 1.26 mmol), and 2 drops of *tert*-butyl alcohol were refluxed in 35 mL of benzene for 24.5 h. The reaction mixture was then cooled to room temperature and acidified with 1.2 N HCl. The resulting mixture was made basic with Na_2CO_3, the aqueous layer saturated with NaCl, and the organic layer separated. Extraction of the aqueous layer with 3 × 50 mL of ether, drying of the organic layers with $MgSO_4$, and removal of solvent gave the crude product which was recrystallized from petroleum ether to give 62 mg (61%) of **7** as bright yellow crystals (mp 105–106 °C): NMR ($CDCl_3$) δ 2.40 (s, 3, $-CH_3$), 6.61 (s, 1, CH=C), 7.40, 8.52, 9.20 (AMX, 3, ArH); IR (paraffin oil) 5.75 (s, α,β-unsaturated δ-lactone carbonyl), 5.80 (sh), 6.02 (s, six-membered cyclic vinyl ether C=C), 6.29 (m, aromatic C=C), 6.39 (m, aromatic C=C), 6.76 (vs), 7.66 (m), 7.84 (m), 8.23 (m), 8.70 (m), 9.39 (m), 9.57 (m), 10.36 (m), 11.90 (m), 12.99 (m), 14.08 μ. Anal. ($C_9H_7NO_2$): C, H, N.

General Procedure for the Preparation of 3-Methyl-3,4-dihydroisocoumarins from 2-Acetonylaromatic Esters. The method of Tirodkar and Usgaonkar[5] was used without alteration.

Reaction of 2-Acetonylaromatic Esters with Sodium Borohydride. A. (±)-3-Methyl-3,4-dihydroisocoumarin (3'a). Methyl 2-acetonylbenzoate (0.31 g, 1.61 mmol) and $NaBH_4$ (0.20 g, 5.34 mmol) were stirred at 25 °C in 10 mL of methanol for 2 h. After routine isolation and purification by preparative layer chromatography (5:1 benzene–ether, R_f 0.44) 0.20 g (75%) of pale yellow oil was obtained which was identical with the product described below prepared in a different manner.

B. (±)-3-Methyl-6,7-dimethoxy-3,4-dihydroisocoumarin (3'b). Methyl 2-acetonyl-4,5-dimethoxybenzoate (0.30 g, 1.19 mmol) and $NaBH_4$ (0.20 g, 5.24 mmol) were stirred at 25 °C in 10 mL of methanol for 2 h. After routine isolation and purification by preparative layer chromatography (5:1 benzene–ether, R_f 0.35) 0.21 g (81%) of white solid (mp 105–106 °C, lit.[5] 104–105 °C) was obtained: NMR (acetone-d_6) δ 1.46 (d, J = 6 Hz, 3, $-CH_3$), 2.90 (d, J = 6 Hz, 3, $-CH_3$), 3.84 (s, 3, $-OCH_3$), 3.88 (s, 3, $-OCH_3$), 4.68 (m, 1, C–H), 6.94 (s, 1, ArH), 7.44 (s, 1, ArH); IR (paraffin oil) 5.83 (vs, α,β-unsaturated γ-lactone carbonyl), 6.21 (m), 6.60 (s), 7.33 (m), 7.60 (s), 7.84 (s), 8.00 (m, asymmetric C–O–C stretch), 8.20 (m), 8.55 (m), 9.30 (vs, symmetric C–O–C stretch), 11.30 (m), 12.20 (w), 12.90 μ (m).

C. (±)-3-Methyl-6-chloro-3,4-dihydroisocoumarin (3'c). Methyl 2-acetonyl-4-chlorobenzoate (0.14 g, 0.62 mmol) and $NaBH_4$ (0.08 g, 2.05 mmol) were stirred in 10 mL of methanol at 25 °C for 2 h. After routine isolation and purification by preparative layer chromatography (28:12:1 hexane–ether–formic acid, R_f 0.20) 0.11 g (94%) of white solid (mp 84–85.5 °C) was obtained: NMR (acetone-d_6) δ 1.49 (d, J = 6 Hz, 3, $-CH_3$), 3.07 (m, 2, $-CH_2-$), 4.74 (m, 1, CH=C), 7.44 (m, 2, ArH), 8.00 (d, J = 4 Hz, 1, ArH); IR (paraffin oil) 5.81 (vs, α,β-unsaturated δ-lactone carbonyl), 5.85 (sh), 6.25 (s), 7.46 (m), 7.84 (s), 8.10 (w), 8.70 (w), 8.93 (m), 9.13 (m), 9.39 (w), 9.66 (m), 10.47 (m), 11.43 (w), 11.70 (m), 11.90 (w), 12.99 (m), 14.71 μ (m). Anal. ($C_{10}H_9ClO_2$): C, H, Cl.

General Procedure for the Preparation of Isocoumarins from 2-Alkenylbenzoic Acids. The desired acid in THF (10 mL/mmol) was stirred with a slight excess of $PdCl_2$·$2CH_3CN$ at 25 °C for 5–10 min, after which time a homogeneous brown solution resulted. Anhydrous Na_2CO_3 (0.5 mmol excess) was added and the resulting mixture stirred at 25 °C for 3–4 h. The reaction mixture was then filtered to remove palladium metal, and the solvent stripped by rotary evaporator to yield a crude product which was purified by preparative layer chromatography.

Reaction of 2-Alkenylbenzoic Acids with Palladium Chloride and Sodium Carbonate. A. 3-Methylisocoumarin (5a). To a stirred solution of 2-(2-propenyl)benzoic acid (0.20 g, 1.23 mmol) and $PdCl_2$·$2CH_3CN$ (0.32 g, 1.24 mmol) in 15 mL of THF was added Na_2CO_3 (0.19 g, 1.78 mmol) and the resulting mixture stirred at 25 °C for 3 h. After routine isolation and purification by preparative layer chromatography (20:1 benzene–ether, R_f 0.69) 0.17 g (86%) of white solid was obtained identical in all respects with material prepared as above, and by yet a different route.[38]

B. 3-Ethylisocoumarin (5b). The reaction was run as in A using 2-(2-butenyl)benzoic acid (0.18 g, 1.0 mmol), $PdCl_2$·$2CH_3CN$ (0.26 g, 1.0 mmol), and Na_2CO_3 (0.16 g, 1.50 mmol) in 10 mL of THF. After routine isolation and purification by preparative layer chromatography (20:1 benzene–ether, R_f 0.64) 0.15 g (86%) of a colorless solid (mp 76–77 °C, lit. 76–77 °C)[3e] was obtained: NMR ($CDCl_3$) δ 1.30 (t, J = 7 Hz, 3, $-CH_3$), 2.60 (q, J = 7 Hz, 2, $-CH_2-$), 6.32 (s, 1, –C=CH), 7.50 (m, 3, ArH), 8.22 (m, 1, ArH); IR (paraffin oil) 5.68 (sh, γ,δ-unsaturated δ-lactone carbonyl), 5.80 (s, α,β-unsaturated δ-lactone carbonyl), 6.02 (s, six-membered cyclic vinyl ether C=C stretch), 6.23 (m), 6.37 (m), 6.76 (s), 7.52 (m), 7.81 (m), 8.33 (m), 8.62 (s), 8.77 (m), 9.26 (m), 9.62 (m), 9.71 (s), 10.64 (m), 12.05 (s), 13.07 (s), 14.60 μ (s).

C. 3-(Isopropyl)isocoumarin (5c). The reaction was run as in A using 2-(3-methyl-2-butenyl)benzoic acid (0.17 g, 0.88 mmol), $PdCl_2$·$2CH_3CN$ (0.23 g, 0.88 mmol), and Na_2CO_3 (0.11 g, 1.0 mmol) in 12 mL of THF, except that the mixture was stirred for 4 h. After routine isolation and purification by preparative layer chromatography (20:1 benzene–ether, R_f 0.67) 0.16 g (96%) of a pale yellow oil was obtained: NMR ($CDCl_3$) δ 1.29 (d, J = 7 Hz, 6, $-CH_3$), 2.80 (m, 1, CH), 6.25 (s, 1, C=CH), 7.50 (m, 3, ArH), 8.22 (m, 1, ArH); IR (neat) 3.23–3.45 (s, C–H), 5.76 (s, α,β-unsaturated δ-lactone carbonyl), 6.02 (s, six-membered cyclic vinyl ether C=C), 6.21 (m), 6.35 (m), 6.71 (s), 6.85 (m), 7.35 (m), 7.46 (m), 7.52 (m), 7.63 (m), 8.00 (m), 8.26 (m), 8.62 (m), 8.85 (s), 9.01 (m), 9.30 (s), 9.52 (m), 9.80 (s), 10.42 (s), 11.36 (m), 12.05 (m), 13.16 (s, four adjacent ArH), 14.49 μ (s). Anal. ($C_{12}H_{12}O_2$): C, H.

D. 3-Methyl-6-chloroisocoumarin (5d). The reaction was run as in A using the crude product obtained above (0.31 g, ca. 1.55 mmol), $PdCl_2$·$2CH_3CN$ (0.40 g, 1.55 mmol), and Na_2CO_3 (0.20 g, 1.91 mmol) in 15 mL of THF, except that the mixture was stirred for 4 h. After routine isolation and purification by preparative layer chromatography (20:1 benzene–ether, R_f 0.67) 0.18 g (63% from sodium 2-iodo-4-chlorobenzoate) of white solid (mp 155–156 °C) was obtained: NMR ($CDCl_3$) δ 2.34 (s, 3, $-CH_3$), 6.25 (s, 1, C=CH), 7.40 (m, 3, ArH), 8.22 (m, 1, ArH); IR (paraffin oil) 5.68 (vs, γ,δ-unsaturated δ-lactone carbonyl), 5.90 (w), 6.02 (s, cyclic six-membered vinyl ether C=C stretch), 6.23 (s), 6.41 (m), 6.78 (m), 7.09 (m), 7.19 (m), 7.46 (s), 7.60 (m), 8.62 (s), 9.17 (m), 9.48 (m), 10.00 (m), 10.20 (m), 11.11 (m), 11.36 (m), 11.56 (m), 11.90 (m), 12.27 (m), 12.90 (m), 14.71 μ (m). Anal. ($C_{10}H_7ClO_2$): C, H, Cl.

E. 3-Ethyl-6-chloroisocoumarin (5e). The reaction was run as in D, using the crude product obtained above (0.45 g, ca. 2.12 mmol), $PdCl_2$·$2CH_3CN$ (0.55 g, 2.12 mmol), and Na_2CO_3 (0.27 g, 2.53 mmol) in 20 mL of THF. After routine isolation and purification by preparative layer chromatography (20:1 benzene–ether, R_f 0.70) 0.23 g (54% from sodium 2-iodo-4-chlorobenzoate) of white solid (mp 94–95 °C) was obtained: NMR ($CDCl_3$) δ 1.30 (t, J = 7 Hz, 3, $-CH_3$), 2.62 (q, J = 7 Hz, 2, $-CH_2-$), 6.25 (s, 1, C=CH), 7.40 (m, 3 H, ArH), 8.20 (d, J = 9 Hz, 1, ArH); IR (paraffin oil) 5.70 (s), 5.81 (vs, α,β-unsaturated δ-lactone carbonyl), 5.92 (w), 6.02 (w, cyclic six-membered vinyl ether C=C stretch), 6.25 (m), 6.41 (w), 7.33 (m), 7.58 (w), 8.06 (w), 8.70 (m), 9.26 (m), 9.71 (m), 10.70 (w), 11.24 (w), 12.99 μ (m). Anal. ($C_{11}H_9ClO_2$): C, H, Cl.

F. 3-Methyl-7-methoxyisocoumarin (5f). The reaction was run as in A using crude 2-(2-propenyl)-5-methoxybenzoic acid (0.40 g, ca. 1.5 mmol), $PdCl_2$·$2CH_3CN$ (0.39 g, 1.51 mmol), and Na_2CO_3 (0.21 g, 2.0 mmol) in 10 mL of THF. After routine isolation and purification by preparative layer chromatography (5:1 benzene–ether, R_f 0.61) 0.28 g (65% from sodium 2-bromo-5-methoxybenzoate) of a pale yellow solid (mp 93–94 °C, lit.[5] 93–94 °C) was obtained: NMR ($CDCl_3$) δ 2.30 (s, 3, $-CH_3$), 3.94 (s, 3, $-OCH_3$), 6.26 (s, 1, C=CH), 7.31 (d, J = 2 Hz, 2, ArH), 7.50 (s, 1, ArH); IR (paraffin oil) 5.62 (w), 5.75 (sh), 5.81 (s, α,β-unsaturated δ-lactone carbonyl), 6.02 (m, cyclic six-membered vinyl ether C=C stretch), 6.17 (m), 6.67 (s), 6.85 (m), 7.41 (s), 7.75 (m), 7.81 (m), 8.06 (s), 8.62 (m), 9.39 (s), 9.71 (s), 10.26 (m), 11.24 (m), 11.83 (s), 12.90 (m), 14.29 μ (m).

G. Isocoumarin (1). To a stirred solution of 2-vinylbenzoic acid (0.22 g, 1.46 mmol) and $PdCl_2$·$2CH_3CN$ (0.38 g, 1.46 mmol) in 10 mL of THF was added Na_2CO_3 (0.16 g, 1.47 mmol) and the resulting mixture stirred for 2 h at 25 °C. An additional portion (0.08 g, 0.75 mmol) of Na_2CO_3 was added and the reaction mixture stirred for an additional 1 h. After routine isolation and purification by preparative layer chromatography (20:1 benzene–ether) two major products were obtained.

Compound 1: R_f 0.59; 45 mg (21%) of yellow solid; NMR ($CDCl_3$) δ 5.28 (s, 2, C=CH_2), 7.78 (m, 4, ArH); IR (paraffin oil) 5.56 (sh, five-membered unsaturated lactone carbonyl, due to double bond adjacent to –O–), 5.62 (s, five-membered unsaturated lactone carbonyl), 5.71 (sh, five-membered unsaturated lactone carbonyl due to double bond adjacent to carbonyl), 5.78 (sh), 5.99 (s, alkene adjacent to –O–), 6.76 (s), 7.43 (m), 7.84 (s), 8.40 (w), 8.99 (m), 9.13 (m), 9.90 (s), 10.53 (s), 11.30 (m), 11.63 (m), 12.90 (m), 13.05 (s), 14.49 μ (s). From spectral data, this compound is 3-methylenephthalide (**8**). Upon reduction (H_2/Pd) the δ 5.28 singlet was replaced by signals at δ 1.75 (d, J = 7 Hz, 3, CH_3), 5.60 (q, J = 7 Hz, 1, CH), 7.50 (m, 4, ArH).

Compound 2: R_f 0.47; 0.13 g (62%) of a pale yellow solid (mp 46–47

°C, lit.[39] 46–47 °C); with IR and NMR spectra identical with those reported for isocoumarin.[39]

H. (±)-3-(Isopropenyl)phthalide (9). A slurry of 2-(2-propenyl)benzoic acid (0.21 g, 1.21 mmol) and $PdCl_2{\cdot}2CH_3CN$ (0.32 g, 1.23 mmol) was stirred in 15 mL of THF at 25 °C for 1 h. Na_2CO_3 (0.16 g, 1.56 mmol) was then added and the mixture stirred for an additional 4 h. After routine isolation and purification by preparative layer chromatography (22:3 benzene–ether, R_f 0.52), 0.07 g (31%) of **9**, a white solid (mp 56–57 °C), was obtained: NMR ($CDCl_3$) δ 1.78 (d, J = 1 Hz, 3, $-CH_3$), 5.32 (m, 2, $C{=}CH_2$), 5.87 (s, 1, CH), 7.64 (m, 4, ArH); IR (paraffin oil) 5.65 (vs, α,β-unsaturated γ-lactone carbonyl), 6.21 (m), 6.23 (m), -6.80 (s), 7.69 (s), 7.81 (s), 8.26 (m), 9.01 (m), 9.13 (m), 9.35 (s), 9.85 (m), 10.00 (m), 10.36 (s), 12.50 μ (w).

Preparation of 3-Methylisocoumarin Using a Catalytic Amount of Palladium Chloride. A slurry of 2-(2-propenyl)benzoic acid (0.30 g, 1.86 mmol), $PdCl_2{\cdot}2CH_3CN$ (0.011 g, 0.04 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.19 g, 0.93 mmol), and Na_2CO_3 (0.21 g, 2.00 mmol) in 25 mL of THF was refluxed for 119 h. Oxygen was bubbled through the mixture during the entire period. Saturated aqueous Na_2SO_3 (50 mL) was added to destroy any peroxides, and the organic products extracted with 5 × 40 mL of ether and dried with $MgSO_4$. Removal of solvent by rotary evaporator gave the crude product which was purified by preparative layer chromatography (20:1 benzene–ether, R_f 0.55) to give 0.12 g (1900% based on palladium chloride, 41% based on the alkenyl acid) of 3-methylisocoumarin.

(±)-3-Methyl-3,4-dihydroisocoumarin via $PdCl_2$ Cyclization. A slurry of 2-(2-propenyl)benzoic acid (0.24 g, 1.49 mmol), $PdCl_2{\cdot}2CH_3CN$ (0.39 g, 1.49 mmol), and Na_2CO_3 (0.21 g, 2.0 mmol) in 15 mL of THF was stirred at 25 °C for 5 h. A hydrogen-filled balloon was then affixed and the reaction mixture was stirred at 50 °C for 16 h. After routine isolation and purification by preparative layer chromatography (5:1 benzene–ether, R_f 0.58) 0.16 g (65%) of pale yellow oil was obtained: NMR ($CDCl_3$) δ 1.46 (d, J = 7 Hz, 3, $-CH_3$), 2.91 (d, J = 7 Hz, 2, $-CH_2-$), 4.57 (m, 1, CH), 7.26 (m, 3, ArH), 8.00 (m, 1, ArH); IR (neat) 3.27–3.56 (m, C–H), 5.81 (vs, α,β-unsaturated δ-lactone carbonyl), 6.23 (m), 6.87 (m), 7.25 (m), 7.41 (m), 7.84 (vs), 8.10 (s, C–O), 8.97 (s, C–O), 9.26 (m), 9.62 (m), 9.76 (m), 10.53 (m), 11.25 (m), 12.58 (m), 13.61 (s, four adjacent ArH), 14.08 (m), 14.71 μ (m). Anal. ($C_{10}H_{10}O_2$): C, H.

Reaction of 2-Alkenylbenzamides with Palladium Chloride and Sodium Hydride. A. 3-Methylisocarbostyril. 2-(2-Propenyl)-benzamide (0.16 g, 1.0 mmol), $PdCl_2{\cdot}2CH_3CN$ (0.26 g, 1.0 mmol), and NaH (0.04 g, 1.65 mmol) in 12 mL of THF was stirred at 25 °C for 4 h. After routine isolation and purification by preparative layer chromatography (triethylamine, R_f 0.57) 0.11 g (68%) of white solid was obtained with identical IR, NMR spectra, and melting point with authentic material.[38]

B. 3-Methyl-*N*-methylisoquinolone. 2-(2-Propenyl)-*N*-methylbenzamide (0.16 g, 0.90 mmol), $PdCl_2{\cdot}2CH_3CN$ (0.24 g, 0.93 mmol), and NaH (0.03 g, 1.25 mmol) in 10 mL of THF was stirred at 25 °C for 4 h. After routine isolation and purification by preparative layer chromatography (10:1 chloroform–methanol, R_f 0.48) 0.14 g (91%) of a colorless solid (mp 102–103 °C, lit.[40] 102–103 °C) was obtained: NMR ($CDCl_3$) δ 2.39 (s, 3, CCH_3), 3.54 (s, 3, NCH_3), 6.31 (s, 1, C=CH), 7.76 (m, 4, ArH); IR (paraffin oil) 6.06 (s, α,β-unsaturated δ-lactam), 6.15 (s), 6.21 (m), 6.71 (m), 7.04 (m), 7.43 (m), 7.63 (m), 7.75 (m), 8.62 (m), 9.62 (w), 9.90 (w), 11.36 (w), 12.05 (m), 13.25 (m), 14.49 μ (m).

Acknowledgments. This investigation was supported by Grant 5 RO1 CA15529 awarded by the National Cancer Institute, DHEW. Outstanding technical assistance was afforded by Roy Odle.

Registry No.—**1**, 491-31-6; **2a**, 7115-18-6; **2b**, 61436-69-9; **2c**, 61436-70-2; **3a**, 29539-21-7; **3'a**, 25222-31-5; **3b**, 31706-51-1; **3'b**, 31759-12-3; **3c**, 61436-71-3; **3'c**, 61436-72-4; **4a**, 61436-73-5; *cis*-**4b**, 61436-74-6; *trans*-**4b**, 61436-75-7; **4c**, 61436-76-8; **4d**, 61436-77-9; **4e**, 61436-78-0; **4f**, 61436-79-1; **5b**, 26477-57-6; **5c**, 61436-80-4; **5e**, 61436-81-5; **5f**, 18781-14-1; **6**, 61436-82-6; **7**, 61436-83-7; **8**, 3453-63-2; **9**, 61436-84-8; π-allylnickel bromide, 12012-90-7; π-crotylnickel bromide, 12145-58-3; π-(1,1-dimethylallyl)-nickel bromide, 32650-02-5; π-(2-methylallyl)nickel bromide, 12300-62-8; methyl 2-bromobenzoate, 610-94-6; methyl 2-bromo-4,5-dimethoxybenzoate, 17667-32-2; methyl 2-iodo-4-chlorobenzoate, 13421-13-1; methyl 2-bromo-3-pyridinecarboxylate, 52718-95-3; sodium 2-bromobenzoate, 17264-73-2; sodium 2-iodo-4-chlorobenzoate, 61436-85-9; sodium 2-bromo-5-methoxybenzoate, 61436-86-0; 2-(2-propenyl)-benzamide, 61436-87-1; 2-bromobenzamide, 4001-73-4; 2-(2-propenyl)-*N*-methylbenzamide, 15482-10-7; 2-bromo-*N*-methylbenzamide, 61436-88-2; palladium chloride, 7647-10-1; sodium carbonate, 497-19-8; 2-vinylbenzoic acid, 27326-43-8; 3-methyl-*N*-methylisoquinolone, 7114-78-5; 2-(2-methyl-2-propenyl)benzoic acid, 61436-89-3.

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Carbon-13 Magnetic Resonance Spectroscopy of Coumarins. Carbon-13–Proton Long-Range Couplings

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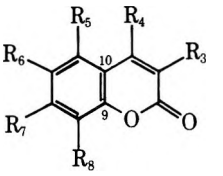
Received September 21, 1976

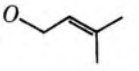
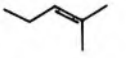
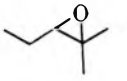
The high-resolution ^{13}C magnetic resonance spectra of eight coumarins have been determined. The ^{13}C–^{1}H long-range couplings are extensively analyzed, and utilized in the spectral interpretation, particularly for the differentiation of some very close resonance signals. The dynamic equilibrium of hydrogen-bonding and stereochemical effects on long-range couplings has been studied. The anti ^{13}C–^{1}H three-bond coupling constants are greater than the syn ones.

A large number of natural products incorporate the coumarin skeleton,[2] which is derived from a cinnamic acid unit. Biosynthetic isoprenylation of coumarins is common, frequently appearing in its simplest form, as the γ,γ-dimethylallyl substituent either on a phenolic oxygen or its adjacent carbon.[2] Progress on the structure elucidation of new coumarins has been tremendously enhanced by the application of proton magnetic resonance spectroscopy.[3] Lately, carbon-13 magnetic resonance (^{13}C NMR) spectroscopy has also been applied in the structural analysis of coumarins. The ^{13}C spectra of some coumarins have been analyzed,[4-8] based on the structural dissimilarily and the additivity principle of chemical shift. Until very recently, the ^{13}C–^{1}H coupling patterns have not been utilized in the spectral analysis of natural products and drugs. We have successfully applied the unique coupling information in the spectral analysis of sulfonamides,[9] antihistaminics,[10] flavonoids,[11,12] and a number of antibiotics.[12] Although Cussans and Huckerby[13] recently used the coupling patterns in their analysis of the ^{13}C spectra of coumarin and its bromo, hydroxy, methoxy, methyl, and glucosyl derivatives, some specific ^{13}C–^{1}H long-range couplings have not been properly assigned. Here we would like to present a detailed discussion of these long-range couplings, including the influence of stereochemical and substitution factors, and the dynamic equilibrium.

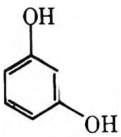
In previous reports,[7b,13] the ^{13}C–^{1}H-long-range coupling constants of coumarins have been partially assigned. An intensive analysis of the ^{13}C–^{1}H coupling patterns of nine coumarins is summarized in Tables I and II. The interpretation follows from the known data on simple aromatic compounds:[10,11,14] (1) $^{3}J_{CH}$ is normally in the range of 4–10 Hz; (2) $^{2}J_{CH}$ is no larger than 4 Hz; and (3) $^{4}J_{CH}$ is less than 2 Hz.

The ^{13}C–^{1}H coupling patterns of the C_9 and C_{10} resonance signals of coumarin (1) were not previously analyzed owing to the complex fine splittings.[7b,13] However, their patterns can be unraveled based on our high-resolution data, and further verified by analysis of the previously undefined coupling constants (Table III). The largest three-bond splitting of the C_9 signal is assigned to the coupling between C_9 and H_5 by comparison with the coupling patterns of 4-, 5-, 7- and 8-substituted coumarins. These comparative studies also indicate the relative magnitude of the other two three-bond couplings [$^{3}J(C_9–H_7) > {}^{3}J(C_9–H_4)$]. Similarly, the order of $^{3}J(C_{10}–H)$ can be determined [$^{3}J(C_{10}–H_6) \geq {}^{3}J(C_{10}–H_3) > {}^{3}J(C_{10}–H_8)$]. The reduction of $^{3}J(C_{10}–H_8)$ can be ascribed to the coupling through an oxygen-substituted carbon.[11] This characteristic reduced coupling has diagnostic value for the spectral analysis of the other oxygen-substituted coumarins except in 6,7- and 7,8-dioxygen-substituted systems.



	R_3	R_4	R_6	R_5	R_7	R_8
1	H	H	H	H	H	H
2	CO_2H	H	H	H	H	H
3	OH	H	H	H	H	H
4	H	OH	H	H	H	H
5	H	H	OH	H	H	H
6	H	H	H	H	OH	H
7	H	H	H	H	OCH_3	H
8	H	H	H	H	*O*-β-D-Glu	H
9	H	H	H	H		H
10	H	H	OH	H	OH	H
11	H	H	*O*-β-D-Glu	H	OH	H
12	H	H	H	H	OH	OH
13	H	H	H	OCH_3	OCH_3	
14	H	H	H	H	OCH_3	
15	H	CH_3	H	H	OH	H
16	H	CH_3	H	H	*O*-β-D-Glu	H
17	H	CH_3	OH	H	OH	H
18	H	CH_3	H	H	OH	OH

A rather large two-bond coupling is observed in 7-oxygen substituted coumarins [$^{2}J(C_9–H_8)$], and 5,7-dihydroxyflavonoids[11,12] [$^{2}J(C_5–H_6)$ and $^{2}J(C_7–H_6)$] as well. It can most likely be attributed to the specific meta-dioxygen substitution which is manifested in the model studies. The $^{2}J(C_1–H_2)$ (4.1 Hz) of resorcinol is greater than that (2.5 Hz) of phenol.[11]



$^{3}J(C_1–H_5) = 11.0$ Hz
$^{2}J(C_1–H_2) = 4.1$ Hz
$^{3}J(C_2–H_4) = 4.8$ Hz

These ^{13}C–^{1}H two-bond coupling constants were tentatively assigned to the ^{13}C–OH coupling.[13] However, this ^{13}C–OH coupling can be ruled out in normal dimethyl sulfoxide solution because of the demonstrated fast dynamic equibration.[11] These two- and three-bond couplings can be very helpful in locating the oxygen substituents in the coumarin system.

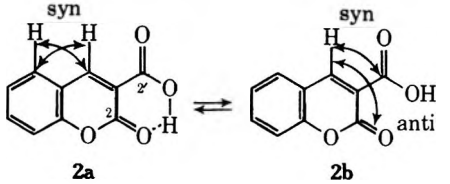
The assignments of $^{2}J(C_2–H_3)$ (4.5 Hz) and $^{3}J(C_2–H_4)$ (11.5

Table I. ^{13}C Chemical Shifts (δ) and ^{13}C–^{1}H Coupling Constants (Hz) of Coumarins [a]

Carbon	1	2	6	10
2	159.2 dd 11.5 (H_4) 4.5 (H_3)	157.5 d 10.3 (H_4)	161.0 dd 11.5 (H_4) 4.9 (H_3)	161.2 dd 11.4 (H_4) 4.8 (H_3)
3	115.2 d 172.6 (H_3)	118.3 d 1.0 (H_4)	111.6 d 172.6 (H_3)	111.9 d 172.1 (H_3)
4	142.5 ddd 164.7 (H_4) 5.4 (H_5) 1.1 (H_3)	148.9 dd 168.0 (H_4) 4.4 (H_5)	144.5 dd 164.5 (H_4) 4.8 (H_5)	144.7 dd 164.6 (H_4) 4.9 (H_5)
5	127.0 dddd 162.7 (H_5) 8.2 (H_7) 4.0 (H_4) 1.3 (H_6)	130.5 ddd 165.6 (H_5) 8.0 (H_7) 4.0 (H_4)	129.8 dd 163.6 (H_5) 3.9 (H_4)	112.6 dd 160.7 (H_5) 4.2 (H_4)
6	123.2 dd 163.8 (H_6) 7.7 (H_8)	125.3 dd 165.3 (H_6) 7.6 (H_8)	113.4 dd 163.6 (H_6) 4.9 (H_8)	143.0 dd 7.0 (H_8) 3.3 (H_5)
7	130.6 ddd 163.4 (H_7) 8.9 (H_5) 0.6 (H_8 or H_6)	134.8 dd 164.4 (H_7) 8.5 (H_5)	161.5 dd 10.9 (H_5) 3.4 (H_8) 2.1 (H_6)	150.5 dd 8.1 (H_5) 3.7 (H_8)
8	115.1 dd 165.0 (H_8) 7.7 (H_6)	116.5 dd 166.3 (H_8) 7.1 (H_6)	102.5 dd 162.8 (H_8) 4.5 (H_6)	102.9 d 161.6 (H_8)
9	152.6 ddddd 10.2 (H_5) 7.4 (H_7) 5.6 (H_4) 2.8 (H_8) 1.3 (H_6 or H_3)	154.7 m	155.8 ddd 9.9 (H_5) 5.7 (H_4) 4.5 (H_8)	148.8 ddd 10.0 (H_5) 6.2 (H_4) 4.9 (H_8)
10	117.6 tdt 8.5 (H_6, H_3) 4.6 (H_8) 1.5 (H_5 or H_4)	118.2 dd 6.8 (H_6) 5.4 (H_8)	111.6 tdt 7.2 (H_6, H_3) 6.4 (H_8) 1.5 (H_5 or H_4)	111.2 ddd 8.1 (H_3) 5.4 (H_8) 1.5 (H_5 or H_4)

[a] The data for each carbon resonance are shown in the following order: chemical shift, multiplicity, and coupling constants (coupled protons). m: unresolved multiplet.

Hz) of coumarin are ascertained by studying the coupling pattern change of **2**, in which the smaller splitting [$^{2}J(C_2$–$H_3)$] is absent. The allocation of C_2 and $C_{2'}$ resonances of **2** is derived from simple chemical shift theory.[15] Their coupling analyses disclose the stereospecificity of the ^{13}C–^{1}H three-



2a **2b**

bond couplings, $^{3}J(C_2$–$H_4)$ (10.3 Hz) (anti) > $^{3}J(C_{2'}$–$H_4)$ (5.4 Hz) (syn). This result is consistent with Marshall's study on crotonic and isocrotonic acids.[16] The steric dependence of three-bond couplings can also account for the reduction of $^{3}J(C_4$–$H_5)$ and $^{3}J(C_5$–$H_4)$ since they are syn couplings. Based on the coupling analysis described above, the C_{10} peak [118.2 ppm; $^{3}J(C_{10}$–$H_6)$ = 6.8 and $^{3}J(C_{10}$–$H_8)$ = 5.4 Hz] of **2** can be easily distinguished from the C_3 peak [118.3 ppm; $^{2}J(C_3$–$H_4)$

Table II. ^{13}C Chemical Shifts (δ) and ^{13}C–^{1}H Couplings (Hz) of Isoprenyl Coumarins [a]

Carbon	9	13	14	19[c]
2	160.1 dd 11.3 (H_4) 4.6 (H_3)	160.9 dd 11.6 (H_4) 4.3 (H_3)	161.1 dd 11.6 (H_4) 4.9 (H_3)	161.3 dd 11.6 (H_4) 3.9 (H_3)
3	111.9 d 172.1 (H_3)	112.4 d 172.1 (H_3)	110.5 d 172.7 (H_3)	110.4 d 172.7 (H_3)
4	142.7 dd 163.0 (H_4) 4.9 (H_5)	143.5 dd 162.4 (H_4) 4.9 (H_5)	138.6 d 165.4 (H_4)	138.7 d 166.0 (H_4)
5	128.1 dd 163.0 (H_5) 3.7 (H_4)	126.0 dd 163.3 (H_5) 2.8 (H_4)	155.7 m[b]	156.0 m[b]
6	112.1 dd 164.2 (H_6) 4.9 (H_8)	107.0 d 161.7 (H_6)	90.2 d 158.7	95.5 dd 160.8 (H_6) 5.2 (H_8)
7	161.2 dtd 10.0 (H_5) 5.7 (H_{11}) 3.0 (H_8)	159.8 m[b]	161.2 m[b]	163.5 sex.[b] 4.2 (H_6, H_8, OMe)
8	100.6 dd 163.1 (H_8) 4.3 (H_6)	117.3 m[b]	106.0 q 4.9 (H_6, H_{11})	92.5 dd 165.1 (H_8) 4.0 (H_6)
9	154.9 dt 9.8 (H_5) 5.5 (H_4, H_8)	152.4 dq 9.8 (H_5) 5.0 (H_4, H_{11})	153.9 m[b]	156.5 t 5.5 (H_4, H_3)
10	111.6 td 8.1 (H_3, H_6) 4.9 (H_8)	112.6 tt 8.2 (H_3, H_6) 1.8 (H_4, H_5)	103.5 dd 7.6 (H_3) 5.8 (H_6)	104.0 dt 7.9 (H_3) 5.2 (H_6, H_8)
11	64.6 td 143.6 (H_{11}) 2.7 (H_{12})	21.6 td 129.3 (H_{11}) 3.7 (H_{12})	21.8 td 130.6 (H_{11}) 4.3 (H_{12})	65.5 td 143.7 (H_{11}) 2.9 (H_{12})
12	118.1 dm[b] ca. 156 (H_{12})	120.8 dm[b] 161.1 (H_{12})	59.1 dm[b] 175.8 (H_{12})	118.3 dm[b] 151.4 (H_{12})
13	137.9 m[b]	132.1 m[b]	63.1 m[b]	141.8 m[2]
14	17.5 qdq 125.7 (H_{14}) 8.2 (H_{12}) 4.2 (H_{15})	17.6 qdq 125.4 (H_{14}) 8.1 (H_{12}) 4.2 (H_{15})	19.0 qq 126.5 (H_{14}) 3.4 (H_{15})	16.5 qdt 126.0 8.2 (H_{12}) 3.1 (H_{15})
15	25.0 qdq 125.7 (H_{15}) 6.8 (H_{12}) 4.0 (H_{14})	25.4 qdq 125.1 (H_{15}) 7.2 (H_{12}) 3.9 (H_{14})	24.6 bq[b] 126.9 (H_{15})	39.2 bt[b] 127.0 (H_{15})
OMe		55.7 q 144.5 (OMe)	55.9 q 144.7 (OMe) 55.8 q 144.7 (OMe)	55.5 q 144.7 (OMe)

[a] The data of each carbon resonance are shown in the following order: chemical shift, multiplicity, and coupling constants (coupled protons). [b] b = broad; sex. = sextet; m = unresolved multiplet. [c] C_{16} = 26.0, q, 127.0 (H_{16}), 4.9 (H_{15}, H_{17}); C_{17} = 123.4, dm, 151.4 (H_{17}); C_{13} = 131.6, m; C_{19} = 17.5, qdq, 125.4 (H_{19}), 8.2 (H_{17}), 4.1 (H_{20}); C_{20} = 25.4, qdq, 125.1 (H_{20}), 7.3 (H_{17}), 4.0 (H_{19}).

Table III. ^{13}C–^{1}H Long-Range Couplings of Coumarins[13,a]

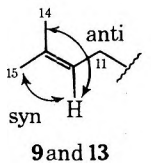
	Coupled proton						
	C_9				C_{10}		
Compd	H_5	H_7	H_4	H_8	H_6	H_3	H_8
3	7.5	6	6		5[c]		4.5[c]
4	9.5	8		2.5	8	5.5[c]	4.5[c]
5	8	8	6	2		8	5
7	*b*				8	8	5
8	*b*				7.5	7.5	5
11	10	6[c]	5[c]	?		8	6
12	8.5		6.5		8	8	
13							
14	10.5			5		b	
15	10.5			5		b	
16	10			4.5		b	
17	9					b	

[a] Carbon spectra were determined at 20 MHz using a Varian CFT-20 spectrometer with 4K data points. [b] The coupling patterns were not reported. [c] These assignments within the same line may be reversed.

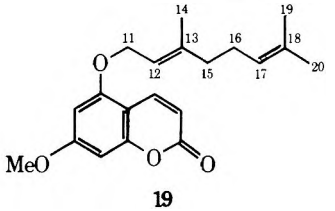
= 1 Hz] despite the fact that their shifts are almost identical, and they cannot be differentiated by conventional chemical shift theory. In the same manner, we can determine the resonance signals of C_3 [115.2 ppm; $^{1}J(C_3–H_3)$ = 172.6 Hz)] and C_8 [115.1 ppm; $^{1}J(C_8–H_8)$ = 165.0, $^{3}J(C_8–H_6)$ = 7.7 Hz] of **1**. Furthermore, in **2** there is no coupling between C_3 and the hydroxy proton, suggesting fast equilibration between conformers **2a** and **2b**, and/or fast intermolecular hydrogen exchange.[11]

The resonance signal assignments of other carbons of **2** can be achieved by analogy to coumarin. These results can then be applied to the spectral interpretation of umbelliferone (**6**) and esculetin (**10**). It is noted that $^{3}J(C_6–H_8)$ and $^{3}J(C_7–H_5)$ have the same magnitude as normal three-bond coupling constants although the coupling occurs through an oxygen-substituted carbon. This seems to be a special case in this particular system because no similar phenomena can be detected in the model study.[17] Further examination of this exception is desirable.

The carbon resonances of the γ,γ-dimethylallyl coumarins (**9** and **13**) can now be assigned, following the approach presented above to unambiguously differentiate C_2 from C_7, and



9 and **13**



19

C_3 from C_6 in spite of their small chemical shift differences. Additionally, it is worth noticing that the stereospecificity of ^{13}C–^{1}H long-range coupling can again be used to distinguish the two methyl resonance signals [$^{3}J(C_{14}–H_{12}) > {}^{3}J(C_{15}–H_{12})$]. These assignments ($C_{14}$ = 17.5 ppm and C_{15} = 25.0 ppm) are in agreement with the chemical shift calculation derived from the well-known γ effect.[15] The complicated multiplicity of the C_{12} (118.1 ppm) and C_{13} (137.9 ppm) signals is attributed to the many ^{13}C–^{1}H long-range couplings. The resonance assignments of sibiricin (**14**) can then be made without difficulty based on the conventional chemical shift theory and coupling patterns. However, the stereospecificity of the ^{13}C–^{1}H long-range coupling in an epoxide system is still too uncertain to determine their accurate couplings.

From Roberts' extensive chemical shift analysis of alkenes[18] and the previous interpretation of the γ,γ-dimethylallyl unit, the chemical shifts of the geranyl portion of 5-geranyloxy-7-methoxycoumarin (**19**) can be determined. The relative position of the resonance peaks for C_{12} and C_{17}, and C_{13} and C_{18} are predictable,[18] i.e., $C_{12} < C_{17}$ and $C_{18} < C_{13}$. Therefore, we can assign the peaks at 118.3, 123.4, 131.6, and 141.8 ppm to C_{12}, C_{17}, C_{18}, and C_{13}, respectively. The assignment of the C_{14} signal (~6.5 ppm) is derived from the long-range fine splittings [$^{3}J(C_{14}–H_{12})$ (anti) = 8.2 and $^{3}J(C_{14}–H_{15})$ = 3.1 Hz]. On the other hand, the splitting patterns of the C_{19} and C_{20} signals are identical with those in **9** and **13**. The determination of the other resonances is straightforward except the differentiation of C_5 from C_9, and C_6 from C_8. The triplet at 156.5 ppm is assigned to C_9 because of the specific ^{13}C–^{1}H couplings [$^{3}J(C_9–H_4) = {}^{2}J(C_9–H_8)$] while the partially resolved quintet at 156.0 ppm is designated as the C_5 signal. This splitting is probably due to the less well-defined couplings [$^{3}J(C_5–H_4) \approx {}^{3}J(C_5–H_{12}) \approx {}^{2}J(C_5–H_6)$]. Comparing the C_6 chemical shifts and ^{13}C–^{1}H one-bond coupling constants of osthol (**13**) and umbelliferone (**6**), the shielding effects ($\Delta\delta$ 6.4 ppm and ΔJ = 1.9 Hz) of the large alkyl group (γ,γ-dimethylallyl) at C_8 on the C_6 signal can be predicted. The corresponding values for the C_6 resonance of **19** may then be approximately estimated from those of sibiricin (**14**). The calculated values, 96.6 ppm and 160.6 Hz, permit us to assign the peak at 95.5 ppm [$^{1}J(C_6–H_6)$ = 160.8 Hz] to the C_6 resonance.

Experimental Section

The ^{13}C NMR spectra were obtained in a 10-mm spinning tube. The ^{13}C resonances of deuteriodimethyl sulfoxide and/or deuteriochloroform served as internal references, and converting to the Me_4Si scale involved the following corrections: $\delta(Me_4Si) = \delta(Me_2SO\text{-}d_6) + 39.6$ ppm; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. The instrument employed was a JEOL PFT-100 Fourier transform NMR spectrometer operating at 23 kG, interfaced with a JEOL EC-100 Fourier transform computer with 20K memory. The normal spectra were recorded at ambient temperature using an internal deuterium lock, the chemical shifts were measured at 5 kHz spectral width for proton-decoupled spectra, and at 1.25 kHz (resolution 0.19 Hz) (coumarin in $CDCl_3$), 2 kHz (resolution 0.24 Hz) (umbelliferone and esculetin in $Me_2SO\text{-}d_6$), 4 kHz (resolution 0.48 Hz) (coumarin-3-carboxylic acid in $Me_2SO\text{-}d_6$), and 5 kHz (resolution 0.61 Hz) (*O*-γ,γ-dimethylallylumbelliferone in $CDCl_3$; osthol in $CDCl_3$; sibiricin in $CDCl_3$; 5-geranyloxy-7-methoxycoumarin in $CDCl_3$) for proton-coupled spectra. The typical pulse width was 27.5 μs, and the repetition time between pulses was 8 s. All proton resonances were decoupled by a broad band (2.5 kHz) irradiation from an incoherent 99.99-MHz source for proton noise-decoupled spectra. The absolute magnitudes of the long-range coupling constants of coumarin are determined less accurately than those of the others owing to the strong couplings of H_5, H_6, H_7, and H_8. All deuterated solvents were purchased from Norell Chemical Co. Normal deuteriodimethyl sulfoxide usually contains 0.2–0.5% of water. The coumarin samples analyzed were either obtained commercially, isolated from natural sources, or had been synthesized earlier in these laboratories using published standard procedures.

Acknowledgment. This work was supported by the U.S. Public Health Service through NIH Research Grant AI-11728.

Registry No. —**1**, 91-64-5; **2**, 531-81-7; **6**, 93-35-6; **9**, 10387-50-5; **10**, 305-01-1; **13**, 17245-25-9; **14**, 18196-01-5; **19**, 7380-39-4.

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(17) ^{13}C NMR spectral data of catechol in Me_2SO-d_6: C_1, 146.0 ppm, $^3J(C_1-H_5)$ = 8.6, $^3J(C_1-H_3)$ = 5.8, $^2J(C_1-H_6)$ = 1.5 Hz; C_3, 117.0 ppm, $^1J(C_1-H_5)$ = 157.4, $^3J(C_3-H_5)$ = 6.4, $^2J(C_3-H_4)$ = 3.1 Hz; C_4, 121.1 ppm, $^1J(C_4-H_4)$ = 160.7, $^3J(C_4-H_6)$ = 8.4 Hz, $^3J(C_1-H_5) > {}^3J(C_1-H_3)$.
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Substituent Effects on the Carbon-13 Spectra of Oxindoles

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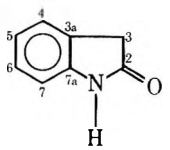
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A detailed study of the ^{13}C NMR spectra of oxindoles has been made. A series of 40 oxindoles with varying substitution in the 3, 4, 5, 6, and 7 positions was investigated. Substituents on the 3 position were hydrogen, methyl, and thiomethoxyl. Substituents on the 4, 5, 6, or 7 positions were methoxyl, methyl, hydrogen, chloro, carboethoxy, cyano, and nitro. A set of shift parameters were established for each of these substituents. These were closely related to (but not identical with) previously published shift effects reported for substituents on simple derivatives of benzene. Certain long-range effects were correlated with σ inductive parameters.

Recently, we described a simple process for the preparation of oxindoles in high overall yield from readily available, inexpensive starting materials.[1-4] This has made oxindoles attractive precursors for a wide variety of synthetic schemes designed for the preparation of indole type alkaloids. Since our process for the preparation of oxindoles permitted the presence of both electron-withdrawing and electron-donating substituents on the aromatic nucleus, it also provided the potential for a wide variation in the substitution patterns of the desired indole derivatives. Since ^{13}C NMR is an extremely powerful tool in the elucidation of structure in the alkaloid field,[5] it became of interest to know the exact effect of substituents on the ^{13}C chemical shifts in indole and oxindole type systems. We report here a detailed study of substituent effects on the ^{13}C chemical shifts in oxindoles.

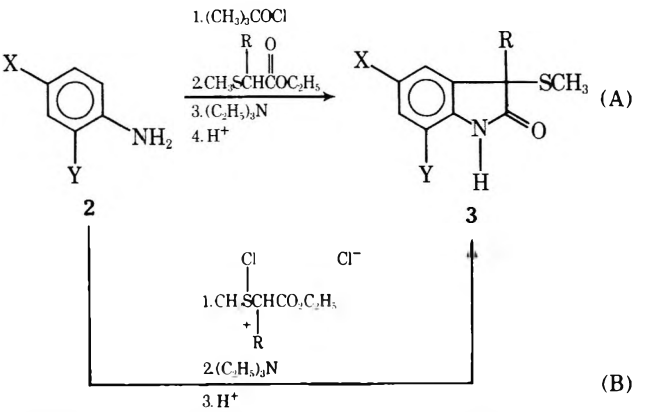
Relatively little is known about the ^{13}C NMR spectral properties of oxindoles. Wenkert and his co-workers have studied the ^{13}C NMR spectrum of oxindole (1) and of a few



1

oxindole derived alkaloids.[6] In the case of **1**, the chemical shifts were based on analogy with aniline.[6] Our current study concurs with the literature assignments and adds considerable supporting evidence for the assignments.

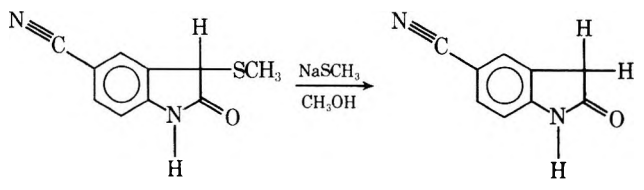
Synthesis of Oxindoles. With the exception of 5-nitrooxindole, which was prepared by the direct nitration of oxindole,[7] all of the oxindoles investigated as part of this study were prepared through either procedure A[1,3] or B.[2,4] In general, method A was used for the preparation of oxindoles bearing electron-withdrawing substituents and process B was used to prepare those oxindoles with electron-donating substituents. Table I lists the yields of oxindoles prepared specifically for this study. All of the other oxindoles investigated were prepared either as previously reported,[1-4] as part of a



(A)

(B)

study of isatin synthesis,[8] or as part of a detailed study of substituent effects on [2,3]-sigmatropic rearrangements of ylides derived from azasulfonium salts.[9] The desulfurization was accomplished in most cases through Raney-nickel reduction. However, in the case of nitro and cyano substituted oxindoles, where side reactions could be noted on Raney-nickel reduction, the thiomethoxyl group was removed via reaction with sodium thiomethoxide in methanol. For example, **4** could be converted into **5** in 62% yield by this method.



4 5

NMR Spectral Studies and Discussion. The ^{13}C NMR spectra of all of the oxindoles studied were obtained in dimethyl sulfoxide-d_6 as solvent with all shifts listed in parts per million relative to tetramethylsilane. Since the values obtained for oxindole (1) were slightly different from those reported by Wenkert and co-workers in chloroform-d, we also

Table I. Conversion of Anilines (2) into 3-Methylthiooxindoles (3)

Registry no.	2			Method	% yield of 3
	X	Y	R		
106-47-8	Cl	H	H	A	77
873-74-5	CN	H	H	A	80
94-09-7	$CO_2C_2H_5$	H	H	A	73
	Cl	H	CH_3	A	81
	CN	H	CH_3	A	67
	$CO_2C_2H_5$	H	CH_3	A	78
106-49-0	CH_3	H	CH_3	B	47
104-94-9	CH_3O	H	CH_3	B	46
88-74-4	H	NO_2	H	A	31
95-53-4	H	CH_3	CH_3	B	43

Table II. ^{13}C Chemical Shifts of Aryl Unsubstituted Oxindoles[a]

Registry no.	Compd (substituents)	Position									
		2	3	3a	4	5	6	7	7a	CH_3	SCH_3
59-48-3	1 (3-H,3-H)[b]	178.6	36.3	125.4	124.4	122.2	127.9	110.0	142.9		
	1 (3-H, 3-H)	176.6	35.9	125.9	124.4	121.3	127.5	109.3	143.8		
1504-06-9	6 (3-H,3-CH_3)	179.7	40.2	131.4	123.7	121.3	127.6	109.1	142.4	15.1	
40800-64-4	7 (3-H,3-SCH_3)	176.2	45.4	126.7	124.8	121.8	128.7	109.3	142.6		11.9
40800-77-9	8 (3-CH_3,3-SCH_3)	178.0	49.3	131.4	123.6	121.9	128.7	109.6	141.1	20.9	11.2

[a] All spectra were measured in dimethyl sulfoxide-d_6 vs. Me_4Si with values listed in parts per million downfield from tetramethylsilane unless otherwise specified. [b] Spectrum measured in chloroform-d for comparison.

Table III. ^{13}C Substituent Parameters for Oxindoles in Dimethyl Sulfoxide-d_6

Substituent	^{13}C shift, ppm			
	C_1	Ortho	Meta	Para
OCH_3	32.8 ± 0.7	−14.8 ± 0.5	1.4 ± 0.4	−7.0 ± 0.6
CH_3	9.4 ± 0.5	0.9 ± 0.7	−0.1 ± 0.2	−2.5 ± 0.2
Cl	5.1 ± 1.3	0.1 ± 0.5	1.6 ± 0.3	−1.1 ± 0.1
$CO_2C_2H_5$	1.7 ± 0.6	1.3 ± 0.7	0.2 ± 0.4	4.5 ± 0.5
CN	−17.4 ± 0.7	4.3 ± 1.1	1.1 ± 0.3	4.5 ± 0.2
NO_2	20.1 ± 0.6	−4.3 ± 1.0	0.9 ± 0.7	6.3 ± 0.6

ran 1 in the same solvent and reproduced the reported values within ±0.1 ppm. Thus, the differences noted in dimethyl sulfoxide-d_6 could be attributed to solvent effects. Table II lists the spectral data for a series of oxindoles differing only in the substitution at the 3 position. As can be seen from this table, substitution at the 3 position by a thiomethoxy group had little effect on the chemical shifts of carbons other than C-3. Comparison of 7 with 1 and of 8 with 6 indicated a shift of +9.3 ± 0.2 ppm as a result of this substitution. Interestingly, comparison of **1, 6, 7,** and **8** showed that placement of a methyl group at the 3 position shifted C-3a more than it did C-3 (+5.1 ± 0.4 vs. +4.1 ± 0.2 ppm). A significant shift of +2.4 ± 0.7 ppm due to the C-3 methyl was also noted at C-2.

Utilizing the spectral data determined for **1, 7,** and **8** as standards, we could determine the effect of aryl ring substituents on the chemical shifts of the carbons of the oxindole nucleus. In each case a noise decoupled spectrum was obtained. Since the structures of all of the compounds under study were well established, the only problem involved the assignment of the individual resonance signals to the appropriate carbon atoms. The literature contains several empirical methods for the assignment of carbon resonances.[10] For simple benzene derivatives a series of substituent parameters has been developed.[10,11] Utilizing these established parameters and, when necessary, either off-resonance or gated decoupling we were able to assign almost all of the resonance signals. Having assigned the resonance signals to specific carbons, we were able to do a statistical refinement[11] of the shift substituent parameters as applied to oxindoles in dimethyl sulfoxide-d_6. These values and their standard deviations are listed in Table III. The parameters listed in Table III differ by as much as 2 ppm from those described for monosubstituted benzenes in carbon tetrachloride. It was not established whether these small deviations from the literature values were a function of the change in solvent system, the change in the structure of the nucleus, or of both. It should be noted that the chemical shift of the para position correlated reasonably well in a Hammett type correlation with $\sigma+$ as had been previously noted for monosubstituted benzenes.[10,11]

Utilizing the statistical parameters listed in Table III, we were able to calculate "predicted" spectra for the oxindoles studied. Tables IV–VI list these calculated values along with the experimentally determined values. More than 85% of the calculated chemical shifts agree with the experimental value by 1 ppm or less. Of the 222 comparisons which were made, only seven calculated values differed from the experimental values by more than 2 ppm.[12] Interestingly, six of the seven values which varied were the two bridgehead positions and in each of these six examples the substituent was on the adjacent carbon. In each of these cases, the resonance occurred upfield from what had been predicted on the basis of substituent group shift parameters. Whether these variations have their origin in steric interactions between the 4 and 3 substituents and between the 7 and 1 substituents has not been established. However, it should be noted that no major discrepancies occur when the 3 position bears only hydrogens.

Of passing interest as part of this study was the observation

Table IV. ^{13}C Chemical Shifts of Substituted Oxindoles

Registry no.	Substituent		Position, ppm downfield from Me_4Si								
			2	3	3a	4	5	6	7	7a	Substituent
7699-18-5	5-OCH_3	Exptl	176.3	36.3	127.2	109.4	154.7	112.3	111.6	137.1	55.5
		Calcd			127.3	109.6	154.1	112.7	110.7	136.8	
3484-35-3	5-CH_3	Exptl	176.5	35.9	125.9	125.2	130.1	127.7	109.0	141.4	20.8
		Calcd			125.8	125.3	130.7	128.4	109.2	141.3	
17630-75-0	5-Cl	Exptl	176.3	36.0	125.5	124.6	128.1	127.4	110.5	142.7	
		Calcd			127.5	124.5	126.4	127.6	110.9	142.7	
61394-49-8	5-$CO_2C_2H_5$	Exptl	176.7	35.5	126.1	125.2	122.7	129.3	108.9	148.3	165.7, 60.3, 14.2
		Calcd			126.1	125.9	123.0	128.8	109.5	148.3	
61394-50-1	5-CN	Exptl	176.3	35.4	127.2	127.8	103.1	132.9	110.2	148.3	119.7
		Calcd			127.0	128.7	103.9	131.8	110.4	148.3	
20870-79-5	5-NO_2	Exptl	176.7	35.6	127.0	119.9	141.8	124.9	109.0	150.3	
		Calcd			126.8	120.1	141.4	123.2	110.2	150.1	
61394-51-2	4-NO_2	Exptl	175.4	37.2	122.5	143.9	115.7	129.1	114.9	146.0	
		Calcd			121.6	144.5	117.0	128.4	115.6	144.7	

Table V. ^{13}C Chemical Shifts of Substituted 3-Methylthiooxindoles

Registry no.	Substituent		Position, ppm downfield from Me_4Si									
			2	3	3a	4	5	6	7	7a	SCH_3	Substituent
50461-38-6	5-OCH_3	Exptl	176.0	45.9	128.0	109.9	155.0	113.7	111.5	135.9	11.8	55.5
		Calcd			128.1	110.0	154.6	113.9	110.7	135.6		
40800-66-6	5-CH_3	Exptl	176.1	45.4	126.7	125.4	130.7	129.0	109.2	140.1	11.8	20.6
		Calcd			126.6	125.7	131.2	129.6	109.2	140.1		
40800-67-7	7-CH_3	Exptl	176.5	45.5	126.2	122.0	121.6	129.8	118.8	141.1	11.8	16.3
		Calcd			126.6	122.3	121.7	129.6	118.7	143.5[a]		
61394-52-3	4-CH_3	Exptl	176.2	44.7	124.0	135.3	123.3	128.6	107.0	142.6	11.6	17.9
		Calcd			127.6[a]	134.2	122.7	128.6	106.8	142.5		
61394-53-4	5-Cl	Exptl	175.7	45.5	125.9	124.8	129.0	128.6	110.9	141.5	11.8	
		Calcd			128.3	124.9	126.9	128.8	110.9	141.5		
61394-54-5	4-Cl	Exptl	175.1	45.3	123.7	130.5	122.2	130.5	108.3	144.4	11.7	
		Calcd			126.8[a]	129.9	121.9	130.3	108.2	144.2		
61394-55-6	6-Cl	Exptl	176.1	44.9	125.7	126.3	121.5	132.9	109.5	144.1	11.8	
		Calcd			125.6	126.4	121.9	133.8	109.4	144.2		
61394-56-7	5-$CO_2C_2H_5$	Exptl	176.4	45.2	127.1	125.6	123.5	131.0	109.4	147.1	11.8	165.5, 60.5, 14.2
		Calcd			126.9	126.1	123.5	130.0	109.5	147.1		
61394-57-8	4-$CO_2C_2H_5$	Exptl	175.6	45.9	127.7[b]	127.4[b]	122.6	129.0	113.3	143.6	11.9	165.4, 60.9, 14.0
		Calcd			128.0	126.5	123.1	128.9	113.8	142.8		
61394-58-9	5-CN	Exptl	176.0	44.9	128.3	128.3	104.0	134.1	110.4	146.9	11.9	119.3
		Calcd			127.8	129.1	104.4	133.0	110.4	147.1		
61394-59-0	4-CN	Exptl	174.9	45.0	129.9	108.3	125.6	129.9	113.9	143.7	11.7	116.2
		Calcd			131.0	107.4	126.1	129.8	113.8	143.7		
40800-69-9	5-NO_2	Exptl	176.4	45.3	128.0	120.3	142.3	125.9	109.6	149.0	11.9	
		Calcd			127.6	120.5	141.9	124.4	110.2	148.9		
40800-70-2	4-NO_2	Exptl	174.8	45.8	122.5	144.9	116.8	130.4	115.2	144.5	11.9	
		Calcd			122.4	144.9	117.5	129.6	115.6	143.5		
61394-60-3	7-NO_2	Exptl	176.3	44.2	c	131.0	122.0	123.6	130.6	138.9	11.9	
		Calcd			127.6	131.1	122.7	124.4	129.4	138.3		

[a] Value not used in the calculation of substituent shift constants. [b] Values indicated may be reversed. [c] Resonance signal not discernible.

that substituents at C-6 promoted a systematic change in the position of the carbon resonance for C-2 as shown by a correlation of the chemical shift of C-2 with the σ value of the substituent (slope = −1.08, r = 0.980). However, substituents in the 4, 5, or 7 positions resulted in relatively random shifts of the C-2 resonance.[13]

In summary, we have demonstrated that the shift parameters established for monosubstituted benzenes can be extrapolated to much more complex systems with only minor modifications. Furthermore, we have firmly established the ^{13}C spectral properties for oxindoles as a class of compounds.

Experimental Section[14]

^{13}C NMR Spectra. ^{13}C NMR spectra were determined at 20 MHz on a Varian CFT-20 NMR spectrometer. Spectra were obtained in dimethyl sulfoxide-d_6 (Me_2SO-d_6) in 8-mm tubes. The spectra were recorded at ambient temperature by using the deuterium resonance of Me_2SO-d_6 as the internal lock signal. Typical pulse widths were 10 μs. Chemical shifts were measured at 4000-Hz sweep width spectra and referred to the center peak of Me_2SO-d_6 which was set at 39.6 ppm downfield from tetramethylsilane. The accuracy is within ± 0.05 ppm.

3-Methylthiooxindoles. 3-Methylthiooxindole, 3-methyl-3-methylthiooxindole, 5-methyl-3-methylthiooxindole, 7-methyl-3-methylthiooxindole, 5-methoxy-3-methylthiooxindole, 5-nitro-3-methylthiooxindole, and 4-nitro-3-methylthiooxindole were prepared according to the published procedures.[1-4] In all cases the physical constants and spectroscopic properties agreed well with those described in the literature. The 4- or 6-substituted 3-methylthiooxindoles and 3-methyl-3-methylthiooxindoles were prepared as part of another study.[8]

5-Chloro-3-methylthiooxindole. On a 0.055-mol scale, p-chloroaniline was converted to 5-chloro-3-methylthiooxindole according to the general procedure of Gassman and van Bergen.[3] Recrystallization of the crude oxindole from methanol gave 9.1 g (78%) of pure product: mp 171–173 °C; IR (KBr) 3100 (NH) and 1705 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 1.95 (3 H, s, 3-SCH_3), 4.50 (1 H, s, H_3), 6.80 (1 H, d, J = 8 Hz, H_7), 7.30 (2 H, m, H_4 and H_6), and 11.40 (1 H, bs, NH).

Table VI. ^{13}C Chemical Shifts of Substituted 3-Methyl-3-methylthiooxindoles

Registry no.	Substituent		Position, ppm downfield from Me_4Si										
			2	3	3a	4	5	6	7	7a	SCH_3	CH_3	Substituent
61394-61-4	5-OCH_3	Exptl	178.1	50.1	132.8	110.2	155.3	113.8	110.5	134.4	11.4	21.1	55.6
		Calcd			132.8	108.8	154.7	113.9	111.0	134.1			
61394-62-5	4-OCH_3	Exptl	177.9	49.4	116.2	156.2	105.6	130.2	102.9	142.3	11.2	18.8	55.6
		Calcd			116.6	156.4	107.1	130.1	102.6	142.5			
61394-63-6	6-OCH_3	Exptl	178.5	49.0	123.2	124.4	106.9	160.0	96.4	142.4	11.3	21.1	55.3
		Calcd			124.4	125.0	107.1	161.5	94.8	142.5			
61394-64-7	5-CH_3	Exptl	178.0	49.4	131.5	124.2	130.8	129.0	109.3	138.7	11.3	21.0[b]	20.7[b]
		Calcd			131.3	125.5	131.3	129.6	109.5	138.6			
61394-65-8	4-CH_3	Exptl	177.8	50.1	127.9	135.1	124.2	128.6	107.3	141.4	11.1	19.5	17.4
		Calcd			132.3[a]	133.0[a]	122.8	128.6	107.1	141.0			
61394-66-9	6-CH_3	Exptl	178.3	49.2	128.5	123.4	122.5	138.4	110.3	141.2	11.2	21.0[b]	21.3[b]
		Calcd			128.9	123.5	122.8	138.1	110.5	141.0			
61394-67-0	7-CH_3	Exptl	178.6	49.6	131.2	121.0	122.0	131.0	119.1	139.8	11.3	21.1	16.5
		Calcd			131.3	121.1	121.8	129.6	119.0	142.0[a]			
61394-68-1	5-Cl	Exptl	177.6	49.7	133.6	123.8	126.1	128.6	111.1	140.0	11.3	20.7	
		Calcd			133.0	123.7	127.0	128.8	111.2	140.0			
61394-69-2	4-Cl	Exptl	176.9	50.7	130.1	126.9	122.9	130.5	108.6	143.3	11.3	18.6	
		Calcd			131.5	128.7	122.0	130.3	108.5	142.7			
61436-90-6	6-Cl	Exptl	177.9	49.1	130.4	125.1	121.7	133.0	109.8	142.6	11.3	20.7	
		Calcd			130.3	125.2	122.0	133.8	109.7	142.7			
61394-70-5	5-$CO_2C_2H_5$	Exptl	178.2	49.2	131.7	124.4	123.7	131.0	109.6	145.7	11.3	20.7	165.5, 60.5,
		Calcd			131.6	124.9	123.6	130.0	109.8	145.6			14.2
61436-91-7	6-CO_2CH_3	Exptl	177.6	49.5	136.8	123.8	123.4	130.0	109.7	141.6	11.3	20.6	165.8, 52.2
		Calcd			135.9	123.8	123.2	130.4	110.9	141.3			
61394-71-6	5-CN	Exptl	177.8	49.2	132.7	127.4	104.1	134.1	110.5	145.5	11.3	20.4	119.3
		Calcd			132.5	127.9	104.5	133.0	110.7	145.6			
61394-72-7	4-CN	Exptl	176.8	49.7	133.5	107.2	126.1	130.0	114.3	142.5	11.4	19.0	116.0
		Calcd			135.7[a]	106.2	126.2	129.8	114.1	142.2			
61394-73-8	6-CN	Exptl	177.3	49.4	137.0	124.7	126.6	111.2	112.2	141.9	11.4	20.4	118.7
		Calcd			135.9	124.7	126.2	111.3	113.9	142.2			
61394-74-9	6-NO_2	Exptl	177.4	49.5	138.9	124.4	117.5	147.8	104.1	142.3	11.3	20.4	
		Calcd			137.7	124.5	117.6	148.8	105.3	142.0			

[a] Value not used in the calculation of substituent shift constant. [b] Values indicated may be reversed within any horizontal line.

Anal. Calcd for C_9H_8ClNOS: C, 50.58; H, 3.78; N, 6.56. Found: C, 50.59; H, 3.83; N, 6.51.

5-Carboethoxy-3-methylthiooxindole. On a 0.05-mol scale, ethyl *p*-aminobenzoate was converted to 5-carboethoxy-3-methylthiooxindole according to the procedure of Gassman and van Bergen.[3] The reaction gave 9.20 g (73%) of the desired oxindole: mp 151–153 °C (recrystallized from C_6H_6); IR (KBr) 3240 (NH), 1735 (C=O), 1695 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.40 (3 H, t, $CH_3CH_2O_2C$), 2.00 (3 H, s, SCH_3), 4.30 (1 H, s, H_3), 4.50 (2 H, q, OCH_2CH_3), 6.95 (1 H, d, J = 8 Hz, H_7), 7.90 (1 H, dd, J_1 = 8, J_2 < 1 Hz, H_6), 8.00 (1 H, J < 1 Hz, H_4), and 9.80 (1 H, bs, NH).

Anal. Calcd for $C_{12}H_{13}NO_3S$: C, 57.35; H, 5.21; N, 5.57. Found: C, 57.36; H, 5.19; N; 5.49.

5-Cyano-3-methylthiooxindole. Utilizing the general procedure for the synthesis of oxindoles, as described by Gassman and van Bergen,[3] *p*-cyanoaniline was converted into 5-cyano-3-methylthiooxindole on a 0.046-mol scale. Recrystallization from methanol gave the pure oxindole (7.30 g, 80% yield): mp 182–183 °C; IR (KBr) 3100 (NH), 2220 (C≡N), and 1720 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 2.03 (3 H, s, SCH_3), 4.66 (1 H, s, H_3), 7.00 (1 H, d, J = 9 Hz, H_7) 7.69 (1 H, d, J = 2 Hz, H_4), 7.73 (1 H, dd, J_1 = 9, J_2 = 2 Hz, H_6), and 11.00 (1 H, bs, NH).

Anal. Calcd for $C_{10}H_8N_2OS$: C, 58.80; H, 3.95; N, 13.72. Found: C, 58.65; H, 4.06; N, 13.40.

5-Chloro-3-methyl-3-methylthiooxindole. The product was obtained from *p*-chloroaniline and ethyl methylthiopropionate by the general procedure of Gassman and van Bergen[3] on a 0.04-mol scale. Recrystallization of the crude product from cyclohexane gave 7.3 g (81%) of pure oxindole: mp 158.0–159.5 °C; IR (KBr) 3100 (NH) and 1710 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.66 (3 H, s, CH_3), 1.89 (3 H, s, SCH_3), 6.87 (1 H, dd, J_1 = 8, J_2 = 1 Hz, H_7), 7.20 (1 H, dd, J_1 = 8, J_2 = 2 Hz, H_6), 7.27 (1 H, bs, H_4), 9.57 (1 H, bs, NH); mass spectrum *m/e* obsd 227.0716 (calcd, 227.0712).

Anal. Calcd for $C_{10}H_{10}ClNOS$: C, 52.75; H, 4.43; N, 6.15. Found: C, 52.78; H, 4.62; N, 6.33.

5-Carboethoxy-3-methyl-3-methylthiooxindole. The oxindole was prepared by the general procedure.[3] *p*-Carboethoxyaniline (4.95 g, 0.03 mol) was transformed into the oxindole (5.3 g, 67%): mp 219–221 °C (recrystallized from ethanol); IR (KBr) 3250 (NH), 1715 (C=O), 1685 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 1.32 (3 H, t, J = 6.7 Hz, CH_3CH_2–), 1.58 (3 H, s, CH_3), 1.90 (3 H, s, SCH_3), 4.30 (2 H, q, J = 6.7 Hz, CH_3CH_2O), 6.96 (1 H, d, J = 9 Hz, H_7), 7.80 (1 H, bs, H_4), 7.88 (1 H, d, J = 9 Hz, H_6), 10.97 (1 H, bs, NH); mass spectrum *m/e* obsd 265.0784 (calcd, 265.0772).

Anal. Calcd for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70; N, 5.28. Found: C, 58.86; H 5.79; N, 5.29.

5-Cyano-3-methyl-3-methylthiooxindole. *p*-Aminobenzonitrile (2.36 g, 0.02 mol) was converted to the corresponding oxindole (3.4 g, 78%) by the general method of Gassman and van Bergen.[3] The product was recrystallized from etaanol: mp 171–173 °C; IR (KBr) 3100 (NH), 2210 (CN), 1705 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 1.57 (3 H, s, CH_3), 1.90 (3 H, s, SCH_3), 6.92 (1 H, d, J = 8 Hz, H_7), 7.57 (1 H, d, J = 8 Hz, H_6), 7.63 (1 H, bs, H_4), 11.08 (1 H, bs, NH); mass spectrum *m/e* obsd 218.0495 (calcd, 218.0514).

Anal. Calcd for $C_{11}H_{10}N_2OS$: C, 60.53; H, 4.62; N, 12.83. Found: C, 60.59; H, 4.71; N, 12.86.

3,7-Dimethyl-3-methylthiooxindole. o-Toluidine (4.70 g, 0.044 mol) was transformed into the corresponding oxindole by the method of Gassman, Gruetzmacher, and van Bergen.[4] The crude product was recrystallized from ethanol to give pure oxindole (3.9 g, 43%): mp 175–177 °C; IR (KBr) 3150 (NH), 1700 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.65 (3 H, s, CH_3), 1.92 (3 H, s, SCH_3), 2.29 (3 H, s, $ArCH_3$), 6.96 (3 H, m, aromatic protons), 10.55 (1 H, bs, NH); mass spectrum *m/e* obsd 207.0715 (calcd, 207.0717).

Anal. Calcd for $C_{11}H_{13}NOS$: C, 63.73; H, 6.32; N, 6.76. Found: C, 63.80; H, 6.32; N, 6.79.

3,5-Dimethyl-3-methylthiooxindole. Using the same method as described in the literature,[4] *p*-toluidine (4.70 g, 0.044 mol) was converted into the corresponding oxindole (4.3 g, 47%): mp 165–167 °C (recrystallized from EtOH); IR (KBr) 3100 (NH), 1705 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.63 (3 H, s, CH_3), 1.85 (3 H, s, SCH_3), 2.30 (3 H, s, $ArCH_3$), 6.63–7.00 (3 H, m, aromatic protons), 9.83 (1 H, bs, NH); mass spectrum *m/e* obsd 207.0711 (calcd, 207.0717).

Anal. Calcd for $C_{11}H_{13}NOS$: C, 63.73; H, 6.32; N, 6.76. Found: C, 63.68; H, 6.30; N, 6.85.

5-Methoxy-3-methyl-3-methylthiooxindole. *p*-Anisidine (5.4

g, 0.044 mol) was converted to the oxindole according to the literature method.[4] The crude material was recrystallized from ethanol to give 4.5 g (46%) of the desired product: mp 182–183 °C; IR (KBr) 3200 (NH), 1700 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 1.50 (3 H, s, CH_3), 1.85 (3 H, s, SCH_3), 3.67 (3 H, s, OCH_3), 6.63–6.93 (3 H, m, aromatic protons), and 10.30 (1 H, bs, NH); mass spectrum *m/e* obsd 223.0668 (calcd, 223.0667).

Anal. Calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87; N, 6.27. Found: C, 59.19; H, 5.83; N, 6.31.

7-Nitro-3-methylthiooxindole. *o*-Nitroaniline (12.14 g, 0.088 mol) was transformed into the corresponding oxindole according to the literature procedure.[3] Recrystallization from methanol gave 3.05 g (31%) of yellow crystals: mp 205–207 °C dec; IR (KBr) 3200 (NH), 1705 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 2.07 (3 H, s, SCH_3), 4.75 (1 H, s, H_3), 7.20 (1 H, dd, $J_1 = 7$, $J_2 = 8$ Hz, H_5), 7.70 (1 H, dd, $J_1 = 7$, $J_3 = 2$ Hz, H_4), 8.10 (1 H, dd, $J_2 = 8$, $J_3 = 2$ Hz, H_6), 11.60 (1 H, bs, NH); mass spectrum *m/e* obsd 224.0258 (calcd, 224.0255).

Anal. Calcd for $C_9H_8N_2O_3S$: C, 48.21; H, 3.60; N, 12.49. Found: C, 48.03; H, 3.68; N, 12.48.

5-Chlorooxindole. 5-Chloro-3-methylthiooxindole (2.0 g, 9.4 mmol) was converted to 5-chlorooxindole by Raney-nickel reduction in the same manner as described in the literature.[3] After crystallization from benzene–cyclohexane, the pure product was obtained (1.0 g, 63%), mp 195–197 °C (lit.[15] mp 198.0–198.5 °C).

5-Methoxyoxindole. The product was obtained by treatment of 5-methoxy-3-methylthiooxindole (1 g, 5.8 mmol) with Raney nickel as described previously[3] to give 0.61 g (64%) of the pure product, mp 268 °C dec (lit.[7] mp 270 °C dec).

5-Carboethoxyoxindole. 5-Carboethoxy-3-methylthiooxindole (2.0 g, 7.97 mmol) was treated in the same manner as described in the literature[3] to give 0.91 g (56%) of the desired product: mp 190–192 °C (recrystallized from ethanol); IR (KBr) 3200 (NH), 1715, 1700 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 1.30 (3 H, t, $J = 7$ Hz, CH_3CH_2). 1.85 (2 H, s, $-CH_2$), 4.25 (2 H, q, $J = 7$ Hz, CH_3CH_2O), 6.87 (1 H, d, $J = 8$ Hz, H_7), 7.72 (1 H, bs, H_4), 7.78 (1 H, d, $J = 8$ Hz, H_6), 10.70 (1 H, bs, NH); mass spectrum *m/e* obsd 205.0753 (calcd, 205.0739).

Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40. Found: C, 64.23; H, 5.42.

5-Nitrooxindole. This compound was prepared by nitration of oxindole as described in the literature,[7] mp 234–236 °C (lit.[7] mp 236 °C).

5-Cyanooxindole. 5-Cyano-3-methylthiooxindole (1.02 g, 5.0 mmol) in methanol (30 mL) was added dropwise to a cooled (0 °C) methanolic solution of sodium methyl mercaptide prepared from 2 g (0.87 g-atom) of sodium and an excess of methyl mercaptan (ca. 15 mL) in methanol (200 mL). The mixture was stirred overnight at room temperature. Part of the solvent was removed in vacuo and the rest was poured onto cold water and extracted with ether. The ethereal solution was dried over anhydrous magnesium sulfate, filtered, and evaporated. The residue was crystallized from ethanol to give pure 5-cyanooxindole (0.49 g, 62%): mp 249–251 °C; IR (KBr) 3200 (NH), 2200 (CN), 1705 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 3.58 (2 H, s, CH_2), 6.95 (1 H, d, $J = 8$ Hz, H_7), 7.97 (1 H, bs, H_4) 8.00 (1 H, d, $J = 8$ Hz, H_6), and 10.87 (1 H, bs, NH); mass spectrum *m/e* obsd 158.0491 (calcd, 158.0480).

Anal. Calcd for $C_9H_6N_2O$: C, 68.34; H, 3.82. Found: C, 68.04; H, 4.00.

Acknowledgment. The authors are indebted to the Public Health Service for Grants GM 22346 and CA 16967 which supported this investigation. We are also indebted to the Graduate School at the University of Minnesota for partial funds for the purchase of the nuclear magnetic resonance spectrometer used in this study.

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(12) Because of the size of these deviations, these seven experimental values were not incorporated into the statistical analysis used to establish the parameters listed in Table III. These values are marked by an "a" in Tables V and VI.
(13) Similarly, little correlation existed between the inductive effect parameters for the substituents and the position of the C-3 resonance. However, the C-3 methyl group was systematically shifted by substituents in both the 5 and 6 positions. A plot of σ vs. chemical shift gave a slope of -0.74 ($r = 0.977$).
(14) All melting points and boiling points are uncorrected. Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark. ^1H NMR spectra were obtained on Varian A-60-D, T-60, or HA-100 nuclear magnetic resonance spectrometers.
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A General Method for the Synthesis of Isatins

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Received August 31, 1976

A new method has been developed for the conversion of anilines into isatins. The general process utilizes our efficient method for the conversion of anilines into 3-methylthiooxindoles, which in turn serve as key intermediates. Oxidation of the methine carbon in the 3 position of the 3-methylthiooxindoles with *N*-chlorosuccinimide, followed by hydrolysis of the chlorinated intermediate, provides a simple route to isatins. This method is compatible with the presence of either strongly electron-withdrawing or strongly electron-donating substituents on the starting aniline. Yields range from good to excellent. An analysis of the ^{13}C NMR spectral properties of isatins is included.

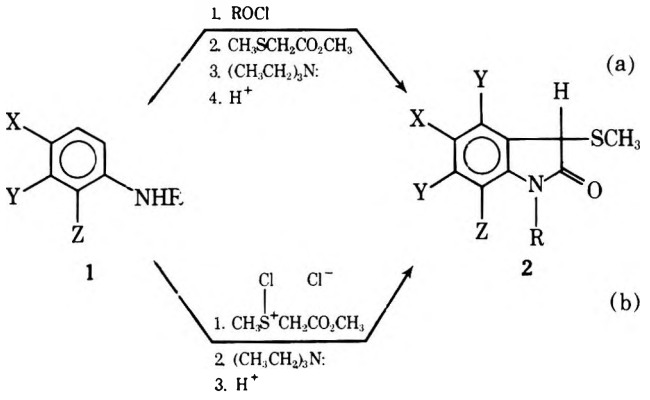
Isatins have long been considered as valuable synthetic intermediates in the preparation of both pharmaceuticals and dyes. Thus, considerable effort has been devoted to developing useful synthetic approaches to this class of compounds. Unfortunately, the most widely utilized procedures required catalysis by strong acid,[2] a condition which imposed rather

Table I. Yields of Isatins from 3-Methylthiooxindoles (2)

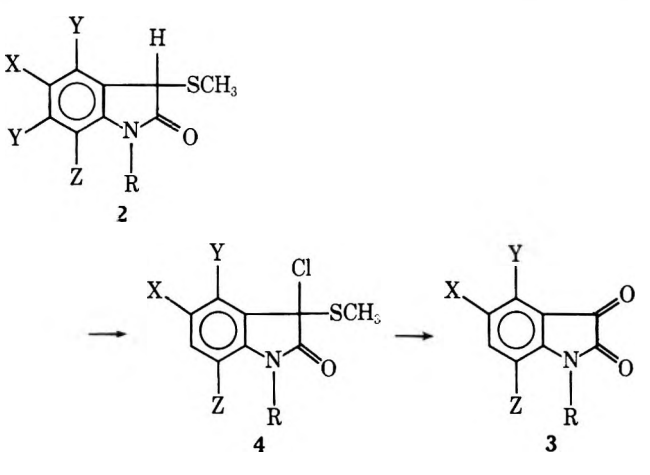
Registry no.	Oxindole X	Y	Z	R	% yield of isatin (3)	Mp, °C	Lit. mp, °C
40800-64-4	H	H	H	H	78	200–202	200–201[12]
40800-66-6	CH_3	H	H	H	74	185–187	187[13]
50461-38-6	OCH_3	H	H	H	81	202–204	201–202[14]
61394-52-4	Cl	H	H	H	75	249–252	247 dec[15]
61394-56-7	$CO_2C_2H_5$	H	H	H	56	206–207	
61394-58-9	CN	H	H	H	65	270–272 dec	
40800-69-9	NO_2	H	H	H	78	252–254 dec	254–255 dec[16]
61394-91-0	CF_3	H	H	H	73	191–193	246[17]
40800-70-2	H	NO_2	H	H	40	248–250 dec	
40800-67-7	H	H	CH_3	H	71	270–272	267[18]
40800-68-8	H	H	H	CH_3	61	132–134	134[19]

severe limitations on the breadth of the method. We now wish to report a new general method for the synthesis of isatins which can tolerate a broad spectrum of electron-withdrawing and electron-donating substituents.

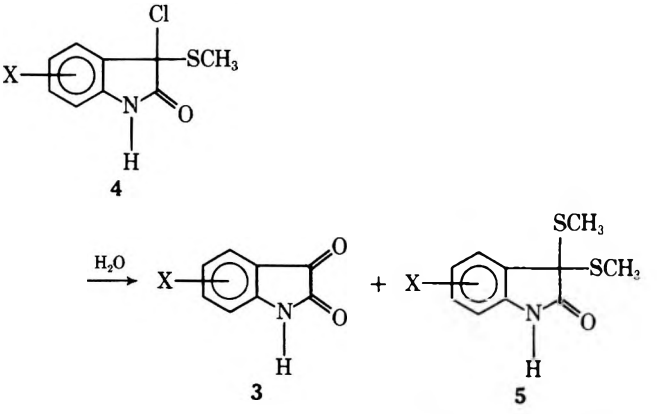
Recently, we reported two general methods for the conversion of anilines into 3-methylthiooxindoles.[3,4] As shown below in eq a and b, both of these processes permit a one-pot sequence of reactions for the conversion of **1** into **2**.[5] In principle, **2** should serve as an excellent isatin precursor if suitably mild conditions could be developed for the oxidation of the 3 position. Previously, we had utilized the directive effect of a neighboring thio function for the conversion of a thiomethyl group into an aldehyde precursor via *N*-chlorosuccinimide oxidation.[6] We reasoned that *N*-chlorosuccinimide might be equally as efficient in replacing the methine hydrogen at the 3 position of **2** with chloride. Hydrolysis of the chloro sulfide would then provide the desired isatins.



In order to establish whether isatins of general formula **3** could be prepared from **2** via the chlorination of **2** to **4** and subsequent hydrolysis of **4**, we subjected a series of 3-methylthiooxindoles[7] to the appropriate reaction conditions. A solution of **2** in carbon tetrachloride or methylene chloride[8] was treated with 1.1–1.3 equiv of *N*-chlorosuccinimide at room temperature for 1–12 h. Since they were relatively unstable, the resulting 3-chloro-3-methylthiooxindoles were dissolved in a minimum amount of tetrahydrofuran without purification and the solutions were added to a vigorously stirred slurry of 1 equiv of red mercuric oxide and 1 equiv of boron trifluoride etherate in 4:1 v/v water–tetrahydrofuran.[9,10] Workup involved extraction with chloroform and chromatography on silica gel to give the pure isatins. As shown in Table I, the yield varied from 40 to 81% for the 11 isatins listed. Substituents could be varied from strongly electron donating (methoxyl) to strongly electron withdrawing (ethoxycarbonyl, cyano, nitro). Substituents in the 4, 5, and 7 positions of **2** provided no complications. Even the N-substituted isatins were available through this process.



In an attempt to simplify the hydrolysis step, the conversion of **4** into **3** was attempted without the aid of the sulfur scavenging red mercuric oxide and the boron trifluoride etherate catalyst. When **4** was refluxed in 20% aqueous tetrahydrofuran for 4–18 h, it completely converted into a mixture of two products. The major product was the desired isatin, **3**. Spectroscopic analysis (IR, NMR) combined with mass spectrometric and elemental analysis identified the minor product as the 3,3-dithioketal **5**. The formation of this dithioketal



presumably resulted from the reaction of **3** or **4** with the methanethiol generated in the hydrolysis of **4**. When X was hydrogen, we obtained a 68% yield of isatin and a 24% yield of its 3,3-dithioketal. For X equal to 5-methoxyl, 5-methyl, and 5-chloro the yields of isatins were 62, 63, and 68%, respectively, while the yields of the 3,3-dithioketals were 24, 14, and 12%, respectively. Unfortunately, column chromatography was necessary for the efficient separation of the isatin from the 3,3-dithioketal.

^{13}C Chemical Shifts of Isatins. Our detailed study of the ^{13}C chemical shifts of oxindoles and our determination of

Table II. ^{13}C Chemical Shifts for Substituted Isatins

Registry no.	Compd		2	3	3a	4	5	6	7	7a	Substituent
91-56-5	Isatin	Obsd	159.5	184.6	117.9	138.5	124.8	122.9	112.4	150.9	
608-05-9	5-CH_3	Obsd	159.5	184.6	117.8	138.8	132.0	124.8	112.1	148.5	20.1
		Calcd			117.8	139.2	133.9	123.6	112.1	148.4	
39755-95-8	5-OCH_3	Obsd	159.6	184.1	118.1	124.9	155.4	108.8	113.3	144.7	55.8
		Calcd			118.3	123.8	157.2	108.2	113.6	144.1	
17630-76-1	5-Cl	Obsd	159.1	183.4	119.1	137.3	126.9	124.2	113.9	149.2	
		Calcd			119.2	138.5	129.5	122.9	113.7	149.8	
25128-38-5	5-$CO_2C_2H_5$	Obsd	159.4	183.4	117.8	139.0	124.6	125.0	112.3	154.1	164.6, 60.9, 14.2
		Calcd			118.0	139.8	126.5	124.2	112.3	155.2	
345-32-4	5-CF_3	Obsd	159.9	183.2	118.2	134.8[a]	123.3[b]	121.3[c]	112.9	153.6	124.0[d]
		Calcd			118.2	136.3	115.8	120.7	112.7	154.1	
61394-92-1	5-CN	Obsd	159.4	182.6	118.6[e]	141.7	104.9	128.5	113.1	153.7	118.3[e]
		Calcd			119.0	142.5	107.2	126.9	113.5	155.4	
611-09-6	5-NO_2	Obsd	159.9	182.4	118.2	133.2	142.7	119.6	112.6	155.3	
		Calcd			118.7	135.0	145.1	119.4	113.2	157.0	
1127-59-9	7-CH_3	Obsd	159.6	184.3	117.3	139.2	122.3[e]	121.6[e]	121.1	149.0	15.9
		Calcd			117.8	136.0	124.7	123.8	121.8	151.8	

[a] J_{CCCF} = 3.4 Hz. [b] J_{CCF} = 33 Hz. [c] J_{CCCF} = 3.6 Hz. [d] J_{CF} = 272 Hz. [e] Values may be interchanged.

chemical shift substituent constants for such systems[20] prompted us to provide similar data for the isatins prepared as part of this study. Table II lists the isatins prepared and the positions of their carbon resonances. In arriving at the calculated values, we used the shift parameters which we had established for oxindoles. In the case of the 5-trifluoromethylisatin, we used the literature value for the trifluoromethyl group.[21,22] In general, the values calculated on the basis of these shift parameters agreed very well with the observed values.

In summary, we have developed a relatively simple, good yield method for the preparation of isatins from anilines via oxindoles. Since our published methods for the conversion of anilines into oxindoles give high yields, the overall yields of the isatins listed in Table I from the appropriate ortho, meta, or para-substituted anilines vary from 25 to 66%.

Experimental Section[23]

3-Methylthiooxindoles. 3-Methylthiooxindole, 5-methyl-3-methylthiooxindole, 5-methoxy-3-methylthiooxindole, 5-nitro-3-methylthiooxindole, 4-nitro-3-methylthiooxindole, 7-methyl-3-methylthiooxindole, and 1-methyl-3-methylthiooxindole were prepared according to the published procedures.[3,4] In all cases the physical constants and spectroscopic properties agreed well with those described in the literature.

5-Chloro-3-methylthiooxindole. On a 0.055-mol scale *p*-chloroaniline was converted to 5-chloro-3-methylthiooxindole according to the general procedure of Gassman and van Bergen.[3] Recrystallization of the crude oxindole from methanol gave pure product (9.10 g, 77.5%): mp 171–173 °C (recrystallized from methanol); IR (KBr) 3100 (NH) and 1705 cm^{-1} (C=O); NMR (Me_2SO-d_6) τ −1.40 (bs, 1 H, NH), 2.70 (m, 2 H, H_4 and H_6), 3.20 (d, 1 H, $J_{6,7}$ = 8 Hz, H_7), 5.50 (s, 1 H, H_3), and 8.05 (s, 3 H, 3-SCH_3).

Anal. Calcd for C_9H_8ClNOS: C, 50.58; H, 3.73; N, 6.56. Found: C, 50.59; H, 3.83; N, 6.51.

3-Methylthio-5-trifluoromethyloxindole. Utilizing the general procedure described in the literature,[3] *p*-trifluoromethylaniline was converted to 3-methylthio-5-trifluoromethyloxindole on a 0.0124-mol scale. Recrystallization of the product from cyclohexane gave pure 3-methylthio-5-trifluoromethyloxindole (2.32 g, 76%): mp 139.0–140.5 °C (recrystallized from cyclohexane); IR (KBr) 3200 (NH) and 1730 cm^{-1} (C=O); NMR ($CDCl_3$) τ 0.57 (bs, 1 H, NH), 2.37 (d, 1 H, $J_{4,6}$ = 1 Hz, H_4), 2.47 (d of d, $J_{4,6}$ = 1, $J_{6,7}$ = 8 Hz, H_6), 3.00 (d, 1 H, $J_{6,7}$ = 8 Hz), 5.67 (s, 1 H, H_3), and 7.90 (s, 3 H, 3-SCH_3).

Anal. Calcd for $C_{10}H_8F_3NOS$: C, 48.58; H, 3.26; N, 5.67. Found: C, 48.48; H, 3.29; N, 5.58.

5-Ethoxycarbonyl-3-methylthiooxindole. On a 0.05-mol scale ethyl *p*-aminobenzoate was converted to 5-ethoxycarbonyl-3-methylthiooxindole according to the procedure of Gassman and van Bergen.[3] The reaction gave 9.20 g (73%) of the desired oxindole: mp 151–153 °C (recrystallized from benzene); IR (KBr) 3240 (NH), 1735 (C=O), and 1695 cm^{-1} (C=O); NMR ($CDCl_3$) τ 0.20 (1 H, bs, NH), 2.00 (d, 1 H, $J_{4,5}$ < 1 Hz, H_4), 2.10 (d of d, 1 H, $J_{4,6}$ < 1, $J_{6,7}$ = 8 Hz, H_6), 3.05 (d, 1 H, $J_{6,7}$ = 8 Hz, H_7), 5.50 (q, 2 H, $CO_2CH_2CH_3$), 5.70 (s, 1 H, H_3), 8.00 (s, 3 H, SCH_3), 8.60 (t, 3 H, $CO_2CH_2CH_3$).

Anal. Calcd for $C_{12}H_{13}NO_3S$: C, 57.35; H, 5.21; N, 5.57. Found: C, 57.36; H, 5.19; N, 5.49.

5-Cyano-3-methylthiooxindole. Utilizing the general procedure for the synthesis of oxindoles, as described by Gassman and van Bergen,[3] *p*-cyanoaniline was converted into 5-cyano-3-methylthiooxindole on a 0.0466-mol scale. Recrystallization from methanol gave the pure oxindole (7.30 g, 80% yield): mp 182–183 °C; IR (KBr) 3100 (NH), 2220 (C≡N), and 1720 cm^{-1} (C=O); NMR (Me_2SO-d_6) τ −1.00 (bs, 1 H, NH), 2.27 (d of d, 1 H, $J_{4,6}$ = 2, $J_{6,7}$ = 9 Hz, H_6), 2.31 (d, 1 H, $J_{4,6}$ = 2 Hz, H_4), 3.00 (d, 1 H, $J_{6,7}$ = 9 Hz, H_7), 5.34 (s, 1 H, H_3), 7.97 (s, 3 H, SCH_3).

Anal. Calcd for $C_{10}H_8N_2OS$: C, 58.80; H, 3.95; N, 13.72. Found: C, 58.65; H, 4.06; N, 13.40.

Isatin. A solution of 3-methylthiooxindole (1.70 g, 0.0095 mol) and *N*-chlorosuccinimide (1.34 g, 0.01 mol) in 100 mL of carbon tetrachloride was stirred at room temperature for 1 h, the precipitate of succinimide was removed by filtration, and the filtrate was evaporated. The residue, which was obtained, was dissolved in a minimum of tetrahydrofuran and added to a vigorously stirred slurry of red mercuric oxide powder (2.17 g, 0.01 mol) and boron trifluoride etherate (1.43 g, 0.01 mol) in 20% aqueous tetrahydrofuran (70 mL). After stirring at room temperature for 1 h, 200 mL of ether was added, the reaction mixture was filtered through a pad of Celite, the organic phase of the filtrate was separated, dried over anhydrous magnesium sulfate, and filtered, and this filtrate was evaporated to give isatin (1.07 g, 78%), mp 200–202 °C (lit.[12] mp 200–201 °C), after recrystallization from benzene.

5-Methylisatin. A solution of 5-methyl-3-methylthiooxindole (1.00 g, 0.0052 mol) and *N*-chlorosuccinimide (700 mg, 0.0053 mol) in carbon tetrachloride (100 mL) was stirred at room temperature for 1 h. The precipitate was removed by filtration and the filtrate was evaporated to give the crude 3-chloro-5-methyl-3-methylthiooxindole, which was dissolved in tetrahydrofuran (20 mL) and added to a vigorously stirred slurry of red mercuric oxide (1.13 g, 0.0052 mol) and boron trifluoride etherate (745 mg, 0.0052 mol) in 70 mL of 20% aqueous tetrahydrofuran. After stirring at room temperature for 2 h, the reaction mixture was filtered through a Celite pad, and the filtrate was extracted with two 100-mL portions of chloroform. The chloroform extracts were dried over anhydrous magnesium sulfate and filtered, and the filtrate was evaporated. The residue was chromatographed on silica gel. Elution with chloroform gave 5-methylisatin (610 mg, 0.0038 mol, 74%), mp 185–187 °C (recrystallized from ethanol), as red needles (lit.[13] mp 187 °C).

5-Methoxyisatin. A solution of 5-methoxy-3-methylthiooxindole (420 mg, 2 mmol) and *N*-chlorosuccinimide (270 mg, 2 mmol) in carbon tetrachloride (75 mL) was stirred at room temperature for 1 h. The precipitate was removed by filtration and the filtrate was evaporated to dryness. The residue was dissolved in tetrahydrofuran (10 mL) and added to a vigorously stirred slurry of red mercuric oxide (435 mg, 2 mmol) and boron trifluoride etherate (290 mg, 2 mmol) in

Table II. ^{13}C Chemical Shifts for Substituted Isatins

Registry no.	Compd		2	3	3a	4	5	6	7	7a	Substituent
91-56-5	Isatin	Obsd	159.5	184.6	117.9	124.8	122.9	138.5	112.4	150.9	
39755-95-8	5-OCH_3	Obsd	159.6	184.1	118.1	108.8	155.4	124.9	113.3	144.7	55.8
		Calcd			119.3	110.0	155.7	123.7	113.8	143.9	
608-05-9	5-CH_3	Obsd	159.5	184.6	117.8	124.8	132.0	138.8	112.1	148.5	20.1
		Calcd			117.8	125.7	132.3	139.4	112.3	148.4	
1127-59-9	7-CH_3	Obsd	159.6	184.3	117.3	121.6[a]	122.3[a]	139.2	121.1	149.0	15.9
		Calcd			117.8	122.3	122.8	139.4	121.8	151.8	
	4-Cl	Obsd	158.6	181.2	114.8	131.1	123.6	139.0	111.0	152.1	
		Calcd			118.0	129.9	123.0	140.1	111.3	152.5	
17630-76-1	5-Cl	Obsd	159.1	183.4	119.1	124.2	126.9	137.3	113.9	149.2	
		Calcd			119.5	124.9	128.0	138.6	114.0	149.8	
	6-Cl	Obsd	159.4	183.0	116.8	126.2	122.8	142.4	112.3	151.9	
		Calcd			116.8	126.4	123.0	143.6	112.5	152.5	
25128-38-5	5-$CO_2C_2H_5$	Obsd	159.4	183.4	117.8	125.0	124.6	139.0	112.3	154.1	164.6, 60.9, 14.2
		Calcd			118.1	124.1	124.6	139.8	112.6	155.4	
	4-CF_3[b]	Obsd	158.2	180.5	115.5	126.2[c]	119.2[d]	138.3	116.8	152.5	123.0[e]
		Calcd			114.7	127.3	119.7	138.8	115.7	151.2	
345-32-4	5-CF_3[b]	Obsd	159.4	183.1	118.2	121.4[f]	123.2[g]	134.7[h]	112.8	153.4	124.0[i]
		Calcd			118.2	121.6	125.4	135.3	112.7	154.2	
	6-CF_3[b]	Obsd	159.0	184.6	121.0	125.3	119.5[j]	136.2[k]	108.4[l]	150.7	123.5[m]
		Calcd			121.2	125.1	119.7	141.0	109.2	151.2	
61394-92-1	5-CN	Obsd	159.4	182.6	118.6[a]	128.5	104.9	141.7	113.1	153.7	118.3[a]
		Calcd			119.0	129.1	105.5	142.8	113.5	155.4	
	4-NO_2	Obsd	158.1	178.1	109.3	144.4	116.8[a]	138.8	117.1[a]	151.8	
		Calcd			113.6	144.9	118.6	139.4	118.7	151.8	
611-09-6	5-NO_2	Obsd			118.2	119.6	142.7	133.2	112.6	155.3	
		Calcd			118.8	120.5	143.0	134.2	113.3	157.2	

[a] Values may be interchanged for this compound. [b] Contrary to the literature values[21,22] for the ^{13}C substituent effect of substituted benzenes, we found that a study of α,α,α-trifluorotoluene vs. benzene indicated that the shifts should be: C-1, +2.5; C_{ortho}, −3.2; C_{meta}, +0.3; and C_{para}, +3.3. [c] J_{CCF} = 35 Hz. [d] J_{CCCF} = 5.6 Hz. [e] J_{CF} = 277 Hz. [f] J_{CCCF} = 3.6 Hz. [g] J_{CCF} = 33 Hz. [h] J_{CCCF} = 3.4 Hz. [i] J_{CF} = 272 Hz. [j] J_{CCCF} = 3.9 Hz. [k] J_{CCF} = 32 Hz. [l] J_{CCCF} = 3.3 Hz. [m] J_{CF} = 276 Hz.

aqueous 20% tetrahydrofuran (40 mL). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was filtered through a pad of Celite and the filtrate was extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate and filtered, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel to give 5-methoxyisatin (287 mg, 81%), mp 202–204 °C (recrystallized from benzene) (lit.[14] mp 201–203 °C).

5-Chloroisatin. A solution of 5-chloro-3-methylthiooxindole (1.35 g, 6.3 mmol) and *N*-chlorosuccinimide (950 mg, 7 mmol) in carbon tetrachloride (100 mL) was refluxed for 1 h and cooled, and the precipitate was removed by filtration. The filtrate was concentrated to dryness. The residue was dissolved in 25 mL of tetrahydrofuran and added rapidly to a vigorously stirred slurry of red mercuric oxide (1.37 g, 6.3 mmol) and boron trifluoride etherate (900 mg, 6.3 mmol) in 100 mL of 20% aqueous tetrahydrofuran. After stirring for 3 h, the solution was filtered through a pad of Celite and the filtrate was extracted with chloroform. The chloroform extracts were dried over anhydrous magnesium sulfate and filtered and the filtrates were concentrated to give a red solid which was chromatographed on silica gel with chloroform as the eluent. There was obtained 5-chloroisatin (850 mg, 75%), mp 248–252 °C (recrystallized from ethanol) (lit.[15] mp 247 °C).

5-Ethoxycarbonylisatin. A solution of 5-ethoxycarbonyl-3-methylthiooxindole (1.50 g, 7 mmol) and *N*-chlorosuccinimide (1.25 g, 9.3 mmol) in methylene chloride (150 mL) was stirred at room temperature for 24 h. The solvent was removed in vacuo and the residue was dissolved in tetrahydrofuran and added to a vigorously stirred slurry of red mercuric oxide (1.53 g, 7 mmol) and boron trifluoride etherate (1.00 g, 7 mmol) in 100 mL of 50% aqueous tetrahydrofuran. After stirring at room temperature for 1 h, the red solution was extracted with chloroform. The organic extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated and the residue was chromatographed on silica gel. Elution with chloroform gave 5-ethoxycarbonylisatin (860 mg, 56%) as a yellow solid: mp 205–207 °C (recrystallized from ether); IR (KBr) 3265 (NH), 1765 (ester C=O), 1750 (C=O), and 1700 cm^{-1} (amide C=O); NMR (Me_2SO-d_6) τ −1.00 (1 H, bs, NH), 1.80 (d of d, 1 H, $J_{4,6}$ = 2, $J_{6,7}$ = 9 Hz, H_6), 1.90 (d, 1 H, $J_{4,6}$ = 2 Hz, H_4), 3.20 (d, 1 H, $J_{6,7}$ = 9 Hz, H_7), 5.65 (q, 2 H, $CO_2CH_2CH_3$), and 8.60 (t, 3 H, $CO_2CH_2CH_3$); mass spectrum *m/e* obsd 219.0534 (calcd, 219.0531).

Anal. Calcd for $C_{11}H_9NO_4$: C, 60.27; H, 4.14; N, 6.39. Found: C, 60.23; H, 4.13; N, 6.51.

5-Cyanoisatin. A solution of 5-cyano-3-methylthiooxindole (950 mg, 4.66 mmol) and *N*-chlorosuccinimide (800 mg, 5.95 mmol) in 100 mL of methylene chloride was stirred at room temperature for 24 h. The solvent was removed in vacuo and the residue, which was dissolved in a minimum of tetrahydrofuran, was added to a vigorously stirred slurry of red mercuric oxide (1.00 g, 4.7 mmol) and boron trifluoride etherate (670 mg, 4.7 mmol) in 100 mL of 50% aqueous tetrahydrofuran. After 2 h, the reaction mixture was filtered through a pad of Celite. The pad was washed with three 100-mL portions of chloroform. The organic layer was separated, dried over anhydrous magnesium sulfate, and filtered, and the filtrate was evaporated. The residue was chromatographed on silica gel. Elution with chloroform–ethanol (9:1 v/v) gave 5-cyanoisatin as an orange solid (525 mg, 65%): mp 270–272 °C dec; IR (KBr) 3100 (NH), 2220 (C≡N), 1730 (C=O), and 1710 cm^{-1} (C=O); NMR (Me_2SO-d_6) τ −1.30 (1 H, bs, NH), 2.00 (d of d, 1 H, $J_{4,6}$ = 2, $J_{6,7}$ = 8.5 Hz, H_6), 2.10 (d, 1 H, $J_{4,6}$ = 2 Hz, H_4), and 2.90 (d, 1 H, $J_{6,7}$ = 8.5 Hz, H_7); mass spectrum *m/e* obsd 172.0238 (calcd, 172.0272).

Anal. Calcd for $C_9H_4N_2O_2$: C, 62.80; H, 2.34; N, 16.28. Found: C, 62.37; H, 2.41; N, 16.07.

5-Nitroisatin. A solution of 3-methylthio-5-nitrooxindole (900 mg, 4 mmol) and *N*-chlorosuccinimide (600 mg, 4.5 mmol) in 50 mL of chloroform was stirred at room temperature for 1 h and then evaporated to dryness in vacuo. The residue was dissolved in 15 mL of tetrahydrofuran and added to vigorously stirred slurry of red mercuric oxide powder (900 mg, 4.3 mmol) and boron trifluoride etherate (600 mg, 4.3 mmol) in 100 mL of 20% aqueous tetrahydrofuran. After stirring at room temperature for 2 h, the reaction mixture was extracted with three 100-mL portions of chloroform. The chloroform layer was dried over anhydrous magnesium sulfate, filtered, and evaporated. The residue was recrystallized from 95% ethanol to give 5-nitroisatin (600 mg, 78%), mp 252–254 °C (lit.[16] mp 254–256 °C).

5-Trifluoromethylisatin. A solution of 3-methylthio-5-trifluoromethyloxindole (1.40 g, 0.0057 mol) and *N*-chlorosuccinimide (800 mg, 0.006 mol) in 100 mL of carbon tetrachloride was stirred at room temperature for 1 h. The precipitated succinimide was removed by filtration, and the filtrate was evaporated to give a yellow solid which was dissolved in 30 ml of tetrahydrofuran and added to a vigorously stirred slurry of red mercuric oxide (1.30 g, 5.8 mmol) and boron trifluoride etherate (860 mg, 5.8 mmol) in 100 ml of 20% aqueous tetrahydrofuran. The resulting mixture was stirred for 2 h at room temperature and filtered through a pad of Celite, and the filtrate was extracted with four 100-mL portions of methylene chloride. The methylene chloride extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated to give a residue which was chromatographed on silica gel. Elution with methylene chloride gave 5-trifluoromethylisatin as yellow needles (860 mg, 73%): mp 191–193 °C (recrystallized from benzene) (lit.[17] mp 246 °C); IR (KBr) 3200 (NH), 1750 (C=O), 1710 cm^{-1} (C=O); NMR (Me_2SO-d_6), τ −1.20 (bs, 1 H, NH), 2.15 (d, 1 H, H_6), 2.30 (s, 1 H, H_4), 2.90 (d, 1 H, $J_{6,7}$ = 8 Hz, H_7); mass spectrum *m/e* obsd 215.0196 (calcd, 215.0194).

Anal. Calcd for $C_9H_4F_3NO_2$: C, 50.24; H, 1.87; N, 6.51. Found: C, 50.12; H, 1.92; N, 6.43.

A phenylhydrazone derivative of 5-trifluoromethylisatin was prepared: mp 263–265 °C; mass spectrum *m/e* obsd 305.0767 (calcd for $C_{15}H_{10}F_3N_3C$, 305.0776).

4-Nitroisatin. A solution of 3-methylthio-4-nitrooxindole (1.58 g, 7 mmol) and *N*-chlorosuccinimide (1.20 g, 9 mmol) in 100 mL of methylene chloride was stirred at room temperature for 48 h. The solvent was removed in vacuo. The residue was dissolved in 25 mL of tetrahydrofuran and added rapidly to a vigorously stirred slurry of red mercuric oxide (1.52 g, 7 mmol) and boron trifluoride etherate (1.00 g, 7 mmol) in 100 mL of 50% aqueous tetrahydrofuran. After stirring for 3 h, the solution was filtered through a Celite pad which was then washed with copious amounts of chloroform. The organic layer was separated, dried over anhydrous magnesium sulfate, and filtered and the filtrate was evaporated. The residue was chromatographed on silica gel. Elution with chloroform–ethanol (9:1) gave 4-nitroisatin (535 mg, 40%): mp 248–250 °C dec (recrystallized from ethanol); IR (KBr) 3200 (NH), 1750 (C=O), 1710 (C=O), 1520 (NO_2), and 1350 cm^{-1} (NO_2); NMR (Me_2SO-d_6) τ −1.30 (1 H, bs, NH), 2.20–2.80 (m, 3 H, aryl H).

Anal. Calcd for $C_8H_4N_2O_4$: C, 50.00; H, 2.10; N, 14.58. Found: C, 49.93; H, 2.27; N, 14.46.

7-Methylisatin. A solution of 7-methyl-3-methylthiooxindole (1 g, 0.0052 mol) and *N*-chlorosuccinimide (0.7 g, 0.0052 mol) in chloroform (100 mL) was stirred at room temperature for 1 h. The solution was evaporated and the residue was dissolved in a minimum amount of tetrahydrofuran (ca. 10 mL) and added to a vigorously stirred slurry of red mercuric oxide (1.13 g, 0.0052 mol) and boron trifluoride etherate (0.75 g, 0.0054 mol) in 50 mL of 20% aqueous tetrahydrofuran. After stirring at room temperature for 1 h, 150 mL of ether was added, the reaction mixture was filtered through a pad of Celite, the organic phase of the filtrate was separated, dried over anhydrous magnesium sulfate, and filtered, and the solvent was evaporated. The red residue was recrystallized from methanol to give 0.6 g (71%) of 7-methylisatin, mp 267–269 °C (lit.[18] mp 267 °C).

1-Methylisatin. A solution of 1-methyl-3-methylthiooxindole (1.07 g, 5.56 mmol) and *N*-chlorosuccinimide (800 mg, 6.0 mmol) in 75 ml of carbon tetrachloride was stirred at room temperature for 1 h and filtered, and the filtrate was evaporated to give a residue. The residue was dissolved in 20 mL of tetrahydrofuran and rapidly added to a vigorously stirred slurry of red mercuric oxide (1.20 g, 5.56 mmol) and boron trifluoride etherate (790 mg, 5.56 mmol) in 75 mL of 20% aqueous tetrahydrofuran. After stirring at room temperature for 1 h, the reaction mixture was filtered through a Celite pad, and the filtrate was extracted with ether. Evaporation of the ether layer gave a residue which was purified by chromatography on silica gel. Elution with methylene chloride gave 1-methylisatin (550 mg, 61%): mp 131–133 °C (lit.[17] mp 130–133 °C); NMR ($CDCl_3$) τ 2.23–2.60 (m, 2 H, aromatic H), 2.71–2.90 (m, 2 H, aromatic H), and 6.70 (s, 3 H, NCH_3).

Isatin and 3,3-Dimethylthiooxindole. A solution of 3-methylthiooxindole (1.79 g, 0.01 mol) and *N*-chlorosuccinimide (1.45 g, 0.011 mol) in 100 mL of carbon tetrachloride was stirred at room temperature for 1 h. The precipitated succinimide was removed by filtration and the filtrate was evaporated to dryness on a rotary evaporator. The residue was boiled in 100 mL of 20% aqueous tetrahydrofuran for 6 h and cooled, and the solution was extracted with chloroform. The chloroform extract was dried over anhydrous magnesium sulfate, filtered, and evaporated. The residue was chromatographed on silica gel. Elution with chloroform gave 3,3-dimethylthiooxindole (560 mg, 24%): mp 163–164 °C (recrystallized from benzene); IR (KBr) 3180 (NH) and 1700 cm^{-1} (C=O); NMR ($CDCl_3$) τ 0.98 (bs, 1 H, NH), 2.87 (m, 4 H, aryl H), and 7.83 (s, 6 H, SCH_3).

Anal. Calcd for $C_{10}H_{11}NOS_2$: C, 53.30; H, 4.92; N, 6.22. Found: C, 53.00; H, 5.01; N, 6.12.

Further elution with chloroform gave isatin (1.00 g, 68%), mp 200–202 °C (recrystallized from benzene) (lit.[12] mp 200–201 °C).

5-Methoxyisatin and 3,3-Dimethylthio-5-methoxyoxindole. A suspension of 5-methoxy-3-methylthiooxindole (1.00 g, 4.8 mmol) and *N*-chlorosuccinimide (650 mg, 4.8 mmol) was refluxed for 1 h in 100 mL of carbon tetrachloride. The cooled solution was filtered and the filtrate was evaporated to give a residue which was refluxed in 100 mL of 20% aqueous tetrahydrofuran for 18 h. After cooling, the dark solution was extracted with chloroform. The chloroform layer was separated, dried over anhydrous magnesium sulfate, and filtered and the filtrate was evaporated. The residue was chromatographed on silica gel. Elution with chloroform gave 3,3-dimethylthio-5-methoxyoxindole (300 mg, 24%): mp 167–169 °C (recrystallized from benzene); IR (KBr) 3200 (NH) and 1705 cm^{-1} (C=O); NMR ($CDCl_3$) τ 0.65 (bs, 1 H, NH), 3.10 (m, 2 H, H_6 and H_7), 3.16 (d, 1 H, $J_{4,6}$ = 2 Hz, H_4), 6.20 (s, 3 H, OCH_3) and 7.80 (s, 6 H, SCH_3); mass spectrum *m/e* obsd 255.0382 (calcd, 255.0387).

Anal. Calcd for $C_{11}H_{13}NO_2S_2$: C, 51.74; H, 5.13; N, 5.49. Found: C, 51.88; H, 5.19; N, 5.42.

Further elution with chloroform gave 5-methoxyisatin (525 mg, 62%), mp 202–204 °C (lit.[14] mp 201–202 °C).

5-Methylisatin and 3,3-Dimethylthio-5-methyloxindole. A solution of 5-methyl-3-methylthiooxindole (1.00 g, 5.2 mmol) and *N*-chlorosuccinimide (700 mg, 5.5 mmol) in 100 mL of carbon tetrachloride was stirred at room temperature for 1 h and filtered to remove the succinimide, and the solvent was removed in vacuo. The residue was dissolved in 100 mL of 20% aqueous tetrahydrofuran and refluxed for 5 h. After cooling, the reaction mixture was extracted with three 100-mL portions of chloroform. The chloroform extracts were dried over anhydrous magnesium sulfate and filtered, and the filtrate was evaporated to give a residue which was chromatographed on silica gel. Elution with chloroform gave 3,3-dimethylthio-5-methyloxindole (172 mg, 14%): mp 188–189 °C (recrystallized from methanol); IR (KBr) 3170 (NH) and 1705 cm^{-1} (C=O); NMR ($CDCl_3$) τ 0.60 (1 H, bs, NH), 2.80–3.20 (3 H, m, aryl H), 7.75 (3 H, s, 5-CH_3), and 8.00 (6 H, s, SCH_3); mass spectrum *m/e* obsd 239.0460 (calcd, 239.0438).

Further elution with chloroform gave 5-methylisatin (525 mg, 63%), mp 185–187 °C (recrystallized from 95% ethanol) (lit.[13] mp 187°C).

5-Chloro-3,3-dimethylthiooxindole and 5-Chloroisatin. A solution of 5-chloro-3-methylthiooxindole (1.35 g, 6.3 mmol) and *N*-chlorosuccinimide (935 mg, 7.0 mmol) in 100 mL of carbon tetrachloride was refluxed for 1 h and cooled, and the precipitated succinimide was removed by filtration. The filtrate was evaporated and the residue was dissolved in 100 mL of 20% aqueous tetrahydrofuran and refluxed for 18 h. After cooling, the reaction mixture was extracted with two 100-mL portions of chloroform. The organic solution was dried over anhydrous magnesium sulfate and filtered, and the filtrate was evaporated. The residual solid was chromatographed on silica gel. Elution with methylene chloride gave 5-chloro-3,3-dimethylthiooxindole (200 mg, 12%): mp 222–224 °C (recrystallized from ethanol); IR (KBr) 3150 (NH) and 1700 cm^{-1} (C=O); NMR ($CDCl_3$) τ −0.25 (1 H, bs, NH), 2.75 (1 H, d, $J_{6,7}$ = 8 Hz, H_7), 2.80 (1 H, m, H_6), 3.10 (m, 1 H, H_4), 7.83 (s, 6 H, SCH_3); mass spectrum *m/e* obsd 258.9897 (calcd, 258.9892).

Anal. Calcd for $C_{10}H_{10}NOClS_2$: C, 46.23; H, 3.88; N, 5.39. Found: C, 46.44; H, 4.02; N, 5.28.

Further elution with methylene chloride gave 5-chloroisatin (770 mg, 68%), mp 249–252 °C (recrystallized from ethanol) (lit.[15] mp 247 °C).

^{13}C NMR Spectra. The ^{13}C NMR spectral measurements were made on a Varian CFT-20 nuclear magnetic resonance spectrometer with dimethyl sulfoxide-d_6 as solvent. Chemical shifts are listed in parts per million downfield from tetramethylsilane. Spectra were noise decoupled. In those instances where additional information was needed for specific assignments, off-resonance or gated decoupling was utilized.

Acknowledgement. We are indebted to the Institute of General Medical Sciences of the Public Health Services for Grant GM-22346 which supported this investigation. We also wish to thank the Graduate School of the University of Minnesota for a grant which provided part of the funds used in the purchase of the NMR spectrometer utilized in this investigation.

Registry No.—*p*-Chloroaniline, 106-47-8; *p*-trifluoromethylaniline, 455-14-1; ethyl *p*-aminobenzoate, 94-09-7; *p*-cyanoaniline, 873-74-5; *N*-chlorosuccinimide, 128-09-6; 5-trifluoromethylisatin phenylhydrazone derivative, 61446-52-4; 4-nitroisatin, 61394-93-2; 1-methylisatin, 2058-74-4; 3,3-dimethylthiooxindole, 35524-65-3; 3,3-dimethylthio-5-methoxyoxindole, 61394-94-3; 3,3-dimethylthio-5-methyloxindole, 61394-95-4; 5-chloro-3,3-dimethylthiooxindole, 61394-96-5.

References and Notes

(1) National Institutes of Health Postdoctoral Fellow, 1974–1975.
(2) The most commonly quoted methods for the preparation of isatins are those of Sandmeyer [T. Sandmeyer, *Helv. Chim. Acta*, **2**, 234 (1919)] and of Stollé [R. Stollé, *J. Prakt. Chem.*, **105**, 137 (1922)]. The Sandmeyer approach involves treatment of an aniline with trichloroacetaldehyde and then with hydroxylamine in base. The resulting isonitrosoacetanilide is then heated in sulfuric acid. The Stollé method involves initial treatment of an aniline with oxalyl chloride followed by Friedel–Crafts type acylation in the presence of a strong Lewis acid. Since both methods require electrophilic attack on the aromatic ring, the presence of strong electron-withdrawing groups tends to inhibit the reaction. For a recent review of isatin chemistry see F. D. Popp, *Adv. Heterocycl. Chem.*, **18**, 1 (1975).
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(5) In the case of meta substituents (**1**, Y ≠ H), a mixture of 4- and 6-substituted oxindoles is often formed. In general, the 4:6 ratio of the products is a function of the electronic nature of the substituents. Electron-withdrawing substituents tend to direct the site of attack so that 4-substituted oxindoles predominate. Electron-donating substituents tend to reside primarily on the 6 position of the resulting oxindoles (P. G. Gassman, B. W. Cue, Jr., and T.-Y. Luh, unpublished studies).
(6) P. G. Gassman and H. R. Drewes, *J. Am. Chem. Soc.*, **96**, 3002 (1974); P. G. Gassman and D. R. Amick, *Tetrahedron Lett.*, 3463 (1974).
(7) Some of the 3-methylthiooxindoles utilized in this study are previously unreported. These new oxindoles were prepared via the previously mentioned literature procedures.[3,4]
(8) The choice of solvent was determined by the relative solubilities of the appropriate oxindole.
(9) Hydrolysis could be accomplished without the aid of mercuric oxide and boron trifluoride etherate. However, yields were lower under simple aqueous conditions owing to the competitive formation of the dithioketal of the isatin (see below).
(10) The hydrolysis procedure described is a modification of the Vedejs–Fuchs[11] procedure as previously described by us.[6]
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(17) P. M. Maginnity and C. A. Gaulin, *J. Am. Chem. Soc.*, **73**, 3579 (1951). The discrepancy between our melting point and that reported in the literature is of concern. All spectroscopic data were consistent with our assigned structure. In an attempt to resolve this inconsistency, we attempted to repeat the preparation described in the literature. However, we were unable to reproduce the results described by Maginnity and Gaulin for the preparation of 5-trifluoromethylisatin. Since our sample had been purified by recrystallization from benzene, while that described in the literature had been recrystallized from acetic acid, we thought that the different melting points might be associated with different crystalline forms. However, recrystallization of our sample from acetic acid failed to change the melting point.
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(23) Melting points and boiling points are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 137 infrared spectrophotometer. NMR spectra were obtained on a Varian associates T-60 or A-60-D nuclear magnetic resonance spectrometer. Microanalyses were performed by the Scandinavian Microanalytical Laboratories, Herlev, Denmark.

The Chemistry of γ-Oxo Sulfones. 1. A Novel Rearrangement and a Method for the β-Alkylation of α,β-Unsaturated Ketones

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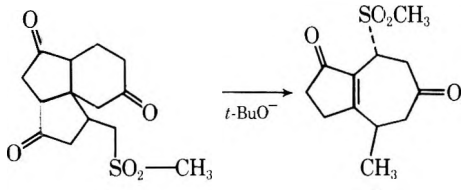
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Received June 13, 1975

The base-induced rearrangement of the tricyclic diketo sulfone 1 into the hydroazulene derivative 2 is described. The structure of 2 is secured by x-ray crystallography. A reaction sequence for this novel transformation is proposed which involves addition of methanesulfinic acid to an α,β-unsaturated ketone. This reaction was examined in model compounds and a method for the β-alkylation of α,β-unsaturated ketones is reported.

During a study of the synthesis of gibberellic acid, the diketo sulfone 1 was found to undergo an extensive rearrangement upon treatment with potassium *tert*-butoxide.[2] The synthesis of 1 along with some of its transformations was presented previously along with the description of the rearrangement reaction.[2] We now wish to report the structure of the rearranged compound obtained previously and present a new method for the β-alkylation of α,β-unsaturated ketones which was suggested by the remarkable transformation of 1 in the presence of potassium *tert*-butoxide. The major product of the reaction, obtained in 30% yield after chromatography and recrystallization, has now been identified as the hydroazulene derivative **2.**



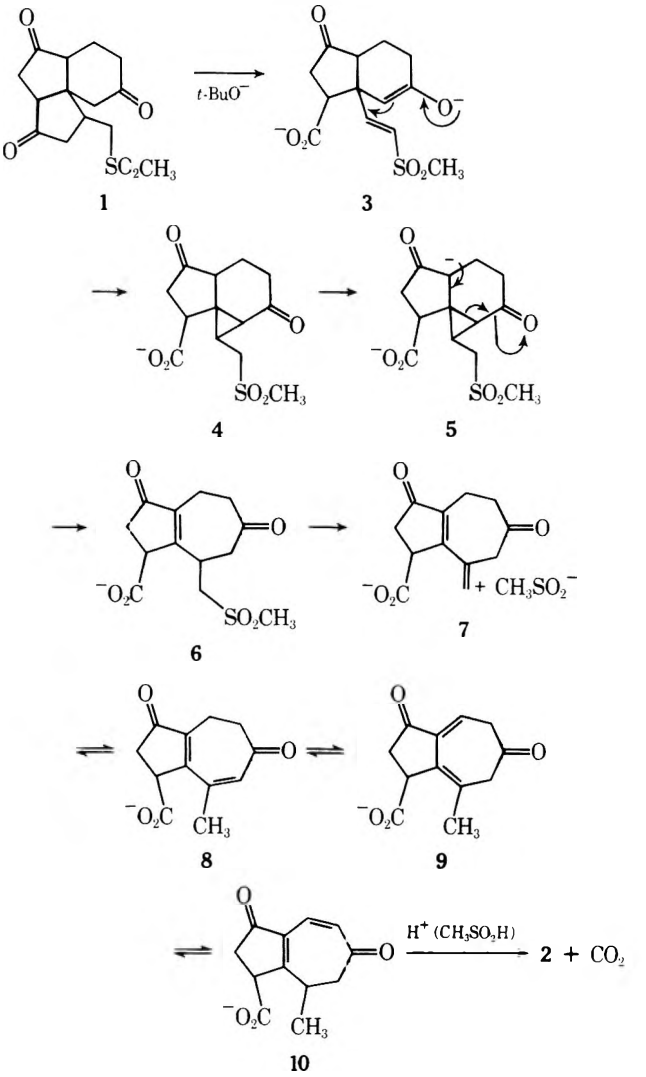
1 2

Crystals of **2**, $C_{12}H_{16}SO_4$, belong to the monoclinic crystal class with $a = 8.374$ (3), $b = 9.427$ (6), $c = 16.578$ (5) Å, and $\beta = 114.17$ (2)°. A calculated density of 1.42 g/cm^3 for $Z = 4$ indicated that the asymmetric unit of the uniquely determined space group $P2_1/c$ consisted of one molecule. A total of 1888 independent reflections were measured on a fully automated Hilger-Watts four-circle diffractometer using Ni-filtered Cu Kα (1.5418 Å) radiation. Following Lorentz, polarization, and background corrections a total of 1649 reflections with $F_o > 3\sigma(F_o)$ were considered observed. The structure was solved by a multisolution tangent formula approach using the program MULTAN[3] and the 134 normalized structure factors greater than 1.70. All nonhydrogen atoms were clearly revealed in the three-dimensional *E*-synthesis of the best set. Full-matrix least-squares refinement converged to the present minimum of 0.097 for the unweighted discrepancy index.

Figure 1 shows a computer generated drawing of the x-ray model. There is a double bond between atoms C(6) and C(10) with a bond length of 1.35 (1) Å. Atoms C(1), C(10), C(9), O(1), C(8), C(7), C(6), and C(5) are planar with an average deviation from the least-squares plane of 0.043 Å and no deviations greater than 0.10 Å. The methyl group, C(11), and the methanesulfonyl groups are on opposite sides of the seven-membered ring. All bond distances and angles agree well with generally accepted values and there are no abnormally short intermolecular contacts.

Scheme I is proposed as a working hypothesis to account for the base-induced conversion of 1 into **2.** Elimination of carboxylate ion to give vinyl sulfone **3** is entirely expected since the corresponding ketal of 1 yields the ketal of **3** under identical reaction conditions. The formation of the seven-membered ring may be accounted for by cyclopropane formation and subsequent cleavage to give **6.** The cyclopropane intermediate **4** could also be formed by a direct internal nu-

Scheme I



1 3 4 5 6 7 8 9 10

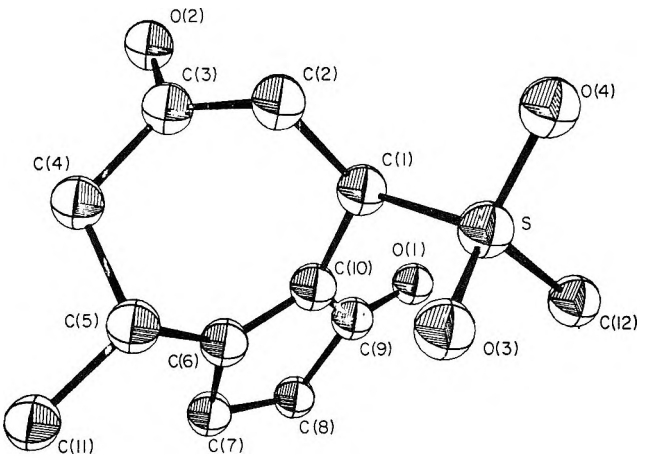
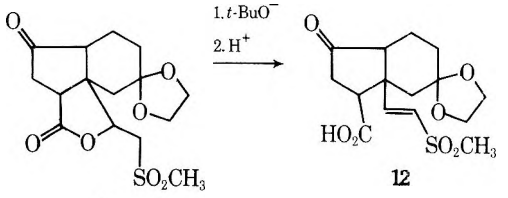
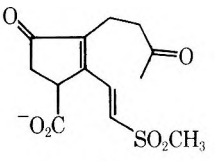


Figure 1.

cleophilic displacement. An alternative route would involve a retro-Michael reaction of **3** to give the dienedione **13** which



11 **12**

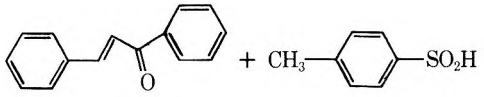


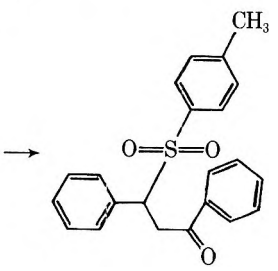
13

could give rise to intermediate **6** by a Michael condensation.

In any case, elimination of methanesulfonate from **6** would afford the diketodiene **7.** We find, in related systems, that such eliminations are rapid. The chance arrangement of carbonyl groups and double bonds in **7** ensures that the double bonds will be very mobile. Hence, isomers **8, 9,** and **10** are expected under the strongly alkaline reaction conditions. Finally, acidification of the reaction mixture would be expected to cause decarboxylation of the vinylogous β-keto acid and result in addition of methanesulfinic acid to the α,β-unsaturated ketone moiety.

The remarkable migration of the methanesulfonyl group has occupied our attention and has suggested some very useful new synthetic sequences. Examination of the literature revealed that *p*-toluenesulfinic acid readily adds to the double bond of chalcone to give the keto sulfone **14.** In our initial

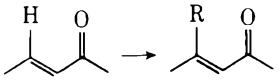




14

experiments we found that sodium *p*-toluenesulfinate does not react with α,β-unsaturated ketones but the reaction readily proceeds upon addition of 1 equiv of a proton source; acetic acid serves nicely. Methyl vinyl ketone and cyclohexenone are converted to the corresponding γ-oxo sulfones in better than 90% yields upon warming in ethanol solution with a slight excess of sodium *p*-toluenesulfinate and acetic acid. The ^{1}H NMR spectra of these materials rule out the isomeric sulfinate ester structures. The chemical shifts of the proton or protons attached to the sulfonyl-bearing carbon are consistent only with the sulfone structure.

The easily obtained γ-oxo sulfones suggested a new method for the β-alkylation of α,β-unsaturated ketones. While this manuscript was in preparation Kondo and Tunemoto[5] presented their results on this same synthetic scheme. In our



study of this process, the γ-keto sulfones were prepared by the addition of *p*-toluenesulfonic acid to the α,β-unsaturated ketones. This reaction proceeds in excellent yields. Kondo and Tunemoto used this reaction in one instance and also employed a sequence involving addition of benzenethiol to the unsaturated ketone or aldehyde and oxidation to the corresponding sulfone at a later stage, a method which requires an additional step.

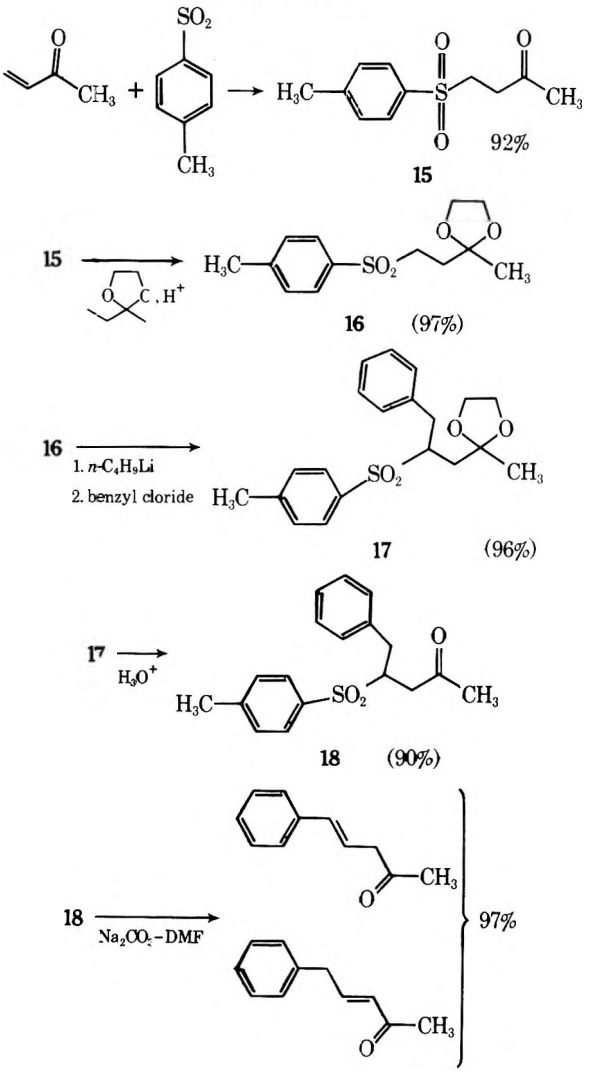
We reasoned that if the carbonyl group of a γ-oxo sulfone were blocked as a ketal or acetal, the sulfonyl group could be used to introduce alkyl groups. Subsequent hydrolysis of the protecting group and elimination of *p*-toluenesulfinic acid would complete the transformation indicated above. This proved to be the case. In the only sequence shown in Scheme II each of the individual steps proceeds in better than 90% yields. Moreover, all of the sulfone intermediates are nicely crystalline and easy to handle.

In the sequence shown in Scheme II, each of the intermediates was isolated, purified, and characterized. However, in routine synthetic applications, it would not be necessary to purify after the alkylation step. We observed no indication of dialkylation and the reaction product was remarkably clean. Hydrolysis of the ketal function and elimination of *p*-toluenesulfinic acid could undoubtedly be carried out without purification of the alkylated γ-oxo sulfone.

In the example shown in Scheme II elimination of *p*-toluenesulfinate from **21** under mild conditions produces nearly pure 5-phenylpent-3-en-2-one as judged from its spectral properties. This material has not been previously reported and earlier work indicated that the β,γ-unsaturated isomer, 5-phenylpent-4-en-2-one, was the only isomer obtainable in this tautomeric system.[6] We find that attempted purification causes equilibration to a mixture of the double bond isomers and more drastic elimination conditions produce a mixture containing 5-phenylpent-4-en-2-one and 5-phenylpent-3-en-2-one in a ratio of about 3:1. This mixture gives an easily purified semicarbazone of the β,γ-unsaturated isomer.[6,7]

The second example of this synthetic method demonstrates the application to cyclic α,β-unsaturated ketones and the preparation of β,β-dialkyl α,β-unsaturated ketones. Cyclohexenone was converted to 3-(*p*-toluenesulfonyl)cyclohexanone, which was in turn converted to the ketal and alkylated with methyl iodide. Hydrolysis of the ketal and elimination of the elements of *p*-toluenesulfinic acid afforded 3-methylcyclohex-2-en-1-one. Each of the steps proceeded in reasonable yield and this approach to the β-alkylation of α,β-unsaturated ketones appears to be a useful synthetic method.

Scheme II



Experimental Section[8]

4-(*p*-Toluenesulfonyl)butan-2-one (15). To 14.54 g (0.204 mol) of methyl vinyl ketone in a 300-mL flask equipped with magnetic stirrer was added a solution of 64.03 g (0.30 mol) of sodium *p*-toluenesulfinate dihydrate in 200 mL of 95% ethanol and 19.0 g of glacial acetic acid. The solution was stirred for 12 h at room temperature, then extracted with two 150-mL portions of $CHCl_3$. The $CHCl_3$ was washed with 150 mL of saturated $NaHCO_3$, dried over Na_2SO_4, and evaporated under reduced pressure to give a viscous yellow residue which afforded 42.62 g (92%) of crystalline sulfone after triturating with hexane. Two recrystallizations from EtOH–Et_2O gave translucent needles: mp 74.5–75 °C; ^1H NMR ($CDCl_3$) δ 7.79, 7.37 (AB q, 4 H, J = 8 Hz) 3.37, 2.91 (t, 4 H, J = 7 Hz), 2.46 (s, 3 H), 2.18 (s, 3H).

Anal. Calcd for $C_{11}H_{14}O_3S$: C, 58.38; H, 6.24. Found: C, 58.23; H, 6.20.

4-(*p*-Toluenesulfonyl)-2,2-ethylenedioxybutane (16). A mixture of **15** (22.055 g, 97 mmol) and *p*-toluenesulfonic acid monohydrate (100 mg) in 100 mL of 2-ethyl-2-methyl-1,3-dioxolane was distilled through a short Vigreux column such that 30 mL of butanone-enriched distillate was obtained over 7 h. The residual dioxolane reagent was removed under reduced pressure to yield a golden, crystalline aggregate which afforded 25.56 g (97%) of **16** after recrystallization from ethyl acetate–hexane. After a second recrystallization: mp 121–122 °C; ^1H NMR ($CDCl_3$) δ 7.80, 7.37 (AB q, 4 H, J = 8 Hz), 3.89 (d, 4 H, J = 4 Hz), 3.18, 2.04 (2 p, 2 H each, J = 4 Hz), 2.46 (s, 3 H), 1.28 (s, 3 H).

Anal. Calcd for $C_{13}H_{18}O_4S$: C, 57.76; H, 6.71. Found: C, 57.54; H, 6.78.

4-(*p*-Toluenesulfonyl)-5-phenyl-2,2-ethylenedioxypentane (17). To 21.729 g (80 mmol) of **16** in a 250-mL three-neck flask fitted with magnetic stirrer and reflux condenser were added 150 mL of freshly distilled THF and 50 mg (indicator amount) of triphenylmethane. Butyllithium (55 mL, 1.5 M in hexane) was added to give a persistent orange color and the resulting solution allowed to stir for 10 min. Cautious addition of 10.10 g (80 mmol) of freshly distilled benzyl chloride produced a yellow slurry which was refluxed for 3 h, then extracted with two 150-mL portions of ether. Evaporation under reduced pressure yielded 28.40 g (98%) of **16** as beige crystals from petroleum ether (bp 30–60 °C). Recrystallization from ethyl acetate–hexane gave fine, white needles: mp 73–73.5 °C; ^1H NMR ($CDCl_3$) δ 7.68, 7.27 (AB q, 4 H, J = 8 Hz), 7.16 (bs, 5 H), 4.0–2.8, 2.6–2.3 (m, 7 H), 2.41 (s, 3 H), 1.90 (p, 2 H), 1.10 (s, 3 H).

Anal. Calcd for $C_{20}H_{24}O_4S$: C, 66.64; H, 6.71. Found: C, 66.22; H, 6.65.

5-Phenyl-4-(*p*-toluenesulfonyl)pentan-2-one (18). To 1.200 g (3.3 mmol) of alkylated ketal sulfone dissolved in 30 mL of methanol was added 1 g of $HClO_4$ (70%). After 30 min, the mixture was extracted with 50 mL of ether, neutralized with 50-mL saturated $NaHCO_3$ wash, dried over Na_2SO_4, concentrated to 1.015 g (94%) of a yellow syrup under reduced pressure, and crystallized twice from hexane–ethyl acetate to yield white crystals: mp 85.5–86.5 °C; IR ($CHCl_3$) 1716 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.79, 7.35 (AB q, 4 H, J = 8 Hz), 7.3–7.0 (m, 5 H), 4.14 (m, 1 H), 3.4–2.3 (m, 4 H), 2.45 (s, 3 H), 1.96 (s, 3 H).

Anal. Calcd for $C_{18}H_{20}O_3S$: C, 68.33; H, 6.37. Found: C, 68.14; H, 6.57.

5-Phenyl-3-penten-2-one. A sample of **18** (0.2025 g, 0.64 mmol) in a 25-mL flask was dissolved in 10 mL of *N,N*-dimethylformamide and sodium carbonate (100 mg) added with continuous magnetic stirring. After 2.5 h, the cloudy mixture was extracted with 25 mL of hexanes, dried over Na_2SO_4, and evaporated to give a sample of the α,β-unsaturated phenyl pentenone isomer (0.0995 g, 97%): IR (CCl_4) 1673 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.16 (bd, 5 H, J = 6 Hz), 6.93 (m, 1 H, C-4 vinyl), 6.09 (d, 1 H, J = 16 Hz, C-3 vinyl), 3.55 (d, 2 H, J = 6 Hz), 2.22 (s, 3 H). A satisfactory combustion analysis was not obtained.

5-Phenyl-4-penten-2-one. A second sample of alkylated keto sulfone (13.3 g, 42 mmol) treated in similar fashion but heated to 60 °C for 9 h yielded 5.09 g (75%) of an isomeric mixture in 78:22 ratio favoring the β,γ-unsaturated component (thermodynamic equilibrium). A fraction of the styryl isomer was difficultly isolated by VPC, 20% Carbowax on Chromosorb W 20–10 mesh, 5 ft × 0.375 in. column, 150 °C: IR (CCl_4) 1713 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.5–7.1 (m, 5 H), 6.51 (d, 1 H, J = 16 Hz), 6.45–6.15 (m, 1 H), 3.33 (d, 2 H, J = 6 Hz), 2.20 (s, 3 H); semicarbazone mp 155–157 °C (EtOH–H_2O) (lit.[6] mp 160 °C).

3-*p*-Toluenesulfonylcyclohexanone. Sodium *p*-toluenesulfinate dihydrate (78.21 g, 0.37 mol) was dissolved in 250 mL of ethanol with 1 equiv (22 g) of glacial acetic acid, and added to 28.44 g (0.296 mol) of 2-cyclohexen-1-one in a 500-mL flask eqipped with a magnetic stirrer. The reaction mixture was maintained at 40–45 °C for 24 h, then extracted with two 250-mL portions of ether, washed with two 125-mL portions of saturated $NaHCO_3$, filtered, and evaporated to a bronze sludge (58.0 g, 78%). Two recrystallizations from hexane–ethyl acetate yielded white needles: mp 83–84 °C; ^1H NMR ($CDCl_3$) δ 7.76, 7.39 (q, 4 H, J = 8 Hz), 3.5–3.0 (m, 1), 2.47 (s, 3), 2.7–1.5 (m, 8 H).

Anal. Calcd. for $C_{13}H_{16}O_3S$: C, 61.88; H, 6.39. Found: C, 61.80; H, 6.32.

3-(*p*-Toluenesulfonyl)-1,1-ethylenedioxycyclohexane. A mixture of 58.0 g (0.23 mol) of crude keto sulfone and 50 mg of *p*-toluenesulfonic acid monohydrate was dissolved in 250 mL of boiling 2-ethyl-2-methyl-1,3-dioxolane in a 500-mL flask equipped with a short Vigreux column. The rate of reflux was adjusted so that 100 mL of butanone-enriched dioxolane reagent was obtained over 7 h. The resulting product was initially isolated as off-color prisms from the residual dioxolane. Recrystallization from ethyl acetate–hexane afforded 65.47 g (96%) of beige prisms: mp 104–105 °C; ^1H NMR ($CDCl_3$) δ 7.75, 7.36 (q, 4 H, J = 8 Hz), 3.92 (s, 4 H), 3.4–3.0 (m, 1 H), 2.46 (s, 3 H), 2.3–1.2 (m, 8 H).

Anal. Calcd for $C_{15}H_{20}O_4S$: C, 60.79; H, 6.80. Found: C, 60.41; H, 6.93.

3-(*p*-Toluenesulfonyl)-3-methyl-1,1-ethylenedioxycyclohexane. A mixture of ketal sulfone obtained above (22.45 g, 0.0758 mol) and triphenylmethane (50 mg) in a 250-mL flask fitted with magnetic stirrer and reflux column was dissolved in 100 mL of THF. Approximately 50 mL of *n*-butyllithium (1.5 M in hexane) was added to a well-defined red end point, and, after 5 min, was followed by cautious addition of 5.0 g (0.08 mol) of methyl iodide with constant stirring. Refluxing for 1 h and in succession, ether extractions (300 mL), drying (Na_2SO_4), and evaporation yielded a brown gum which crystallized. The product was isolated as 23.29 g (99%) of discolored prisms after titrating with petroleum ether (bp 30–60 °C). Two recrystallizations

from hexane–ethyl acetate yielded beige prisms: mp 88–90 °C; ^{1}H NMR ($CDCl_3$) δ 7.74, 7.25 (q, 4, J = 8 Hz), 3.90 (s, 4), 2.46 (s, 3), 2.0–1.5 (m, 8), 1.44 (s, 3).

Anal. Calcd for $C_{16}H_{22}O_4S$: C, 61.91; H, 7.14. Found: C, 61.79; H, 7.26.

3-Methyl-2-cyclohexen-1-one. A sample (0.5180 g, 1.67 mmol) of methylated ketal sulfone was dissolved in 11 mL of acidic aqueous 1,4-dioxane (3.5 mL of 50% $HClO_4$ in 7.5 mL of dioxane) and warmed (50 °C) for 12 h. The resulting auburn solution was made strongly alkaline with excess solid K_2CO_3, and after 30 min, extracted with three 50-mL portions of ether, dried over Na_2SO_4, and evaporated to a clear orange liquid. The residual dioxane was eliminated by preparative TLC (20 × 20 cm, 1000-μm silica gel GF in chloroform) to afford the crude ketone (0.156 g) which was isolated as the 2,4-DNP derivative. Recrystallization from ethyl acetate gave 0.242 g (50%) of dark red flakes, mp 176–178 °C corrected (lit.[9] mp 177–178 °C).

Registry No.—1, 28269-19-4; 2, 61476-93-5; 15, 61476-94-6; 16, 61476-95-7; 17, 61476-96-8; 18, 61476-97-9; methyl vinyl ketone, 78-94-4; sodium *p*-toluenesulfinate, 824-79-3; 2-ethyl-2-methyl-1,3-dioxolane, 126-39-6; benzyl chloride, 100-44-7; 5-phenyl-3-penten-2-one, 10521-97-8; 5-phenyl-4-penten-2-one, 877-94-1; 3-*p*-toluenesulfonylcyclohexanone, 14444-30-5; 2-cyclohexen-1-one, 930-68-7; 3-(*p*-toluenesulfonyl)-1,1-ethylenedioxycyclohexane, 61476-98-0; 3-(*p*-toluenesulfonyl)-3-methyl-1,1-ethylenedioxycyclohexane, 61476-99-1; 3-methyl-2-cyclohexen-1-one, 1193-18-6; methyl iodide, 74-88-4.

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Decomposition of Conjugated *p*-Tosylhydrazones in Base. Partition between Solvolysis and Cycloaddition Products

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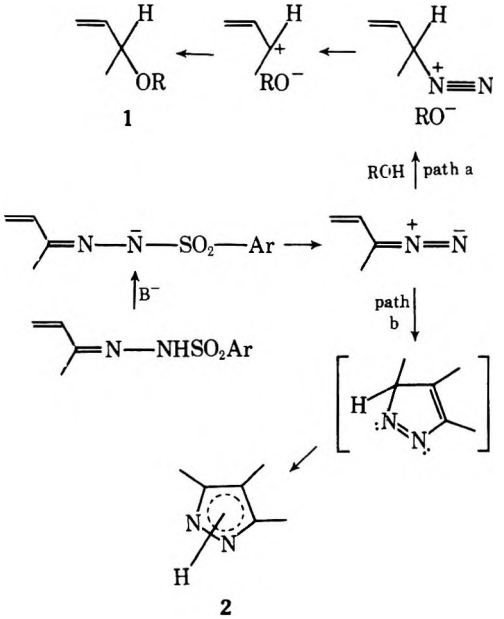
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Received August 11, 1976

The *p*-tosylhydrazones of conjugated carbonyl compounds are not deoxygenated by $NaBH_4$ in methanol, but undergo an alkaline decomposition to diazoalkenes. The partition of the diazo compound between the solvolysis and intramolecular 1,3-dipolar cycloaddition processes depends on the degree and type of substitution at the β position. The use of base ($NaBH_4$, NaOR, or K_2CO_3) in alcoholic solvents provides a mild, convenient, and high-yield procedure for the preparation of a variety of (a) allylic ethers, in the case of cyclohexenones and β,β-dialkyl substituted carbonyl compounds; and (b) pyrazoles, in the case of acyclic α,β-unsaturated substrates having a β hydrogen.

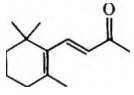
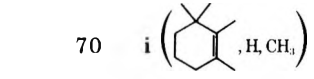
Recently, we have found[1] that *p*-tosylhydrazones of some conjugated carbonyl compounds on treatment with $NaBH_4$ in alcoholic solvents undergo an elimination–substitution reaction in preference to the expected deoxygenation.[2,3] Allylic ethers are obtained in high yields by this method. A similar behavior was observed when RONa or K_2CO_3 was used instead of $NaBH_4$. The sequence *p*-tosylhydrazone → diazoalkene (aryldiazomethane) → diazonium–alkoxide ion pair[4] → ether (1) was suggested as the most suitable mechanistic description (path a). Hart and Brewbaker have shown[5,6] that 3-diazoalkenes, generated from the corresponding alkyl allylnitrosocarbamates, rapidly undergo intramolecular cycloaddition[7] to form pyrazoles (path b).[8] Although for the cyclohexenone and aromatic substrates previously examined by us[1] this cycloaddition was clearly impossible, the formation of only products of solvolysis (e.g., methyl ethers) for the case of the acyclic substrate, neral, was surprising since some intramolecular cycloaddition product may reasonably have been expected.

Scheme I



In a continuation of our studies on the anomalous behavior of *p*-tosylhydrazones of conjugated carbonyls toward $NaBH_4$ we wished to investigate how structural factors may determine the course of decomposition of these compounds. We therefore chose substrates (entries 1, 2, 5–8, Table I) which would yield diazoalkenes structurally analogous to those studied by Hart and Brewbaker. In these cases it could be expected that intramolecular cycloaddition should compete favorably with the elimination–substitution reaction process. In fact, treatment of these substrates with each of the three basic reagents employed previously[1] ($NaBH_4$, MeONa, and K_2CO_3 in methanol) leads to pyrazoles (**2a,b,c–f**) in high yields. No methyl ethers could be detected in the reaction mixtures. In Table I are reported the data for the reagent that is more generally useful (K_2CO_3 in methanol). With $NaBH_4$ or

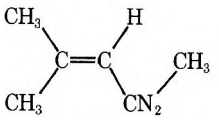
Table I. Decomposition of Conjugated *p*-Tosylhydrazones with K_2CO_3 in Methanol

Registry no.	Entry	*p*-Tosylhydrazone of	Time, h	Product 2 (R, R', R'')	Physical Data of Pyrazoles: Yield,[a] %	Bp, °C (mmHg)	Mp, °C	UV,[b] nm ($\epsilon \times 10^3$)	NMR data, δ[c] (60 MHz, $CDCl_3$)
4170-30-3	1	$CH_3CH{=}CHCHO$	6	a (CH_3, H, H)	78	204[d]		212 (4.1)[e]	2.32 (3 H, s, CH_3C), 6.06 and 7.48 (1 H each, d (J = 1.7 Hz), H_4 and H_5)[25b]
13019-16-4	2	$C_5H_{11}CH{=}C(C_4H_9){-}CHO$[f]	30	b (C_5H_{11}, H, C_4H_9)	81	116–118 (10)		222 (5.0)	0.6–1.9 (16 H, CH_3C, CH_2C), 2.1–2.8 (4 H, m, $CH_2C{=}$), 7.31 (1 H, br s, H_5)
	3	$CH_3C(CH_3){=}CH(CH_2)_2C(CH_3){=}CHCHO$[g,h]	40	[methyl ether,[i,g] 69[l]]					
141-79-7	4	$CH_3C(CH_3){=}CHCCH_3$ (O)	30	[methyl ether, 64[l]]					
14371-10-9	5	PhCH=CHCHO (trans)	24	c (Ph, H, H)	93		75–76[m]	207 (11.0); 248 (14.3)[n]	6.60 (1 H, d (J = 2.2 Hz), H_4), 7.60 (1 H, d (J = 2.2 Hz), H_5), 7.2–8.0 (5 H, aromatic)[26]
6203-18-5	6	*p*-$N(CH_3)_2PhCH{=}CHCHO$	12	d (*p*-$N(CH_3)_2Ph$, H, H)	86		147–149	208 (10.1); 289 (18.3)	2.98 (6 H, s, $(CH_3)_2N$), 6.50 (1 H, br s, H_4), 7.61 (1 H, br s, H_5), 6.74 and 7.64 (2 H each, d, aromatic)
1466-88-2	7	*o*-$NO_2PhCH{=}CHCHO$	12	e (*o*-NO_2Ph, H, H)	94		74–76	209 (13.5); 234 (13.0)	6.48 (1 H, d (J = 2 Hz), H_4), 7.60 (1 H, d (J = 2 Hz), H_5), 7.40–7.85 (4 H, aromatic)
122-57-6	8	$PhCH{=}CHCCH_3$ (O)	24	f (Ph, H, CH_3)	96		125–126	207 (18.5); 252 (15.9)[p]	2.20 (3 H, s, CH_3C), 6.31 (1 H, s, H_4), 7.1–7.9 (5 H, aromatic)[25b]
1210-39-5	9	$PhC(Ph){=}CHCHO$	12	g (Ph, Ph, H) [methyl ether, 25[l]]	59		153–154	209 (19.6); 227 (16.6); 251 (10.2)	7.37 (10 H, aromatic), 7.61 (1 H, s, H_5)
5910-85-0	10	$C_2H_5(CH{=}CH)_2CHO$	24	h ($C_2H_5CH{=}CH$, H, H)	87	120–122 (10)		240 (10.8)	1.08 (3 H, t, CH_3C), 2.25 (2 H, m, CH_2C), 6.35 (1 H, d (J = 2 Hz), H_4), 6.42 (2 H, m, CH=), 7.57 (1 H, d (J = 2 Hz), H_5)
79-77-6	11		70	i 	92	148–150 (0.01)		212 (7.5)	0.97 (6 H, s, $(CH_3)_2C$), 1.46 (3 H, s, $CH_3C{=}$); 2.3 (3 H, s, CH_3C), 5.84 (1 H, s, H_4)
	12	$CH_3C(CH_3){=}CHC(CH_3){=}CHCHO$[h]	12	[methyl ether,[i] 39[l]]					

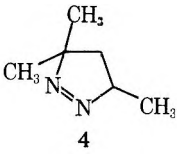
[a] Yields were determined by isolation. Pyrazoles gave satisfactory elemental analyses the results of which have been provided to the Editor. [b] Recorded in absolute EtOH. [c] Downfield from Me_4Si standard. [d] Lit. 204°C (ref 22). [e] Lit. 213°C (3.7) in 95% EtOH (ref 25a). [f] Oily *p*-tosylhydrazone, not purified. [g] See ref 1. [h] *p*-Tosylhydrazone not isolated. [i] Mixture of isomers. [l] Yields of allylic methyl ethers. [m] Lit. 78°C (ref 23); 72–73°C (ref 5). [n] Lit. 248°C (13.8) in 95% EtOH (ref 25a). [o] Lit. 124°C (ref 24). [p] Lit. 251°C (15.6) in MeOH (ref 24); 252.5°C (15.8) in 95% EtOH (ref 25a).

MeONa the same products are obtained in slightly lower yields.

The clear difference between the behavior of these substrates on the one hand and neral (entry 3) on the other agrees with the finding that alkyl disubstitution in the β position of 3-diazoalkenes drastically reduces the rate of cycloaddition, both for thermal[9] and photochemical[10] processes. In order to see whether the enhanced[5,8] reactivity of secondary diazoalkenes could lead, at least in part, to cycloaddition in a β,β-dialkyl substituted substrate, we used mesityl oxide as a probe (entry 4). In this case only the methyl ether was formed. It is useful to note that, in contrast to a previous report,[9] the cycloaddition of the diazoalkene **3**, generated from the *p*-tosylhydrazone of mesityl oxide, is possible. Although in methanol the diazoalkene **3** reacts rapidly to form the methyl ether, in an aprotic solvent (diglyme) it is slowly transformed into the pyrazolenine **4**.



3

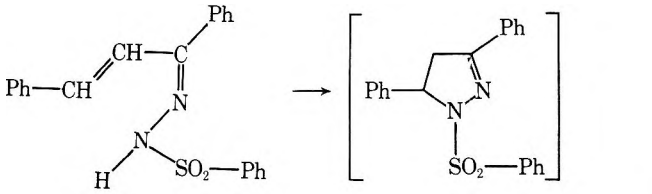


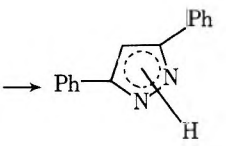
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Thus, α,β-unsaturated carbonyl derivatives lacking hydrogens in the β position (entries 3, 4) undergo an elimination–substitution process to form ethers, as previously observed for cyclohexenone derivatives.

The rather different result obtained with β-phenylcinnamaldehyde (entry 9), a β,β-diaryl substituted substrate, deserves some comment. On treatment with base the corresponding *p*-tosylhydrazone produces a deep red color after only 30 min.[11] From the reaction mixtures both the allylic methyl ether and the pyrazole **2g**, in which a phenyl group has migrated,[12] could be obtained.[13] That under these conditions the diazoalkene was the intermediate common to both products was confirmed by another experiment, in which the diazo compound from the *p*-tosylhydrazone of β-phenylcinnamaldehyde was isolated and then allowed to react with boiling methanol. Both the pyrazole **2g** and the allylic methyl ether increased by 62 and 30%, respectively (determined by using an internal standard), compared to the amounts found to be present after isolation of the diazoalkene.

Thus, the pyrazole appears to be formed from the *p*-tosylhydrazone by a cycloaddition mechanism involving a 3-diazoalkene, rather than by an internal Michael addition followed by elimination of sulfinate.[14] This latter path was proposed,[15] for example, in the "unusual" formation of 3,5-diphenylpyrazole from the benzenesulfonylhydrazone of benzalacetophenone by EtONa in boiling acetonitrile.[16]





The observation that for entry 9 the cycloaddition process occurs to some extent is in contrast with the behavior of the neral and mesityl oxide derivatives (entries 3, 4). This difference may be due to one or both of the following factors: (a) the enhancement[5,17] of dipolarophilicity in the β,β-diphenyl derivative due to extensive conjugation, and/or (b) the greater migratory aptitude of the phenyl group compared to that of the methyl, thus favoring[18] the formation of a stable pyrazole.

Table II. Carbonyl Tosylhydrazones[a]

Tosylhydrazone	Mp, °C	Yield, %
Crotonaldehyde	124[b]	81
Mesityl oxide	110–114[c]	79
trans-Cinnamaldehyde	162–164	85
p-Dimethylaminocinnamaldehyde	180–181	77
o-Nitrocinnamaldehyde	165–167	69
Benzalacetone	201–203	86
β-Phenylcinnamaldehyde	174–175	81
2,4-Heptadienal	124–125	68
β-Ionone	170–171[d]	83

[a] All tosylhydrazones gave satisfactory elemental analyses the results of which have been provided to the Editor. [b] Lit. 125 °C (ref 9). [c] Lit. 105–110 °C (ref 9). [d] Lit. 169–171 °C (ref 3).

A γ–δ carbon–carbon double bond, extending the conjugation, does not confer sufficient activation to induce a β,β-dialkyl substituted substrate (entry 12) to undergo cycloaddition. Again the methyl ether derivative was the only transformation product obtained from the reaction mixtures.

On the other hand, similarly conjugated systems containing a β hydrogen (entries 10, 11) readily undergo intramolecular cycloaddition and the pyrazoles **2h,i** can be obtained in high yields, uncontaminated by the methyl ethers.

In conclusion, the results presented in this and our previous[1] paper on this topic provide methods for the synthesis of allylic ethers or pyrazoles. In fact, treatment of the *p*-tosylhydrazones of conjugated cyclohexenones or acyclic β,β-dialkyl substituted carbonyl compounds with base in alcoholic solvents is a mild, convenient, and efficient procedure for the preparation of a variety of allylic ethers (Scheme I, path a). For acyclic α,β-unsaturated *p*-tosylhydrazones containing a β hydrogen pyrazoles are, virtually, the sole conversion products (path b). Furthermore these results should be useful as a caution for those who might expect to obtain hydrocarbons in the reactions of conjugated *p*-tosylhydrazones with $NaBH_4$ in alcoholic solvents.

Experimental Section

$NaBH_4$ was obtained from Carlo Erba and used without purification. 2-*n*-Butyl-2-octen-1-al and 3,5-dimethyl-2,4-hexadien-1-al were prepared according to literature methods.[19,20] The other ketones and aldehydes used were commercial products. The physical characteristics were obtained as follows: melting points in a Mel-Temp apparatus (uncorrected); UV curves on a Beckman DB-GT; mass spectra on a Varian MAT 112 by GLC insertion; NMR spectra on a JEOL C-60 using Me_4Si as internal standard. Microanalyses were performed by the Istituto di Chimica Generale, University of Modena. The allylic ethers were compared (GC/MS, IR, and NMR) with samples prepared from the corresponding carbonyl compounds by hydride reduction and subsequent methylation (NaH/CH_3I).[21]

***p*-Tosylhydrazone Formation. General Procedure.** The *p*-tosylhydrazones were readily prepared in good yields by addition of *p*-tosylhydrazine (10% mole excess) to a solution of the carbonyl compound in methanol and heating under reflux for 0.5–5 h. Cooling afforded crystalline products in good to excellent yields (Table II).

General Decomposition Procedures. 1. With $NaBH_4$ in Methanol. To a stirred solution of 3 mmol of the *p*-tosylhydrazone in 40–50 mL of methanol, $NaBH_4$ (45 mmol) was added in small portions during 1.5 h. The solution was then refluxed for the appropriate length of time (Table I), the reaction being monitored by TLC and GLC. Water was then added and the mixture extracted with $CHCl_3$ (3 × 25 mL); the organic solution was then washed with water, dried (Na_2SO_4), and concentrated. The residue was analyzed by GLC on a 4 m 5% DEGS column and on a 2 m 5% SE-30 column, giving es-

sentially identical information; for methyl ethers the first column was more convenient and for pyrazoles the second column. The products were fractionated by using a silica gel column (*n*-hexane–ether gradient) and purified by distillation or crystallization. The physical data of the pyrazoles are reported in Table I.

2. With MeONa in Methanol. Reaction mixtures made 0.045 M in the *p*-tosylhydrazone and 0.05 M in MeONa in methanol were refluxed for the appropriate length of time (Table I). Water was then added and the above workup employed to obtain the reaction products.

3. With K_2CO_3 in Methanol. The procedure was identical, except that the solution was 0.06 M in anhydrous K_2CO_3.

As a representative preparative application, the reaction of β-phenylcinnamaldehyde is described (entry 9). Anhydrous K_2CO_3 (1.5 g, 11 mmol) was added to a solution of *p*-tosylhydrazone (1 g, 2.7 mmol) in methanol (50 mL), which was then heated to reflux for 12 h. After dilution with water (150 mL), extraction with light petroleum (3 × 30 ml) and evaporation of the solvent afforded a residue which was purified by chromatography and distillation to yield 0.15 g (0.67 mmol, 25% yield) of β-phenylcinnamyl methyl ether: bp 138–140 °C (0.01 mm); *m/e* (rel intensity) 224 (M^+, 17), 192 ($M^+ - 32$, 100); NMR ($CDCl_3$) δ 3.32 (3 H, s, CH_3O); 4.01 [2 H, d (J = 6.9 Hz), CH_2O], 6.22 (1 H, t (J = 6.9 Hz) CH=), and 7.1–7.7 (10 H, aromatic).

Anal. Calcd for $C_{16}H_{16}O$: C, 85.67; H, 7.19. Found: C, 85.51; H, 7.34.

The aqueous phase was further extracted (3 × 40 mL) with $CHCl_3$, and the organic solution dried and concentrated to a residue which was twice crystallized (diisopropyl ether) to obtain pure 3,4-diphenylpyrazole (see Table I), *m/e* 220 (M^+, 100).

In a parallel run, after 40 min, the diazo compound was extracted with *n*-pentane (4 × 10 mL). The organic solution was concentrated under vacuum (at 15 °C) to 20 mL and then methanol (10 mL) added. After addition of naphthalene as internal standard for GLC monitoring, the mixture was refluxed for 2 h; then, the increase (62 and 32%, respectively) in the amounts of pyrazole **2g** and methyl ether was determined.

2-Methyl-4-methoxy-2-pentene: *m/e* (rel intensity) 114 (M^+, 5), 99 ($M^+ - 15$, 100); NMR ($CDCl_3$) δ 1.2 (3 H, d, CH_3C), 1.72 (6 H, br s, CH_3C=), 3.26 (3 H, s, CH_3O), 4.0 (1 H, m, CHO), and 5.07 (1 H, d, CH=).

2-*n*-Butyl-2-octen-1-al. This was prepared according to ref 19: bp 74–76 °C (10 mm); *m/e* (rel intensity) 182 (M^+, 8); NMR ($CDCl_3$) δ 0.7–1.8 (16 H, aliphatic), 2.0–2.6 (4 H, m, CH_2C=), 6.48 [1 H, t (J = 7.5 Hz), CH=], and 9.34 (1 H, s, CHO).

Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.17. Found: C, 79.30; H, 11.94.

3,5-Dimethyl-2,4-hexadien-1-al. This was prepared according to ref 20: bp 103–110 °C (18 mm); *m/e* (rel intensity) 124 (M^+, 3), 109 ($M^+ - 15$, 100); NMR ($CDCl_3$) δ 1.88 (6 H, s, CH_3C=), 2.23 (3 H, s, CH_3C=), 5.76 (1 H, br s, CH=), 5.85 [1 H, d (J = 8 Hz), CH=], and 9.96 [1 H, d (J = 8 Hz), CHO].

Dimethylhexadienyl Methyl Ether (mixture of isomers): bp 75–79 °C (25 mm); NMR ($CDCl_3$) δ 1.77 (9 H, CH_3C=), 3.29, 3.33, 3.45 (three s, 3 H, CH_3O), 3.4–4.0 (2 H, CH_2O), and 5.2–5.7 (2 H, CH=). The mixture of isomers (three) proved to be identical (GC/MS) with that obtained from the aldehyde by the procedure described above in the introduction to the Experimental Section.

Reactions of 4-Diazo-2-methyl-2-pentene (3). The title compound was prepared according to Closs et al.,[9] by the action of NaH on the *p*-tosylhydrazone of mesityl oxide in triglyme. 3,3,5-Trimethylpyrazolenine **4** accompanied the diazo derivative. The following reactions were monitored by GLC using *tert*-butylbenzene as internal standard.

a. Reaction with Methanol. To a 0.5 M solution (10 mL) of the diazoalkene in diglyme, methanol (10 mL) was added. After 3 h at room temperature the red-violet color faded and the mixture was analyzed by GLC for 2-methyl-4-methoxy-2-pentene (47% yield), which was then isolated by the general procedure described above.

b. Conversion to 3,3,5-Trimethylpyrazolenine (3). A 0.5 M solution (10 mL) of the diazoalkene in diglyme was heated at 95 °C for 1 h. By this time the color faded and the pyrazolenine content was found to be clearly increased (+51%). **3:** *m/e* (rel intensity) 110 (M^+, 8), 109 $M^+ - 1$, 11), 82 ($M^+ - 28$, 19), 67 ($M^+ - 43$, 100); the other physical data corresponded to those reported in ref 9.

Acknowledgment. We gratefully acknowledge support of this work by the Consiglio Nazionale delle Ricerche, Rome.

Registry No.—**2b,** 61490-97-9; **2d,** 61490-98-0; **2e,** 59844-05-2; **2g,** 24567-08-6; **2h,** 61490-99-1; **2i,** 61490-96-8; **3,** 61491-00-7; **4,** 2721-30-4; β-phenylcinnamyl methyl ether, 61491-01-8; 2-methyl-4-methoxy-2-pentene, 61491-02-9; 2-butyl-2-octen-1-al, 13019-16-4; 3,5-dimethyl-2,4-hexadien-1-al, 61491-03-0; dimethylhexadienyl methyl ether, 61528-78-9.

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Action of Hydroxylamine on Chromone and Khellin. Oxime vs. Isoxazoles Structures

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Received September 21, 1976

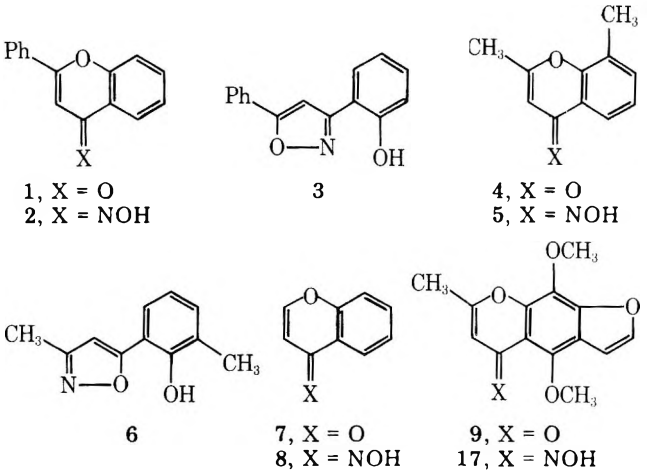
When treated by hydroxylamine under standard conditions, chromone (**7**) does not yield the oxime **8**, but rather two isoxazoles **10** and **11**. The khellin derived isoxazole **14** (mp 120 °C) is the main product formed under similar standard conditions, and its structure has been reassigned. Another isoxazole, having the structure **15**, has also been isolated. On the other hand, the chromone oxime (**8**) and khellin oxime (**17**) are obtained under new oximation conditions (anhydrous methanol, $NH_2OH{\cdot}HCl$). Their structures are unambiguously established by a ^{13}C NMR study.

Nucleophilic attack of hydroxylamine on the γ-pyrone system usually proceeds through opening of the ring and recyclization to yield various nitrogen-containing heterocycles (4-pyridones, isoxazoles). However, scattered examples of oxime formation have been reported.[2,3]

Owing to the difficulty in differentiating γ-pyrone oximes from their isomeric isoxazoles, there has been some confusion in the literature. For example, the compound isolated from the reaction of flavone (**1**) under classical conditions was at first assigned structure **2**.[4] It was much later shown that **3** was actually the correct structure.[5] Similarly, the oxime **5** was thought to be the product isolated by Wittig and Bangert,[6] after treatment of chromone (**4**) with hydroxylamine, but the structure was then revised to **6** by Basinski and Jerzmanowska.[7]

We have applied a one-step oximation method to chromone (**7**) and to khellin (**9**)[8] and we have thus obtained the oximes **8** and **17**. In connection with the structure elucidation, we repeated the previously reported reactions of **7** and **9** (Scheme I).

Scheme I

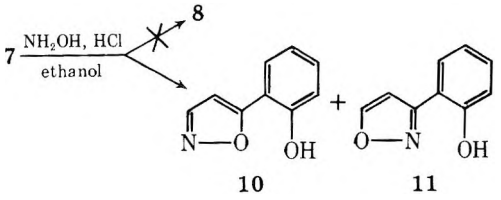


I. Under Standard Conditions. A. Chromone (7) has been recently reported in a patent application[9a] to react with hydroxylamine in ethanol to give chromone oxime (**8**).[9b] We have repeated the experiment and two products **10** and **11** were obtained, both different from the oxime **8** which we have prepared independently by our method (vide infra) (Scheme II).

As no physical data are given in the patent literature it was not possible to tell which product has been obtained by the authors.

Structural data presented in Table I show that neither IR nor NMR allows one to differentiate between **8**, **10**, and **11**. However, the UV spectra of **10** and **11** agree with an isoxazole

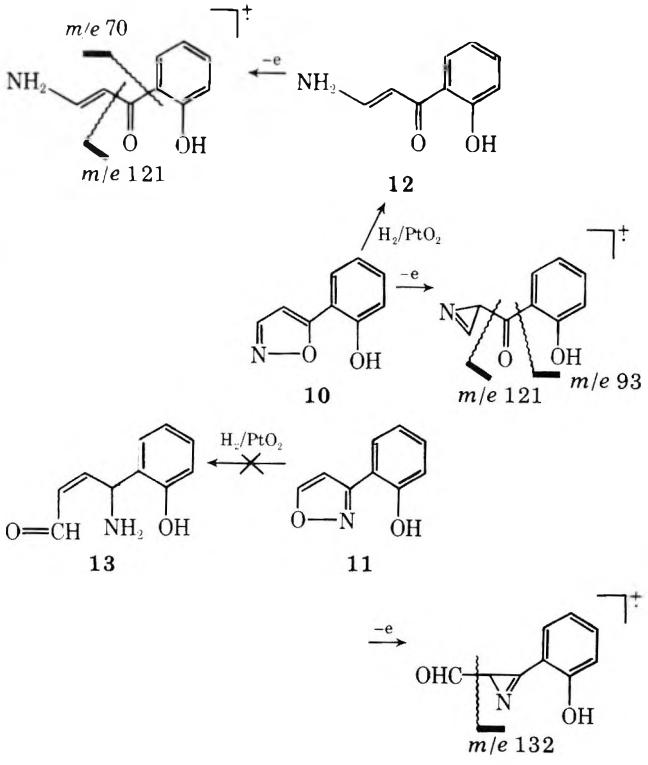
Scheme II



structure[10] and exhibit respectively four bands for the 5-substituted isoxazole and three bands at lower wavelength for the 3-substituted isoxazole in agreement with Crabbé's results.[11]

The fragmentation patterns of isoxazoles in the mass spectrometer are well known[12-15] and ions at *m/e* 121 and 93 are expected and indeed observed for **10**, whereas an ion at *m/e* 132 is similarly predicted and observed for **11** (Scheme III).

Scheme III



The catalytic hydrogenation of **10** yields **12** after absorption of 1 mol of hydrogen. The disappearance of the IR band at ν 1130 cm^{-1} (O–N) and the two units increase of the molecular ion in the mass spectrum of **12** suggest the hydrogenolysis of the N–O bond, and the formation of the vinylogous amide **12**

Table I. Physical Data of Isoxazoles 10 and 11 and Oxime 8

	Isoxazoles		Oxime
	10	11	8
Mp, °C	181 (benzene) (lit. 184[9b])	Liquid	127 (benzene)
IR, ν, cm^{-1} (OH)	3260	3260	3580, 3270
(C=N)	1620	1630	1650
(C=C)	1580	1595	1625
(O–N)	1130	1130	1135
NMR, δ, ppm	6.9 d J = 1.5 Hz	6.7 d J = 2 Hz	6.65 d J = 5 Hz
	8.4 d J = 1.5 Hz	8.4 d J = 2 Hz	7.2 d J = 5 Hz
	AX system	AX system	AB system
UV, λ_{max}, nm (log ϵ)	219 (4.60)	217 (4.35)	240 (3.98)
	261 (4.61)	249 (4.06)	316 (3.89)
	272 (4.49)	293 (3.56)	
	306 (4.43)		
MS, m/e	161 (M^+), 121, 93	161 (M^+), 132	161 (M^+), 145, 130, 102

Table II. Physical Data of Isoxazoles 14 and 15 and Oxime 17

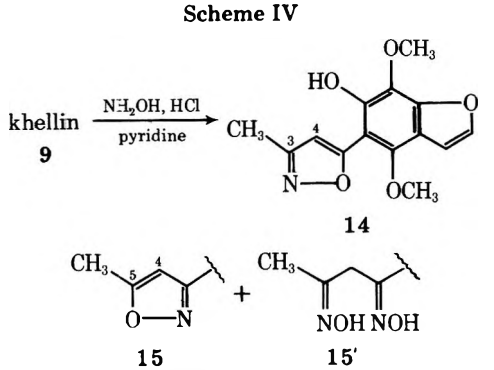
	Isoxazoles		Oxime
	14	15	17
Mp, °C	120 (ethanol–water) (lit. 120–121[23])	124–126 (ether)	224–225 dec (acetone–ether)
IR, ν, cm^{-1} (OH)	3500	3500	3200
(C=N)	1630	1625	1675 br
(C=C)	1590	1605	
(O–N)	1135	1140	1130
NMR, δ, ppm	CH_3 2.35 s $W_{1/2}$ = 1.6 Hz	CH_3 2.4 d J = 0.8 Hz	CH_3 2.3 s
	C_4 H 6.5 s $W_{1/2}$ = 1.4 Hz	C_4 H 6.7 s $W_{1/2}$ = 2 Hz	C=CH 6.75 s
UV, λ_{max}, nm (log ϵ)	221 (4.47)	220 (4.39)	226 (4.63)
	245 (4.58)	244 (4.51)	269 (4.25)
	310 (3.4)	265 shoulder	323 (4.0)
		313 (3.6)	333 (3.98)
MS, m/e	275 (M^+), 205, 177	275 (M^+), 260, 43	275 (M^+), 257

by a well-documented process.[16–19] The presence in the mass spectrum of **12** of an ion at m/e 121 can be explained, as for **10**, by the cleavage α to the carbonyl. The fragment at m/e 70 characterizes **12**. Conversely the α cleavage occurring in the rearranged structure obtained from **11** gives rise to the m/e 132 ion, which does not appear for **10**. The isoxazole **11** failed to hydrogenolyze, as has been reported for other isoxazoles.[20]

All these data completely agree with the proposed isoxazoles structures **10** and **11** and not with the oxime structure.

B. Khellin (9). The isoxazole system had been correctly recognized as being formed under classical conditions but the authors were unable to differentiate between the isomers **14** and **15**, although preference was given to structure **15**.[23] We have repeated the experiment and could isolate **14**, **15**, and the dioxime **15'** (Scheme IV).[21]

Scheme IV



We have observed that the main product, **14**, has the same melting point (120 °C) as the product to which structure **15** had been attributed by Schonberg and Sidky.[23] Our structure assignments rely on physical data reported in Table II.

IR and UV spectra of **14** and **15** agree with the proposed isoxazole structures. The NMR spectra allow differentiation between **14** and **15**. In agreement with other studies[7,24] the methyl of **14** resonates at lower field (2.35 ppm) than the methyl of **15**.

Furthermore, allylic coupling is observed for the methyl borne by **15**, in agreement with the reported observations for 3,5-dimethylisoxazole.[25] The mass spectrum exhibits a fragmentation pattern already observed for **10** (vide supra).

The isoxazole **14**, after absorption of 1 mol of hydrogen, gives the ring-opened vinylogous amide **16** which, when treated with $NaOD/CH_3OD$, incorporates four deuterium atoms to give **16**-d_4.[26] Both **16** and **16**-d_4 give a mass spectrum where the main peaks are m/e 220 and 205, which shows that the fragment m/e 220 has incorporated no deuterium, and has indeed the proposed structure. The ion m/e 205 is common to the spectra of **14**, **16**, and **16**-d_4 and arises from the cleavage α to the carbonyl in all cases (Scheme V).

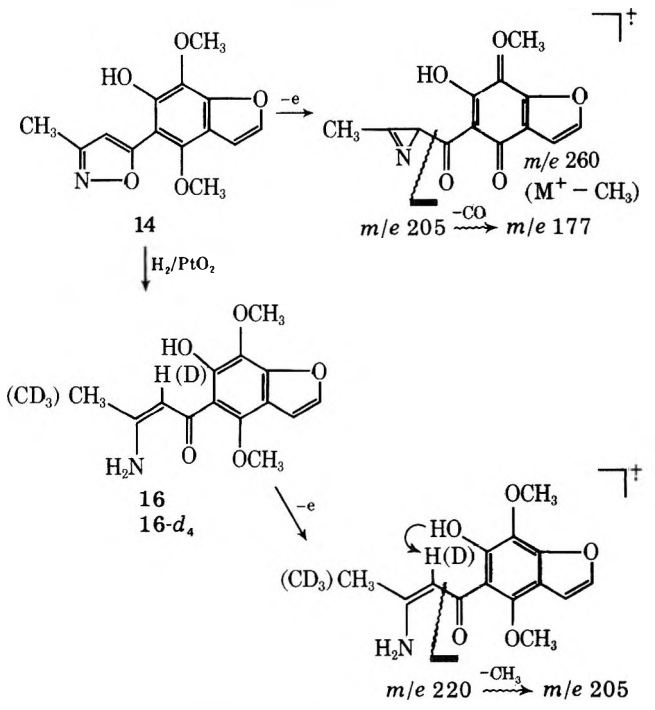
The NMR spectrum of **16** shows at δ 2.02 a signal for a methyl adjacent to a nitrogen atom.[27]

The isomeric isoxazole **15** shows in its mass spectrum an ion at m/e 43 ($CH_3C{\equiv}O^+$) and fails to be hydrogenolyzed as has been similarly observed for the chromone derived isoxazole **11**.

II. Under Anhydrous Acidic Conditions. The compounds **8** and **17** that we have obtained under our conditions[43] (dry, distilled, anhydrous methanol, hydroxylamine hydrochloride)[8] are isomeric with the isoxazoles **10**, **11** and **14**, **15**, respectively. The spectroscopic data of **8** and **17** are in agreement with an oxime structure;[42] but, owing to the confusion we have noted in the literature (see the introduction), a ^{13}C NMR study has been carried out in order to establish unambiguously their structures.

^{13}C NMR Structural Study. A. Calculation of $\Delta\delta^i$ =

Scheme V



$\delta^{i}_{C=O} - \delta^{i}_{C=NOH}$ in the Flavone Series. We took flavone (**1**) and its oxime **2** as reference compounds since they share with chromone (**7**) and khellin (**9**) a common array of carbon atoms α, β, and γ to the carbonyl. Flavone (**1**) ^{13}C chemical shifts have been assigned by Kingsbury and Cooker[28] whose results are taken here;[29] on the other hand, flavone oxime has been prepared through an indirect method.[5] It is thus possible to determine the induced shifts $\Delta\delta^{i}$ on going from **1** to **2**, that is, replacing a carbonyl by an oxime group in a γ-pyrone system.

The flavone oxime ^{13}C spectrum was recorded and assignments are collected in Table III. They are made from single-frequency off-resonance decoupled (sford) data and by comparison with flavone ^{13}C shifts for atoms which are far remote from the substitution site such as 1′, 2′, 3′, 4′, 3a, 9, and 9a (where little or no variation is expected).

B. Chromone Oxime (8). ^{13}C chromone shifts are known[28,32,33] and we have taken the results of Kingsbury.[28] It is then possible to compare the experimental values obtained from the spectrum of 8 with the values calculated by use of the increments obtained from the flavone series.

Table IV shows that agreement is good and fully supports the assigned oxime structure.

C. Khellin Oxime (17). As no ^{13}C study of khellin is known to us, the first step is to assign all the carbon atoms of the parent compound, **9**.

The methyl (20.0 ppm) and the two methoxyls (61.4 and 62.3 ppm) are readily assigned, and the observation in sford mode of a ^{3}J coupling enables us to identify the furan carbon atoms C-2 (146 ppm) and C-3 (105 ppm), in agreement with values obtained for substituted benzofurans.[34] The only remaining nonquaternary carbon atom at 110 ppm is therefore C-6. The carbonyl group (178 ppm) has a δ similar to those borne by several natural γ-pyrone[35-37] and the absorption of the quaternary vinylic carbon (164 ppm) agrees with the value (162 ppm) observed for 3-methylcyclohex-2-enone.[38,39] The aromatic carbon atoms are assigned by means of the known qualitative effects of α, ortho, meta, and para carbon shifts.[40] Thus, carbon atoms 4, 8a, 9, and 9a (α to an oxygen atom) will be shifted downfield (relative to benzene). For carbon atom 9, one has to take into account (1) the effect of an ortho–meta furan ring (−15 ppm); (2) the ortho effect of an α,β-unsaturated ether (−10 ppm); (3) the methoxyl α effect (+30 ppm); (4) the para effect of a methoxyl (−10 ppm), which all leads us to assign the signal at 130 ppm to C-9.

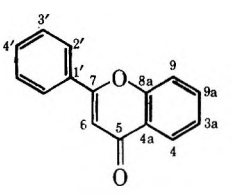
The same calculation is made for carbon atoms 4, 8a, and 9a but their absorption signals are observed within a range of 1 ppm and thus, the assignments cannot be considered to be unequivocal. However, the differentiation of these three signals is not important for subsequent calculations.

It is easily seen in comparing flavone[28] and benzofuran[34] that C-3a will be shifted downfield. Since the khellin skeleton can be formally considered as resulting of the coupling either of (1) flavone + carbon atoms 2 and 3 or (2) benzofuran + carbon atoms 5, 6, and 7, it is possible to determine the relative shift of carbon atoms 3a and 4a by two different approaches (Scheme VI).

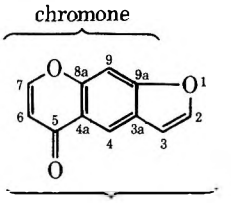
The assignment of C-4a (119 ppm) is thus reasonable and is further supported in that, owing to the presence of a β hydrogen, its relaxation should be more efficient, which is indeed oserved.

Having assigned every carbon resonance of khellin (**9**), it is then possible to calculate the chemical shifts of the carbon atoms of khellin oxime (**17**) as has been done for chromone oxime (**8**). The agreement between calculated and observed

Table III. Calculation of Increments $\Delta\delta^{i} = \delta^{i}_{C=O} - \delta^{i}_{C=NOH}$[a]



flavone



khellin ring

Carbon no.	Flavone (1)	Flavone oxime (2)	Multiplicity	Increment $\Delta\delta^{i}$
3a	125.4[b]	124.8	d	0.6
4	124.9[b]	122.8	d	2.6
4a	123.7	118.4	s	5.3
5	178.0	145.2	s	32.8
6	107.3	93.5	d	13.8
7	163.0	155.3	s	7.7
8a	156.0	152.1	s	3.9
9	117.9	117.7	d	0.2
9a	133.5	132.8	d	0.7
1′	131.5	130.6	s	0.9
2′	126.0	125.8	d	0.2
3′	128.8	128.7	d	0.1
4′	131.3	130.4	d	0.9

[a] For the sake of clarity, we have taken the khellin numbering for all compounds. [b] These values might be interchanged.

Table IV. Comparison of Calculated and Observed ^{13}C Shifts for Chromone Oxime (8)

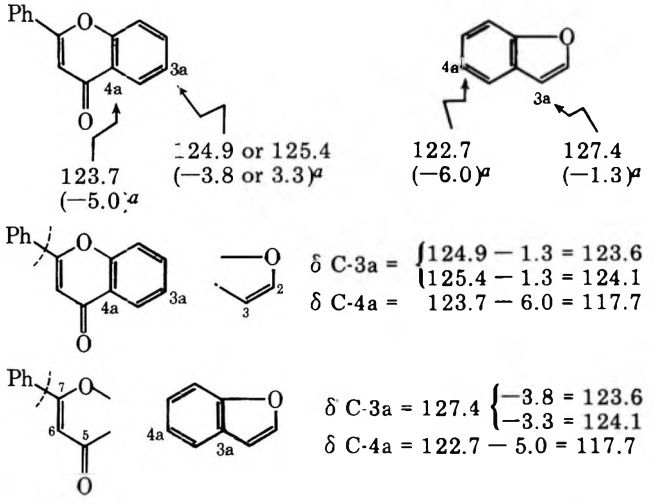
Carbon no.	Chromone (7), δ	Chromone oxime (8)		
		δ_{calcd}	δ_{obsd}	$\Delta\delta_{max}$
3a	125.4	125.4 or 124.3	124.8	0.6
4	124.9	122.4 or 123.4	123.0	0.6
4a	124.6	119.3	118.7	0.6
5	177.1	144.3	143.6	0.7
6	112.7	98.9	98.4	0.5
7	155.0	147.3	147.5	0.2
8a	156.2	152.3	151.7	0.6
9	117.9	117.7	117.6	0.1
9a	133.4	132.7	130.6	2.1

Table V. Comparison of Calculated and Observed ^{13}C Shifts for Khellin Oxime (17)

Carbon no.	Khellin (9), δ	Khellin oxime (17)		
		δ_{calcd}	δ_{obsd}	$\Delta\delta_{max}$
2	145.6		145.3 or 144.7	0.9
3	105.2		105.2	0
3a	119.3	119.2	118.2	1.0
4	148.7	145.9 or 145.5	144.7 or 145.3	1.2
4a	113.6	108.3	107.6	0.7
5	178.1	145.3	144.7 or 145.3	0.6
6	110.5	96.7	94.9	1.8
7	164.0	156.3	155.3	1.0
8a	147.2	143.3 or 143.1	143.2	0.1
9	129.8	129.7	129.7	0
9a	147.0	146.3 or 146.5	147.2	0.9
4-OCH_3	61.4[a]		61.2	1.1
9-OCH_3	62.3[a]		61.2	1.1
7-CH_3	20.0		19.8	0.2

[a] These values might be interchanged.

Scheme VI



[a] Differences relative to unsubstituted benzene are in parentheses.

values is very good, which confirms the structure **17** (Table V).

Chemical Proof of Structure 17. **17**, treated by SO_3HNa, undergoes a smooth deoximation reaction[41] and gives back khellin, identical (melting point, IR) with an authentic sample.[42]

Conclusion

Having prepared by our oximation method authentic samples of chromone oxime (**8**) of khellin oxime (**17**), we were able to re-examine some results of the literature. Firstly, we have shown that the product obtained under standard oximation conditions from the chromone (**7**) was not the oxime **8**, and that instead the isoxazoles **10** and **11** were isolated. Secondly, we have shown that the main product obtained from khellin under standard oximation conditions was not the isoxazole **15**, as previously reported, but instead its isomer **14**.[45]

Experimental Section

General Procedure. Melting points were determined with a Kofler block and are corrected. The ^1H NMR spectra were obtained on a R12 Perkin-Elmer spectrometer with Me_4Si as internal standard. The ^{13}C spectra were obtained on a 22-MHz HX 90E Bruker apparatus. The IR spectra were recorded with an Infracord Perkin-Elmer instrument; the UV spectra were obtained with a Spectronic 505 Bausch and Lomb (ethanol solution). The mass spectra were obtained on a AEI MS9 spectrometer. Microanalysis were performed by the CNRS Service (Gif/Yvette) and satisfactory analytical data were obtained (±0.4% for C, H, N, O) for all new compounds.

Our oximation method was as follows. A solution of γ-pyrone and hydroxylamine hydrochloride (w/w) in anhydrous methanol (obtained by treatment over magnesium and distillation) was refluxed, and the course of the reaction was monitored by TLC. Standard workup yielded the oxime which was purified by crystallization, after column chromatography (SiC_4 Mallinckrodt Silica) if necessary.

2-Phenyl-4*H*-benzopyran-4-one Oxime (Flavone Oxime, 2). The oxime **2** prepared by our method and crystallized from methanol in 37% yield was identical [mp 181–182 °C; IR ν_{max} 1645 (C=N), 1620 cm^{-1} (C=C); mass spectrum *m/e* 237 (M^+), 77] with an authentic sample prepared according to ref 37.

5-*o*-Hydroxyphenylisoxazole (10) and 3-*o*-Hydroxyphenylisoxazole (11). Under the conditions reported by the patent literature, i.e., reflux of a solution of chromone **7** (2 g) and hydroxylamine hydrochloride (2 g) in ethanol (80 mL), we obtained after 24 h a mixture which after column chromatography and benzene elution yielded **11** (1.44 g, 65%) as a colorless liquid. Subsequently ether eluted **10** (0.45 g, 20%) crystallized from benzene, mp 181 °C (lit.[9b] mp 184 °C).

4*H*-Benzopyran-4-one Oxime (Chromone Oxime, 8). Our oximation method yielded **8** in 31% yield, mp 127 °C (from benzene).

Anal. Calcd for $C_9H_7O_2$: C, 67.07; H, 4.38; N, 8.69. Found: C, 67.06; H, 4.37; N, 8.60.

1-(o-Hydroxyphenyl)-3-amino-2-propen-1-one (12). A solution of isoxazole **10** (0.161 g) in ethanol (15 mL) was hydrogenated at atmospheric pressure with PtO_2. After uptake of one hydrogen equivalent the catalyst was removed by fiber glass filtration and classical workup gave **12** (0.146 g, 89%): mp 99–100 °C; IR ν_{max} 3500 (OH), 1650–1620 cm^{-1} (C=N and C=O); NMR δ 5.9 (d) and 7.45 (d) (J = 8 Hz, AX system), 13.05 (OH), 9.5 (NH_2); mass spectrum *m/e* 163 (M^+), 146, 121, 70, 43.

Anal. Calcd for $C_9H_9NO_2$: C, 66.24; H, 5.56; N, 8.58. Found: C, 66.19; H, 5.54; N, 8.32.

5-(3-Methyl-5-isoxazoyl)-4,7-dimethoxy-6-hydroxybenzofuran (14), 5-(5-Methyl-3-isoxazoyl)-4,7-dimethoxy-6-hydroxybenzofuran (15), and 1-(4,7-Dimethoxy-6-hydroxy-5-benzofuranyl)-1,3-butanedione Dioxime (15'). A solution of khellin (**9**) and hydroxylamine hydrochloride (2 g) was refluxed in pyridine (50 mL) for 5 h according to Schonberg and Sidky.[23] Column chromatography of the crude extract and benzene elution yielded **15** (110 mg, 6%), mp 124–126 °C (from ether).

Anal. Calcd for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.73; N, 5.09. Found: C, 61.06; H, 4.73; N, 5.06.

Further elution (benzene–ether, 4:1) yielded **14** (1.41 g, 67%), mp 120 °C (from ethanol–water).

Final elution with pure ether yielded **15'** (0.21 g, 10%) purified by column chromatography, preparative thin layer chromatography, and crystallization: mp 155–159 °C (methanol–ether); IR ν_{max} 3400 (OH), 1620 cm^{-1} (C=N); NMR (CD_3OD) δ 1.6 (s) CH_3, 3.6 (m) $-CH_2-$. The mass spectrum shows peaks at *m/e* 308 (M^+), 275.

Anal. Calcd for $C_{14}H_{16}O_6N_2$: C, 54.54; H, 5.19; N, 9.09. Found: C, 54.69; H, 5.28; N, 9.06.

1-(4,7-Dimethoxy-6-hydroxy-5-benzofuranyl)-3-amino-2-buten-1-one (16). Under the same hydrogenation conditions as used for **10**, the isoxazole **14** yielded **16**: mp 87 °C (from ether); IR ν_{max} 3480 (OH), 1640–1600 cm^{-1} (C=C, C=O); NMR δ 2.02 (s, $W_{1/2}$ = 0.8 Hz, CH_3C=C), 6.2 (s, $W_{1/2}$ = 0.8 Hz, CH_3C=CH). The mass spectrum shows peaks at *m/e* 277 (M^+), 220, 205.

Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.41; N, 5.05. Found: C, 60.92; H, 5.64; N, 5.22.

Deuteration of 16. **16** (100 mg) was refluxed with MeOD (1 mL), D_2O (1 drop), and a small piece of sodium for 2 h. After workup **16-d_4** was obtained. NMR: the peaks at δ 2.02 and 6.2 have disappeared. The mass spectrum shows peaks at *m/e* 281 (277 + 4) (M^+), 220, 203, 177.

4,9-Dimethoxy-7-methyl-5*H*-furo[3,2-*g*]-1-benzopyran-5-one Oxime (Khellin Oxime, 17). Our oximation method on khellin (see **8**) yielded **17** (84% yield), mp 224–225 °C dec (from acetone–ether).

Anal. Calcd for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09. Found: C, 60.94; H, 4.86; N, 4.94.

Deoximation of 17. **17** (100 mg) was refluxed with sodium bisulfite (0.5 mL) for 1 h, acidified with diluted HCl, and then worked up. After

crystallization from methanol and filtration on a column of silica, khellin, identical with **9**, was obtained.

Registry No.—**1**, 525-82-6; **2**, 22115-89-5; **7**, 491-38-3; **8**, 61348-46-7; **9**, 82-02-0; **10**, 61348-47-8; **11**, 61348-48-9; **12**, 30992-84-8; **14**, 61348-49-0; **15**, 61348-50-3; **15'**, 61348-51-4; **16**, 61348-52-5; **17**, 61348-53-6; hydroxylamine hydrochloride, 5470-11-1.

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(42) A radiocrystallographic study of a suitable crystalline derivative of the khellin oxime (methyl ether) carried out by Dr. Guilhem (I.C.S.N., C.N.R.S., Gif-sur-Yvette) which will be published elsewhere confirms the oxime structure of **17** and therefore also the structures **8** and **2**. The khellin oxime methyl ether has the geometry anti, which is the more stable one. This result does not allow us to ascribe the stereochemistry of the parent oxime.
(43) We believe that under our conditions the chromone behaves like a 4-hydroxypyrilium derivative and the nucleophilic attack occurs at position **4** as has been observed on other pyrylium compounds bearing a leaving group in position **4** [see J. Farkas, B. Costisella, M. Rabosi, H. Gross, and R. Bognar, *Chem. Ber.*, **102**, 1333 (1969); S. Yoneda, T. Sugimoto, O. Tanaka, Y. Moriya, and Z. Yoshida, *Tetrahedron*, **31**, 2669 (1975)].
(44) The ^{13}C NMR spectra of the isoxazoles have been recorded; they are different from those of the isomeric oximes but do not allow differentiation between isomeric isoxazoles [see G. M. Buchan and A. B. Turner, *J. Chem. Soc., Perkin, Trans. 1*, 2115 (1975)].
(45) **Notes Added in Proof.** (i) W. Basinski and Z. Jerzmanovska, *Rocz. Chem.*, **50**, 1067 (1976), report that flavone **1** heated with hydroxylamine hydrochloride in pyridine yields oxime **2** and a coproduct previously assigned structure **3** (**5**) but now reassigned as the isomeric 3-phenyl-5-*o*-hydroxyphenylisoxazole. (ii) Recently a number of pryones and flavones ^{13}C studies relevant to our work have appeared: M. J. Looks, L. R. Weingarten, and R. Levin, *J. Am. Chem. Soc.*, **98**, 4571 (1976); C. A. Kingsbury, M. Clifton, and J. H. Looker, *J. Org. Chem.*, **41**, 2777 (1976); A. Pelter, R. S. Ward, and T. I. Gray, *J. Chem. Soc., Perkin Trans. 1*, 2475 (1976). (iii) We have been able to improve the yield of oxime formation by passing dry gaseous hydrogen chloride in anhydrous methanol until pH 1 is reached; thus khellin oxime (**17**) is obtained in >95% yield.

Selective Monodeoxygenation of Certain Quinoxaline 1,4-Dioxides with Trimethyl Phosphite

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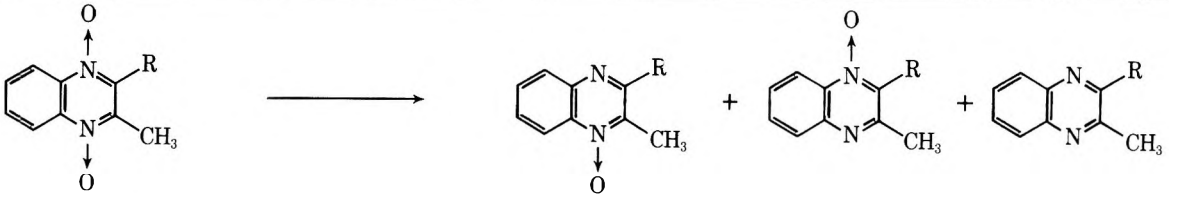
Received November 8, 1976

The reduction of some 2,3-disubstituted quinoxaline 1,4-dioxides with trimethyl phosphite in refluxing alcohol solvent furnished the corresponding monooxides selectively in good yield. Deoxygenation occurred exclusively at the nitrogen adjacent to carbon bearing an electron-withdrawing group. These results are quite remarkable when compared with the reduction of the same quinoxaline 1,4-dioxides with other commonly used reducing agents such as phosphorus trichloride and sodium dithionite which afforded a mixture of isomeric monooxides and dideoxygenated product. The scope and limitations of this reaction are discussed.

Recent interest in the preparation and reactions of quinoxaline 1,4-dioxides (QNO's) has remained at a high level[1] owing in part to the commercial importance of this class of compounds. For example, the QNO carbadox[2] is highly effective as a growth promotant for swine.[3] Quinoxaline monooxides have been isolated as QNO metabolites in several different experimental animals.[4] We desired to prepare a number of quinoxaline 1-oxides for biological study, and have discovered that trimethyl phosphite is a superior reducing agent for the selective monodeoxygenation of certain QNO's.

Although trialkyl phosphites have been used in several instances for the deoxygenation of heterocyclic *N*-oxides, to our knowledge their application in the QNO series has not been reported. Emerson and Rees[5] were able to reduce pyridine 1-oxides with triethyl phosphite in diethylene glycol diethyl

Table I. Reduction of Quinoxaline 1,4-Dioxides



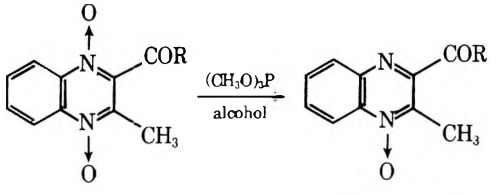
Compd	R	Reagent	Products[a] (%)		
1	CO_2CH_3	$(CH_3O)_3P$	2 (>95)	3 (<5)	4 (<5)
		PCl_3	(16)	(57)	(27)
		$Na_2S_2O_4$	(66)	(20)	(14)
6	$COCH_3$	$(CH_3O)_3P$	7 (>99.5)[b]	8 (<0.5)[b]	9 (<0.5)[b]
		PCl_3	(30)	(50)	(20)
		$Na_2S_2O_4$	(63)	(11)	(26)

[a] Determined by NMR as described in the Experimental Section, unless otherwise noted. [b] Determined by HPLC as described in the Experimental Section.

ether if both oxygen and peroxide, formed adventitiously from the solvent, were present. However, these reductions did not go to completion even with triethyl phosphite in a 100-fold excess. A free-radical chain mechanism was proposed to explain their kinetic results. 5-Chlorobenzofurazan 1-oxide was reduced to 5-chlorobenzofurazan in 60% yield with trimethyl phosphite in refluxing ethanol by Boulton, Gray, and Katritzky.[6] Recently, Boulton and co-workers[7] deoxygenated some furazan 1-oxides using both trimethyl and triethyl phosphite. The convenient and selective synthesis of several quinoxaline monooxides by the use of trimethyl phosphite is the topic of this paper.

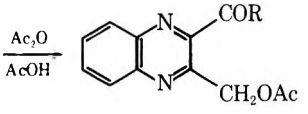
Results and Discussion

Methyl 3-methylquinoxaline-2-carboxylate 1,4-dioxide (**1**) was allowed to react with excess trimethyl phosphite in refluxing 1-propanol. NMR analysis of the crude product mixture indicated the sole formation of the monooxide **2**. None of isomeric monooxide **3** was detected (<5%), nor was any of the totally deoxygenated quinoxaline **4** observed (<5%). Upon

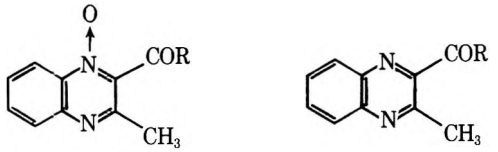


1, R = OCH_3
6, R = CH_3

2, R = OCH_3
7, R = CH_3



5, R = OCH_3
10, R = CH_3



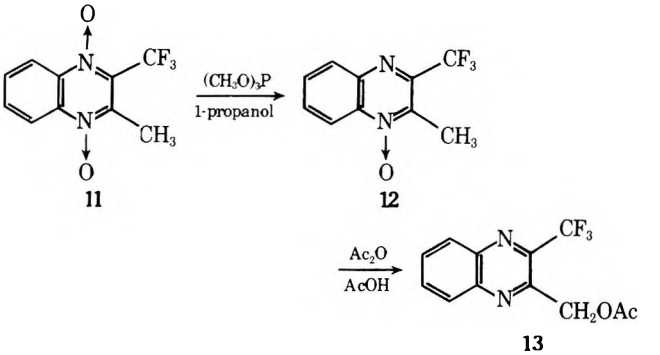
3, R = OCH_3
8, R = CH_3

4, R = OCH_3
9, R = CH_3

purification monooxide **2** was obtained in 81% yield.[8] The present structural assignment for **2**, in which the *N*-oxide is adjacent to the 3-methyl group, was confirmed by acetic anhydride–acetic acid rearrangement[9] of **2** to the corresponding 3-acetoxymethylquinoxaline derivative **5**. The monooxide **3**, prepared in the manner described below, does not react with acetic anhydride–acetic acid under the same conditions.

The selective monodeoxygenation of **1** observed with trimethyl phosphite is quite remarkable when this result is compared with the reduction of **1** with two other commonly used QNO reducing agents such as phosphorus trichloride[1f,10] and sodium dithionite.[1e,11] Indeed, a mixture of all three possible products (**2**, **3**, and **4**) was found upon reduction of **1** with these two reagents (Table I). In the reduction of **1** with phosphorus trichloride, the monooxide **3** was formed as the major product and isolated in 20% yield. The outcome was similar when other 2,3-disubstituted QNO's, wherein R-2 was an electron-withdrawing group and R-3 was methyl, were reduced with trimethyl phosphite, phosphorus trichloride, or sodium dithionite. For example, in the case where R-2 is acetyl (**6**), trimethyl phosphite gave selective monodeoxygenation to form the monooxide **7**; neither the monooxide **8** nor the deoxide **9** was detected by NMR analysis (<5%). A more sensitive analysis of the product mixture by HPLC indicated the sole formation of the monooxide **7** (>99.5%). Treatment of **7** with acetic anhydride–acetic acid gave rise to 2-acetoxymethyl-3-acetylquinoxaline (**10**), whereas the monooxide **8** failed to react with acetic anhydride–acetic acid under conditions that rearrange **7**. As summarized in Table I, phosphorus trichloride and sodium dithionite reduction of **6** gave a mixture of isomeric monooxides (**7** and **8**) and the deoxide (**9**).

Trimethyl phosphite reduction of 2-methyl-3-trifluoromethylquinoxaline 1,4-dioxide (**11**) also gave selective monodeoxygenation to afford **12**. Rearrangement of **12** with acetic anhydride–acetic acid yielded **13**, which confirmed that

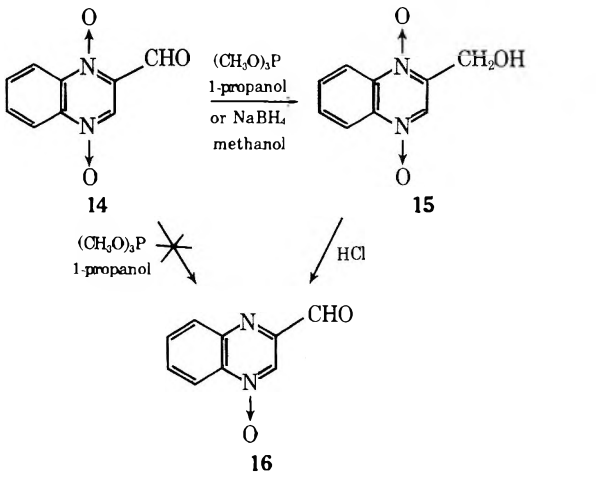


11 12 13

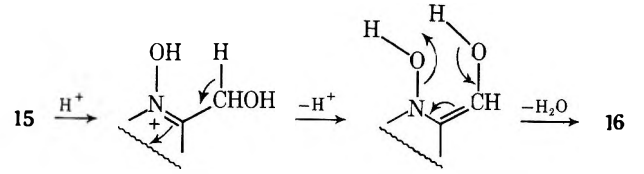
the *N*-oxide was adjacent to the methyl group prior to rearrangement. In contrast, treatment of a quinoxaline 1,4-dioxide without an electron-withdrawing group adjacent to an *N*-oxide, such as 2-methylquinoxaline 1,4-dioxide,[12] with tri-

methyl phosphite in refluxing 1-propanol resulted in no detectable reduction products; starting material was recovered unchanged.

Based on the above results with trimethyl phosphite, a one-step reduction leading to **16** was envisioned, i.e., monodeoxygenation of quinoxaline-2-carboxaldehyde 1,4-dioxide (**14**). Unexpectedly, **14** was instead selectively reduced with trimethyl phosphite to afford the carbinol **15**. This result is

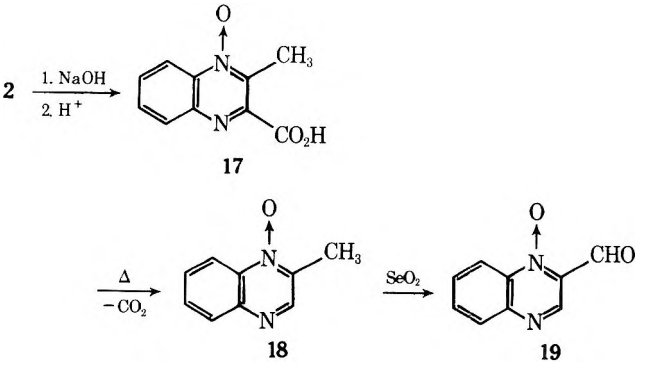


unique in that in previous cases reduction of a functional group on a QNO has resulted in concomitant reduction of one or both *N*-oxides.[13] The use of 0.25 molar equiv of sodium borohydride gave identical results with those found with trimethyl phosphite, and **15** was obtained in 78% yield.[14] The desired quinoxaline-3-carboxaldehyde 1-oxide (**16**) was obtained from 2-hydroxymethyl-QNO (**15**) by rearrangement of this alcohol with concentrated hydrochloric acid. A plausible mechanism is depicted with partial structures shown below. Aldehyde formation from enolamine intermediates has



been suggested previously by Chilton and Butler in the base-catalyzed conversion of 2-hydroxymethylpyridine 1-oxide into pyridine-2-carboxaldehyde.[15]

In order to confirm the structure of **16** the corresponding isomer, quinoxaline-2-carboxaldehyde 1-oxide (**19**), was synthesized by a four-step sequence outlined below. The first step involved selective monodeoxygenation of **1** with trimethyl phosphite as described above to afford **2**. Decarboxylation of **17** proceeded efficiently at 100 °C in toluene and the resulting 2-methylquinoxaline 1-oxide (**18**) was oxidized with selenium oxide to yield **19**.



The present study offers little insight into the mode of action of phosphorus(III) compounds with QNO's. However, trimethyl phosphite in refluxing alcohol appears to be uniquely suitable for selective deoxygenation at the nitrogen adjacent to carbon bearing an electron-withdrawing group in certain QNO's.

Experimental Section

General. Melting points (uncorrected) were taken with a Thomas-Hoover capillary apparatus. NMR spectra were recorded on Varian A-60 and T-60 spectrometers with Me_4Si as internal standard. IR spectra were determined with a Perkin-Elmer Model 21 spectrophotometer. UV spectra were recorded on a Cary Model 14 spectrophotometer. Mass spectra were obtained with a Perkin-Elmer RMU-6E mass spectrometer. Analytical HPLC was performed using a Chromatronix Model 3510 instrument equipped with an Altex LiChrosorb 5-μ column (25 cm × 3.2 mm) and a 254-nm UV detector. Microanalyses were performed by the Pfizer Analytical Department. All evaporations were conducted in vacuo using either a water aspirator or a vacuum pump.

Methyl 3-methyl-2-quinoxalinecarboxylate 1,4-dioxide (1) was prepared in 78% yield according to a published procedure[16] by condensing methyl acetoacetate with benzofurazan 1-oxide in 2-propanol at 65 °C using a catalytic amount of calcium hydroxide: mp 167–169 °C (from methanol); NMR ($CDCl_3$) δ 2.50 (3, s, CH_3), 4.03 (3, s, OCH_3), 7.80 (2, m, H-6, H-7), 8.52 (2, m, H-5, H-8); IR (KBr) 1754 cm^{-1} (C=O); UV λ_{max} (MeOH) 234 nm (ϵ 21 800), 264 (26 700), 383 (12 500); mass spectrum *m/e* 234 $(M)^+$. Anal. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.46; H, 4.31; N, 11.97. Found: C, 56.27; H, 4.24; N, 11.93.

Methyl 2-Methyl-3-quinoxalinecarboxylate 1-Oxide (2). Methyl 3-methyl-2-quinoxalinecarboxylate 1,4-dioxide (200 g, 0.86 mol) was dissolved in 1-propanol (2 L) containing trimethyl phosphite (118 g, 0.95 mol). The reaction mixture was heated under reflux for 2.5 h and then cooled to 15 °C to afford a crystalline precipitate. The tan solid was collected by filtration and recrystallized from methanol to give 152 g (81%) of **2**: mp 109–111 °C; NMR ($CDCl_3$) δ 2.70 (3, s, CH_3), 3.97 (3, s, OCH_3), 7.73 (2, m, H-6, H-7), 8.13 (1, m, H-8), 8.48 (1, m, H-5); IR (KBr) 1739 cm^{-1} (C=O); UV λ_{max} (MeOH) 246 nm (ϵ 33 800), 325 (8500); mass spectrum *m/e* 218 $(M)^+$. Anal. Calcd for $C_{11}H_{10}N_2O_3$: C, 60.61; H, 4.62; N, 12.85. Found: C, 60.70, H, 4.69; N, 13.07.

Methyl 3-Methyl-2-quinoxalinecarboxylate 1-Oxide (3). Phosphorus trichloride (10 mL) was added to a stirred solution of methyl 3-methyl-2-quinoxalinecarboxylate 1,4-dioxide (3.00 g) in chloroform (30 mL). After stirring overnight at room temperature the reaction mixture was diluted with ice–water and excess aqueous sodium hydroxide was added. The chloroform layer was separated and the aqueous phase was extracted with chloroform. The combined chloroform extracts were dried with anhydrous magnesium sulfate and evaporated to give a solid (2.47 g, ca. 85%). NMR analysis of the crude product mixture indicated the presence of three compounds: **3** (57%), **2** (16%), and **4** (27%). Compounds **2** and **4** were removed from the crude product by washing with ether, which left behind **3** (0.56 g, 20%): mp 108–110 °C; NMR ($CDCl_3$) δ 2.60 (3, s, CH_3), 4.00 (3, s, CO_2CH_3), 7.5–8.2 (3, m, H-5, H-6, H-7), 8.47 (1, m, H-8); IR (KBr) 1755 cm^{-1} (C=O); UV λ_{max} (MeOH) 243 nm (ϵ 37 200), 320 (6900); mass spectrum *m/e* 218 $(M)^+$. Anal. Calcd for $C_{11}H_{10}N_2O_3$: C, 60.61; H, 4.62; N, 12.85. Found: 60.44; H, 4.59; N, 12.87.

Methyl 3-Methyl-2-quinoxalinecarboxylate (4). To a stirred, heated solution of methyl 3-methyl-2-quinoxalinecarboxylate 1,4-dioxide (1.00 g, 4.27 mmol) in 60% EtOH (20 mL) was added sodium dithionite (3.27 g, 18.8 mmol) in portions over 30 min. The mixture was heated under reflux for 3 h, diluted with cold water, and extracted with chloroform (2 × 50 mL). The chloroform extract was dried ($MgSO_4$), filtered, and evaporated to dryness. The residue was recrystallized from ether–hexane to yield 0.44 g (50%) of **4**: mp 83–85 °C; NMR ($CDCl_3$) δ 2.90 (3, s, CH_3), 4.00 (3, s, OCH_3), 7.7–8.3 (4, m, H-5, H-6, H-7, H-8); IR (KBr) 1740 cm^{-1} (C=O); UV λ_{max} (MeOH) 241 nm (ϵ 30 200), 315 (5600); mass spectrum *m/e* 202 $(M)^+$. Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.41; H, 4.99; N, 13.87. Found: C, 65.61; H, 5.26; N, 14.08.

When the above procedure was repeated using 0.37 g (2.10 mmol) of sodium dithionite, NMR analysis ($CDCl_3$) of total crude product mixture (0.79 g, ca. 85%) indicated the presence of **3**, **2**, and **4** in the ratio 20:66:14, respectively. The methyl resonances for these three compounds were observed at different chemical shifts, and thus integration of the methyl region allowed relative molar percentages to be readily ascertained.

Methyl 3-Acetoxymethyl-2-quinoxalinecarboxylate (5). A solution of methyl 2-methyl-3-quinoxalinecarboxylate 1-oxide (1.0 g) in acetic anhydride (20 mL) and glacial acetic acid (5 mL) was heated under reflux for 48 h. The solution was cooled and poured onto ice, and the aqueous layer was extracted with chloroform. The chloroform extract was dried ($MgSO_4$), filtered, and evaporated, leaving 1.03 g of **5**, mp 90–92 °C. Recrystallization from ethyl acetate afforded 0.75 g (63%): mp 100–101 °C; NMR ($CDCl_3$) δ 2.43 (3, s, $OCOCH_3$), 4.30 (3, s, OCH_3), 6.23 (2, s, CH_2), 8.50 (4, m, H-5, H-6, H-7, H-8); IR (KBr) 1755, 1725 cm^{-1} (ester C=O's); UV λ_{max} (MeOH) 243 nm (ϵ 35 400), 317 (5710); mass spectrum *m/e* 260 $(M)^+$. Anal. Calcd for $C_{13}H_{12}N_2O_4$: C, 60.06; H, 4.65; N, 10.77. Found: C, 60.01; H, 4.69; N, 10.92.

2-Acetyl-3-methylquinoxaline 1,4-Dioxide (6) was prepared according to the general procedure of Issidorides et al.,[17] by condensing pentane-2,4-dione (180 g, 1.80 mol) with benzofurazan 1-oxide (204 g, 1.50 mol) in ethanol (1 L) using a catalytic amount of sodium hydroxide (6.0 g, 0.15 mol). The reaction was exothermic and was maintained at 55 °C with ice-bath cooling for 30 min, and was then stirred overnight at room temperature. A thick, yellow precipitate was collected, washed with ethanol, and dried to afford 176 g (54%) of **6**: mp 154–155 °C; NMR ($CDCl_3$) δ 2.50 (3, s, CH_3 or $COCH_3$), 2.72 (3, s, $COCH_3$ or CH_3), 7.85 (2, m, H-6, H-7), 8.52 (2, m, H-5, H-8); IR (KBr) 1725 cm^{-1} (C=O); UV λ_{max} (MeOH) 235 nm (ϵ 20 600), 263 (19 700), 384 (10 360); mass spectrum *m/e* 218 $(M)^+$. NMR and IR values are in agreement with values previously reported[18] in the literature. Anal. Calcd for $C_{11}H_{10}N_2O_3$: C, 60.61; H, 4.62; N, 12.85. Found: C, 60.45; H, 4.67; N, 12.87.

3-Acetyl-2-methylquinoxaline 1-Oxide (7). 2-Acetyl-3-methylquinoxaline 1,4-dioxide (20.0 g, 0.092 mol) was dissolved in 1-propanol (200 mL) containing trimethyl phosphite (12.5 g, 0.10 mol). The reaction mixture was heated under reflux for 4 h and then concentrated in vacuo causing a crystalline solid to form. The solid was collected by suction filtration and was washed with ether leaving pale yellow crystals: 4.91 g; mp 93–94 °C. Additional material was collected from a second crop: 6.51 g (total yield of **7** was 63%); mp 91–93 °C; NMR ($CDCl_3$) δ 2.80 (6, s, CH_3, $COCH_3$), 7.82 (2, m, H-6, H-7), 8.15 (1, m, H-8), 8.60 (1, m, H-5); IR (KBr) 1710 cm^{-1} (C=O); UV λ_{max} (MeOH) 258 nm (ϵ 29 200), 325 (7600); mass spectrum *m/e* 202 $(M)^+$. Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.41, H, 4.99; N, 13.87. Found: C, 65.14; H, 5.02; N, 13.94.

The above reaction was repeated with 1.0 g of the quinoxaline 1,4-dioxide and the reaction solution then concentrated in vacuo leaving a pale yellow solid. HPLC analysis of the total product mixture using a flow rate of 0.4 mL/min and a hexane–chloroform–methanol (57.5/41.8/0.7 by volume) solvent system indicated the presence of **7** (retention time 9.6 min). Compounds **8** (retention time 11.6 min), **9** (retention time 8.4 min), and **6** (retention time 21.0 min) were not detected (<0.5%).

2-Acetyl-3-methylquinoxaline 1-Oxide (8). Following a procedure analogous to the preparation of **3**, 1.0 g of 2-acetyl-3-methylquinoxaline 1,4-dioxide was reduced with phosphorus trichloride to furnish 0.72 g (ca. 77%) of material after workup. NMR analysis of the crude product mixture indicated the presence of three compounds: **8** (50%), **7** (30%), and **9** (20%). Compounds **7** and **9** were selectively removed by washing the crude product with hexane, which left behind **8** (0.28 g, 30%): mp 78–81 °C; NMR ($CDCl_3$) δ 2.53 (3, s, CH_3 or $COCH_3$), 2.60 (3, s, $COCH_3$ or CH_3), 7.5–8.2 (3, m, H-5, H-6, H-7), 8.44 (1, m, H-8); IR (KBr) 1725 cm^{-1} (C=O); UV λ_{max} (MeOH) 243 nm (ϵ 30 100), 320 (6800); mass spectrum *m/e* 202 $(M)^+$. Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.41; H, 4.99; N, 13.87. Found: C, 65.16; H, 4.97; N, 13.86.

2-Acetyl-3-methylquinoxaline (9). To a stirred, refluxing solution of 2-acetyl-3-methylquinoxaline 1,4-dioxide (2.00 g, 9.17 mmol) in 60% EtOH (30 mL) was added sodium dithionite (6.28 g, 36.1 mmol) in portions over 20 min. The mixture was heated under reflux for 3 h, cooled to room temperature, and filtered to remove an undesired solid. The aqueous filtrate was extracted with chloroform (5 × 20 mL). The chloroform extract was dried ($MgSO_4$), filtered, and evaporated to dryness to yield an oil (1.26 g, 74%). NMR analysis ($CDCl_3$) of the oil indicated the presence of desired product and 2-methylquinoxaline in a 60:40 ratio, respectively. The oil was crystallized from methanol to afford 0.74 g (8%) of **9**: mp 85–86 °C (lit.[16] mp 85–86 °C); NMR ($CDCl_3$) δ 2.80 (3, s, CH_3 or $COCH_3$), 2.90 (3, s, $COCH_3$ or CH_3), 7.90 (4, m, H-5, H-6, H-7, H-8); IR 1695 cm^{-1} (C=O); UV λ_{max} (MeOH) 244 nm (ϵ 29 900), 310 (5750); mass spectrum *m/e* 186 $(M)^+$.

To a stirred, heated solution of the quinoxaline 1,4-dioxide **6** (10.0 g, 0.046 mol) in 60% EtOH (150 ml) was added dropwise aqueous sodium dithionite (183 mL, 1 M) over 1 h. The mixture was heated at 90 °C for 2 h, diluted with cold water, and extracted with ether. The ether extract was dried, filtered, and evaporated to dryness: 8.42 g (98%) of material, mp 65–72 °C. NMR analysis of the product mixture indicated the presence of three compounds: **8** (11%), **7** (63%), and **9** (26%). No deacetylated product (i.e., 2-methylquinoxaline) was detected in this experiment, which was carried out at a lower temperature than the one described above.

2-Acetoxymethyl-3-acetylquinoxaline (10). A solution of 3-acetyl-2-methylquinoxaline 1-oxide (4.0 g), acetic anhydride (16 mL), and glacial acetic acid (4 mL) was heated under reflux for 2 h. The solution was cooled and poured onto ice, and the aqueous layer was extracted with chloroform. The chloroform extract was dried, filtered, and evaporated, leaving a brown oil, 2.80 g (58%) of **10**: NMR ($CDCl_3$) δ 2.23 (3, s, $OCOCH_3$), 2.84 (3, s, $COCH_3$), 5.72 (2, s, CH_2), 7.6–8.2 (4, m, H-5, H-6, H-7, H-8). An analytical sample was obtained by thick layer chromatography purification using plates coated with silica gel (95% chloroform–5% methanol solvent system): mp 80–82 °C; IR (KBr) 1755 cm^{-1}; UV λ_{max} (MeOH) 247 nm (ϵ 28 000), 320 (5200); mass spectrum *m/e* 244 $(M)^+$. Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.99; H, 4.96; N, 11.48. Found: C, 63.98; H, 4.91; N, 11.46.

2-Methyl-3-trifluromethylquinoxaline 1,4-dioxide (11) was prepared according to the procedure of Abushanab:[11] mp 122–125 °C (lit.[11] mp 126–128 °C); NMR ($CDCl_3$) δ 2.77 (3, q, CH_3, J_{HF} = 2.8 Hz), 7.87 (2, m, H-6, H-7), 8.58 (2, m, H-5, H-8); mass spectrum *m/e* 244 $(M)^+$. The IR and UV spectra were identical with those reported[11] for **11**.

2-Methyl-3-trifluormethylquinoxaline 1-Oxide (12). 2-Methyl-3-trifluoromethylquinoxaline 1,4-dioxide (300 mg, 1.23 mmol) was dissolved in 1-propanol (10 mL) containing trimethyl phosphite (170 mg, 1.37 mmol). The reaction mixture was heated under reflux for 1.5 h and then concentrated under vacuum. Ether–hexane was added and the product precipitated to yield 101 mg (36%) of **12**, mp 112–115 °C. NMR, IR, UV, and mass spectra were identical with those previously reported[11] in the literature for **12**.

2-Acetoxymethyl-3-trifluoromethylquinoxaline (13). A solution of 2-methyl-3-trifluoromethylquinoxaline 1-oxide (150 mg, 0.66 mmol) in 13 mL of acetic anhydride–glacial acetic acid (4:1) was heated under reflux for 3 h. The workup procedure was the same as that described above for the preparation of **5**. The crude product was crystallized from hexane to give 61 mg (34%) of **13**: mp 76–77 °C; NMR ($CDCl_3$) δ 2.23 (3, s, CH_3), 5.60 (2, m, CH_2), 7.8–8.4 (4, m, H-5, H-6, H-7, H-8); IR (KBr) 1770 cm^{-1} (C=O); UV λ_{max} (MeOH) 237 nm (ϵ 37 800), 320 (4860); mass spectrum *m/e* 270 $(M)^+$. Anal. Calcd for $C_{12}H_9F_3N_2O_2$: C, 53.38; H, 3.36; N, 10.38. Found: C, 52.85; H, 3.45; N, 10.24.

2-Hydroxymethylquinoxaline 1,4-Dioxide (15). A. Quinoxalinecarboxaldehyde 1,4-dioxide[12] (1.90 g, 10 mmol) was dissolved in 1-propanol (30 mL) containing trimethyl phosphite (1.24 g, 10 mmol). The reaction mixture was heated under reflux for 30 min and then cooled to 15 °C to afford a precipitate. The yellow solid was collected by suction filtration and washed with methanol to yield 0.64 g, (33%) of **15**: mp 176–178 °C; NMR (CF_3CO_2D) δ 5.47 (2, s, CH_2), 8.28 (2, m, H-6, H-7), 8.85 (2, m, H-5, H-8), 9.37 (1, s, H-3); IR (KBr) 3220 cm^{-1} (OH); UV λ_{max} (MeOH) 232 nm (ϵ 18 270), 259 (22 880), 379 (12 980); mass spectrum *m/e* 192 $(M)^+$.

B. 2-Quinoxalinecarboxaldehyde 1,4-dioxide[12] (1.90 g, 10 mmol) was suspended in 100 mL of methanol. Sodium borohydride (0.095 g, 2.5 mmol) was added in small portions over 20 s, causing starting material to dissolve. The reaction mixture was stirred for 30 min, during which time solid precipitated. The yellow solid was collected by suction filtration and was washed with ether to yield 1.50 g (78%) of **15**, mp 180–182 °C. The NMR, IR, UV, and mass spectra were identical with those obtained from material prepared by using procedure A. An analytical sample was obtained by recrystallization from methanol, mp 214–215 °C (lit.[19] mp 191–192 °C). Anal. Calcd for $C_9H_8N_2O_3$: C, 56.30; H, 4.20; N, 14.59. Found: C, 56.28; H, 4.26; N, 14.89.

Quinoxaline-3-carboxaldehyde 1-Oxide (16). 2-Hydroxymethylquinoxaline 1,4-dioxide (1.00 g, 5.20 mmol) was added to concentrated hydrochloric acid (3 mL) and the reaction mixture was heated at 100 °C with stirring for 1 h. A tan solid precipitated that was collected by suction filtration and recrystallized from acetone to afford 0.57 g (63%): mp 175–176 °C; NMR (CF_3CO_2D) δ 7.6–8.4 (4, m, H-5, H-6, H-7, H-8), 8.87 (1, s, H-3), 9.60 (1, s, CHO); mass spectrum *m/e* 174 $(M)^+$. The IR spectrum (KBr) indicated that this material was most likely hydrated to some extent [3080 (OH) and 1725 cm^{-1} (w, C=O)]. An analytical sample of the aldehyde was obtained by heating 2-acetoxymethylquinoxaline 1,4-dioxide[19] (50.0 g, 0.21 mol) and concentrated hydrochloric acid (150 mL) under reflux for 15 min. Workup as above followed by recrystallization from acetone yielded 16.7 g (45%) of **16**: mp 175–176 °C; NMR same as above; IR (KBr)

1725 cm^{-1} (s, C=O); UV λ_{max} (MeOH) 240 nm (ϵ 41 000), 322 (9500); mixture melting point with material from above was 175–176 °C. Anal. Calcd for $C_9H_6N_2O_2$: C, 62.07; H, 3.47; N, 16.09. Found: C, 62.05; H, 3.73; N, 16.21.

2-Methylquinoxaline-3-carboxylic Acid 1-Oxide (17). Methyl 2-methyl-3-quinoxalinecarboxylate 1-oxide (5.00 g, 23.0 mmol) was suspended in aqueous 0.5 M sodium hydroxide solution (50 mL). All starting material went into solution within 10 min, and a white precipitate formed upon addition of aqueous 0.5 M hydrochloric acid solution (50 mL). The solid was collected and recrystallized from water to give 4.00 g (81%) of **17**:[4b] mp 150–151 °C; NMR (CF_3CO_2D) δ 3.10 (3, s, CH_3), 8.20–8.90 (4, m, H-5, H-6, H-7, H-8); IR (KBr) 1735 cm^{-1} (C=O); UV λ_{max} (MeOH) 244 nm (ϵ 23 800), 330 (7450); mass spectrum *m/e* 204 $(M)^+$. Several attempts to obtain an analytical sample of **17** were unsuccessful apparently owing to the thermal instability of this compound (vide infra).

2-Methylquinoxaline 1-Oxide (18). 2-Methylquinoxaline-3-carboxylic acid 1-oxide (1.00 g, 4.9 mmol) was added to toluene (10 mL). The resulting suspension was heated at 100 °C for 1.5 h, during which time all the starting material went into solution and a gas was evolved. The reaction mixture was cooled to room temperature and the toluene was removed under vacuum, leaving a colorless solid. The crude product was recrystallized from ether to afford 0.66 g (83%) of pure **18**: mp 85–87 °C; NMR ($CDCl_3$) δ 2.69 (3, s, CH_3), 7.77 (2, m, H-6, H-7), 8.16 (1, m, H-5), 8.58 (1, m, H-8), 8.71 (1, s, H-3); UV λ_{max} (MeOH) 240 nm (ϵ 43 300), 320 (10 500); mass spectrum *m/e* 160 $(M)^+$. Anal. Calcd for $C_9H_8N_2O$: C, 67.56; H, 5.04; N, 17.51. Found: C, 67.60; H, 5.15; N, 17.48.

Quinoxaline-2-carboxaldehyde 1-Oxide (19). 2-Methylquinoxaline 1-oxide (0.90 g, 5.6 mmol) was dissolved in ethyl acetate (15 mL). Selenium dioxide (0.75 g, 6.7 mmol) was added and the reaction mixture was refluxed for 5 h, during which time a black precipitate formed. The reaction mixture was filtered through Super-Cel and the filtrate was treated with activated carbon and evaporated, leaving a tan solid. The solid was recrystallized from acetone to give 0.39 g (39%) of **19**: mp 131–132 °C; NMR (CF_3CO_2D) δ 7.3–8.0 (3, m, H-5, H-6, H-7), 8.25 (1, m, H-8), 8.90 (1, s, H-3), 10.00 (1, s, CHO); IR (KBr) 1680 cm^{-1} (C=O); UV λ_{max} (MeOH) 242 nm (ϵ 38 700), 323 (8900); mass spectrum *m/e* 174 $(M)^+$. Anal. Calcd for $C_9H_6N_2O_2$: C, 62.07; H, 3.47; N, 16.09. Found: C, 62.01; H, 3.36; N, 16.03.

Acknowledgment. We thank Kerry Gombatz, Gloria Kostek, Richard Pezzullo, and Lawrence Vincent for their technical assistance.

Registry No.—**1**, 40016-70-4; **2**, 61522-53-0; **3**, 61528-76-5; **4**, 61522-54-1; **5**, 61522-55-2; **6**, 13297-17-1; **7**, 61522-56-3; **8**, 61522-57-4; **9**, 22059-64-9; **10**, 61522-58-5; **11**, 33578-43-7; **12**, 34907-12-5; **13**, 61522-59-6; **14**, 17626-51-6; **15**, 20492-05-1; **16**, 61522-60-9; **17**, 61522-61-0; **18**, 18916-44-4; **19**, 61522-62-1; trimethyl phosphite, 121-45-9.

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Synthesis with Pyridine *N*-Oxides. 3.[1] Synthesis of 2-Arylisoxazolo[2,3-*a*]pyridinium Bromides via Acid-Catalyzed Rearrangements of 1-Aryl-2-(2-pyridinyl)ethanone *N*-Oxides

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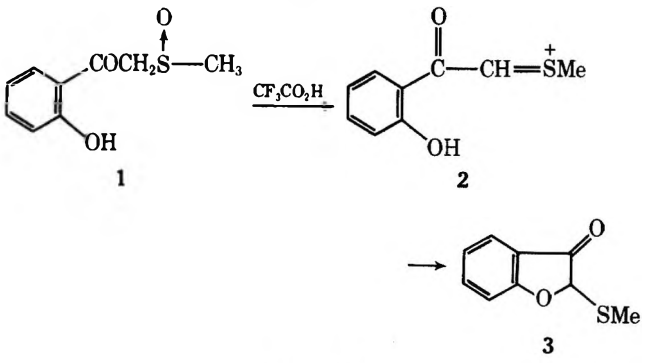
Received September 16, 1976

Reaction of 1-aryl-2-(2-pyridinyl)ethanone *N*-oxides with hydrobromic acid in acetic acid gave 2-arylisoxazolo[2,3-*a*]pyridinium bromides. Cyclization of methoxy-substituted compounds (**21**, **23**, and **31**) gave 2-(2-methoxyaryl)-isoxazolo[2,3-*a*]pyridinium bromides (**22**, **24**, and **32**), which were surprisingly refractory to demethylation. Reaction of 1-phenyl-2-pyridineethanol *N*-oxide with hydrobromic acid in acetic acid gave 2-(2-phenylethenyl)pyridine *N*-oxide hydrobromide and not 2-phenyl-2,3-dihydroisoxazolo[2,3-*a*]pyridinium bromide.

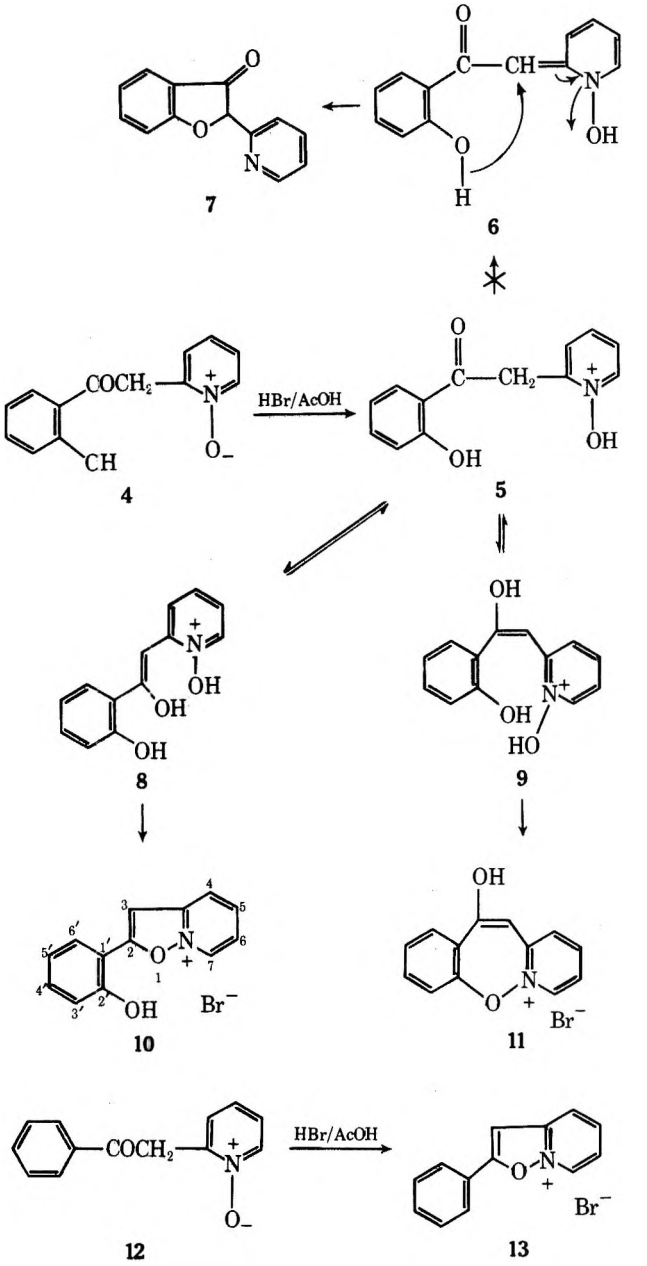
The acid-catalyzed cyclization of **1** to **3** via intramolecular nucleophilic attack on the Pummerer intermediate (**2**) was described previously.[2] 1-(2-Hydroxyphenyl)-2-(2-pyridinyl)ethanone *N*-oxide (**4**) was prepared[3] as an intermediate for the synthesis of various heterocyclic systems.[1] As 2-picoline *N*-oxide is known to undergo a rearrangement[4–6] similar to the Pummerer rearrangement, it was expected that *N*-oxide **4** may cyclize in a manner analogous to sulfoxide **1** to give benzofuranone (**7**).

Treatment of **4** under conditions (trifluoroacetic acid in refluxing benzene) which generate **3** from **1** gave no reaction. Prolonged refluxing (24 h) also failed to give any reaction. A product with the composition expected for the HBr salt of **7** was isolated when **4** was refluxed with hydrobromic acid in acetic acid. Isoxazolo[2,3-*a*]pyridinium bromide (**10**) and 11-hydroxypyrido[1,2-*b*][1,2]benzoazepinium bromide (**11**) are other possible products arising from cyclizations of enolic intermediates **8** and **9**, respectively. The infrared spectrum

Scheme I



Scheme II



of the product showed OH bands but no carbonyl, *N*-oxide, or HBr salt bands, and the relevant features of its NMR spectrum indicated one exchangeable proton and a downfield doublet (9.87 ppm), which cannot arise from the structural features present in **7**. With acetic anhydride the product gave a monoacetate, whose NMR spectrum showed no exchangeable proton but again exhibited a downfield doublet at 9.88 ppm. These observations rule out the HBr salt of **7** as the possible product.

The reaction of *N*-oxide **12** with hydrobromic acid in refluxing acetic acid gave 2-phenylisoxazolo[2,3-*a*]pyridinium bromide (**13**). This structure is supported by analytical and spectral data, in particular the NMR spectrum, which indicates ten aromatic protons including a downfield doublet at 10.07 ppm assigned to the proton at C-7. The similarities between the UV [272 nm (ϵ 16 500) and 322 (19 800)] and NMR spectra of **13** and those of the product from the reaction of **4** with hydrobromic acid in acetic acid suggest that they have analogous structures, and thus **10** is the product formed from **4**. 1-(2-Methoxyphenyl)-2-(2-pyridinyl)ethanone *N*-oxide (**14**), which is more readily available than **4**, also gave **10** when treated under the same conditions.

This reaction represents the first general synthesis of the isoxazolo[2,3-*a*]pyridinium ring system. The compounds prepared by this method are listed in Table I. The reaction is general with the exception of compounds in which the aryl group contains basic moieties. Thus when amine **15** and pyridinyl derivative **16** are subjected to the reaction conditions, the corresponding hydrobromide salts are obtained. The only reference[7] to this ring system in the literature is the synthesis of 5-bromo-4-hydroxyisoxazolo[2,3-*a*]pyridinium bromide by a lengthy route from methyl isoxazolo-3-carboxylate. The final steps (bromination and dehydrobromination of 5-bromo-4,5,6,7-tetrahydro-6-isoxazolo[2,3-*a*]pyridinium bromide) in this synthesis limit it to the preparation of compounds containing hydroxyl and bromine substituents in the pyridinium ring.

In the majority of examples in Table I, the methoxy groups in the starting ketones are converted to hydroxy groups in the products (**10, 18, 20, 26, 28,** and **30**). Exceptions to this concomitant demethylation are **22** and **24** (which contain an halogen para to the methoxyl) and **32** (which contains a methyl group in the 7 position). Prolonged refluxing with hydrobromic acid in acetic acid fails to demethylate these compounds.

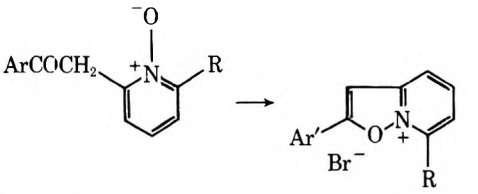
The positive charge on the nitrogen atom in the 2-arylisoxazolo[2,3-*a*]pyridinium system will lead to regions of increased electrophilicity at positions 2′, 4′, and 6′ in the aryl ring and on the 2′-methoxyl oxygen. An electron-withdrawing substituent in the 5′ position will reinforce the increased positive character at positions 2′, 4′, and 6′ and on the methoxyl oxygen. Thus protonation and demethylation at this oxygen are prevented in molecules with electron-withdrawing substituents at position 5′.

An electronic effect cannot be invoked to explain the formation of **32**. The reason for the refractory nature of the 2′-methoxy group in this molecule is not clear at this time.

An attempt was made to extend this work to the synthesis of 2-aryl-2,3-dihydroisoxazolo[2,3-*a*]pyridinium bromides. Ketone **12** was reduced to 1-phenyl-2-pyridineethanol (**33**) with sodium borohydride. The reaction of 3-(2′-pyridinyl)-propan-1-ol *N*-oxide with hydrobromic acid in acetic acid to give 2,3-dihydroisoxazolo[2,3-*a*]pyridinium bromide has been described.[8] 1-Phenyl-2-pyridineethanol *N*-oxide (**33**) was refluxed in hydrobromic acid and acetic acid in expectation that cyclization to **34** would take place; instead, 2-(2-phenylethenyl)pyridine *N*-oxide hydrobromide (**35**) was formed. The opportunity to form a system with extended conjugation by β-elimination from the carbonium ion generated from **33** is the reason for the dichotomy of product formation in these reactions. The free base of **35** had been prepared earlier[9] by the condensation of 2-picoline *N*-oxide with benzaldehyde in the presence of sodium methoxide.

Thus acid-catalyzed cyclization of (2-pyridinyl)ethanone *N*-oxides constitutes a general synthesis of the isoxazolo[2,3-*a*]pyridinium ring system, but 2-pyridineethanol *N*-oxides

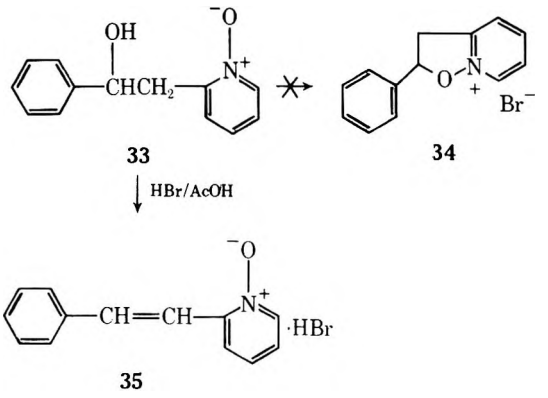
Table I[a]



R	Ar[c]	Ar'[d]	Mp,[b] °C	Yield, %	NMR C, H
H	Phenyl (12)	Phenyl (13)	164–165	60	10.07
H	2-Hydroxyphenyl (4)	2-Hydroxyphenyl (10)	>230 dec	86	9.87
H	2-Methoxyphenyl (14)			40	
H	2,3-Dimethoxyphenyl (17)	2,3-Dihydroxyphenyl (18)	>222 dec	72	9.88
H	2-Methoxy-5-methylphenyl (19)	2-Hydroxy-5-methylphenyl (20)	>220 dec	48	9.89
H	2-Methoxy-5-bromophenyl (21)	2-Methoxy-5-bromophenyl (22)	>202 dec	76	9.98
H	2-Methoxy-5-chlorophenyl (23)	2-Methoxy-5-chlorophenyl (24)	208–210	45	9.99
H	3,4,5-Trimethoxyphenyl (25)	3,4,5-Trihydroxyphenyl (26)	>210 dec	34	9.91
H	4-Methoxyphenyl (27)	4-Hydroxyphenyl (28)	>180 dec	59	9.89
H	3-Chloro-4-methoxyphenyl (29)	3-Chloro-4-hydroxyphenyl (30)	>215 dec	57	9.92
H	2-Aminophenyl (15)	No reaction			
H	2-Pyridinyl (16)	No reaction			C-Me
Me	2-Methoxyphenyl (31)	2-Methoxyphenyl (32)	>220 dec	37	3.04

[a] Satisfactory analytical data (±0.4% for C, H, N, Br, and Cl) were reported for all compounds listed in the table with the exceptions of **24** (C 0.55% out) and **22**. Although accurate analytical data could not be obtained for **22**, its NMR (Me_2SO-d_6) [δ 9.98 (d, 1, J = 8 Hz, C_7 H), 8.7–7.2 (m, 7, ArH), and 4.08 (s, 3, OMe)] and UV (EtOH) [274 nm (ε 13 300), 281 (13 600), 350 (15 400)] spectra were in agreement with the assigned structure. The compounds decomposed in the mass spectrometer without giving recognizable fragments. [b] The compounds were recrystallized from EtOH with the exception of **24** (from 2-propanol). [c] Registry no. are, respectively, 61395-07-1, 61395-08-2, 61436-92-8, 61395-09-3, 61395-10-6, 61395-11-7, 61395-12-8, 61395-13-9, 61395-14-0, 61395-15-1, 60928-33-8, 61395-16-2, 61395-17-3. [d] Registry no. are, respectively, 61395-18-4, 61395-19-5, 61395-20-8, 61395-21-9, 61395-22-0, 61395-23-1, 61395-24-2, 61395-25-3, 61395-26-4, 61395-27-5.

Scheme III



are converted to the 2,3-dihydroisoxazolo[2,3-*a*]pyridinium system only when the C_1 substituent does not promote β-elimination.

Experimental Section

Melting points were measured with a Thomas-Hoover capillary melting point apparatus without correction. NMR spectra were recorded on a Perkin-Elmer R 12 B spectrometer at 60 MHz with Me_4Si as internal standard. Infrared spectra were recorded on a Beckman IR-18A spectrometer. Ultraviolet spectra were recorded on a Beckman DK-I spectrometer. Mass spectra were obtained with an AEI MS-902 instrument.

General Procedure for the Synthesis of 2-Arylisoxazolo[2,3-*a*]pyridinium Bromides. A solution of 1-aryl-2-(2-pyridinyl)ethanone *N*-oxide (20.0 g) in 48% hydrobromic acid (250 mL) and glacial acetic acid (250 mL) was refluxed for 5 h. The solvents were removed under reduced pressure to give crystalline products. Recrystallization (Table I) gave analytically pure material.

2-(2-Acetyloxyphenyl)isoxazolo[2,3-*a*]pyridinium Bromide. A solution of 2-(2-hydroxyphenyl)isoxazolo[2,3-*a*]pyridinium bromide (5.0 g) in acetic anhydride (40 mL) was refluxed for 90 min. The solvent was removed under reduce pressure to give an oil, which crystallized from ethyl acetate. Recrystallization from 2-propanol gave white crystals (4.16 g, 73%): mp 198–201 °C; λ_{max} (EtOH) 270 nm (ε 15 000), 321 (18 000); ν_{max} (Nujol) 1775 cm^{-1} (CO); NMR (Me_2SO-d_6) δ 9.88 (d, 1, J = 8 Hz, C_7 H), 8.55–7.30 (m, 8, ArH), and 2.51 (s, 3, CH_3).

Anal. Calcd for $C_{15}H_{12}BrNO_3$: C, 53.91; H, 3.62; N, 4.19; Br, 23.91. Found: C, 53.95; H, 3.81; N, 4.18; Br, 23.83.

1-Phenyl-2-pyridineethanol *N*-Oxide (33). Sodium borohydride (1.72 g) was added to an ice-cold solution of 1-phenyl-2-(2-pyridinyl)ethanone *N*-oxide (10.0 g) in methanol. The reaction mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure to give a solid residue, which was suspended in water, filtered, washed thoroughly with water, and dried at room temperature. Recrystallization from benzene gave white crystals (7.80 g, 77%): mp 121–123 °C; λ_{max} (EtOH) 216 nm (ε 25 200), 263 (10 100); ν_{max} (Nujol) 3260 (OH), 1250 cm^{-1} (N → O); NMR ($CDCl_3$) δ 8.35–6.80 (m, 9, ArH), 6.42 (bs, 1, OH, exchanges with D_2O), 5.14 (t, 1, J = 6 Hz, CH), and 3.37 (d, 2, J = 6 Hz, CH_2).

Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.56; H, 6.37; N, 6.44.

2-(2-Phenylethenyl)pyridine 1-Oxide Hydrobromide (35). A solution of 1-phenyl-2-pyridineethanol *N*-oxide (20 g) in 48% hydrobromic acid (200 mL) and glacial acetic acid (200 mL) was refluxed for 5 h. The solvents were removed under reduced pressure to give a crystalline product. Recrystallization from absolute ethanol gave white crystals (7.75 g, 30%): mp 187–189 °C; λ_{max} (EtOH) 231 nm (ε 11 700), 270 (21 200), 320 (24 500); ν_{max} (Nujol) 2410 (HBr salt), 1250 cm^{-1} (N → O); NMR (Me_2SO-d_6) δ 9.00–7.05 (m, 12).

Anal. Calcd for $C_{13}H_{12}BrNO$: C, 56.14; H, 4.34; N, 5.04; Br, 28.73. Found: C, 55.99; H, 4.38; N, 4.95; Br, 28.66.

Registry No.—**33**, 61395-28-6; **35**, 61395-29-7; hydrobromic acid, 24959-67-9; 2-(2-acetyloxyphenyl)isoxazolo[2,3-*a*]pyridinium bromide, 61395-30-0; acetic anhydride, 108-24-7.

References and Notes

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Cyclic Diacylhydrazyl Radicals from 1,3,4-Oxadiazolidine-2,5-diones, Pyridazine-3,6-diones, and Phthalazine-1,4-diones[1,2]

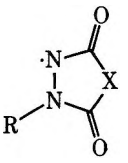
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Received August 20, 1976

When treated with lead dioxide, α-cumyl and *tert*-butyl substituted oxadiazolidinediones (**3b, 3c**), phenyl and α-cumyl substituted tetrahydrophthalazinediones (**4a, 4b**) and tetrahydropyridazinediones (**5a, 5b**), and α-cumylperhydropyridazinedione (**6b**) afford the corresponding hydrazyl radicals. These radicals are transient and unisolable, decomposing within 48 h. Attempts to degas solutions of pyridazinedione radical **5a**• result in excessive effervescence and no observable EPR signal; radical **5a**• can be detected when a mixture of **5a** and lead dioxide in benzene is observed directly in the cavity of an EPR spectrometer. Phenyloxadiazolidinedione **3a**, when treated with lead dioxide, fails to provide an EPR signal; however, when treated with *tert*-butyl hypochlorite or *N*-bromosuccinimide, **3a** affords a radical which gives rise to a three-line pattern from the relatively strong coupling of the unpaired electron to one nitrogen. Treatment of phenylperhydropyridazinedione **6a** with any of the above oxidizing agents does not provide a detectable EPR signal.

The exceptionally persistent[3] triarylhydrazyl radicals [e.g., diphenylpicrylhydrazyl (DPPH)] are well known and have been extensively studied.[4] Only recently, however, has the chemistry of hydrazyl radicals lacking a directly bonded aromatic group been explored.[5-16] We have reported urazole (**1**•) and pyrazolidinedione (**2**•) radicals that are isolable as

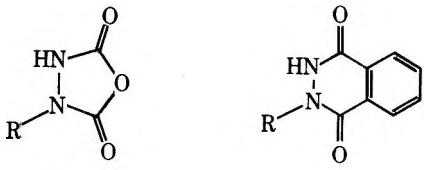


1•, X = NR′
2•, X = CR′$_2$

their tetrazane dimers.[1] We now report three new types of cyclic diacylhydrazyl radicals, one in which the disubstituted carbon of the pyrazolidinedione has been replaced by an ethano group and two in which the urazole imide nitrogen has been replaced by an oxygen or a carbon–carbon double bond. The persistence of these radicals is compared to that of type **1**• and **2**• radicals.

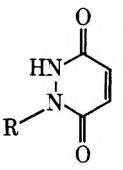
Results

Preparation of Cyclic Diacylhydrazines. 1,3,4-Oxadiazolidine-2,5-diones **3**,[17] 1-phenyltetrahydropyridazine-3,6-dione **5a**,[18] and 1-α-cumyltetrahydropyridazinedione **5b**[19]

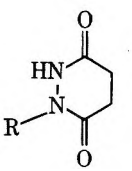


3

4



5



6

a, R = Ph
b, R = PhCMe$_2$
c, R = *t*-Bu

were prepared by literature methods. 2-Phenyltetrahydrophthalazine-1,4-dione was prepared (34%) from phthalic anhydride and phenylhydrazine by a literature method[18] or, in higher yield (52%), by sodium ethoxide treatment of diethyl phthalate and phenylhydrazine, a method similar to that used to prepare pyrazolidinediones **2**.[1,20] Attempts to prepare 2-α-cumyltetrahydrophthalazinedione **4b** by reaction of α-cumylhydrazine[21] with either phthalic anhydride or with diethyl phthalate and sodium ethoxide provided a mixture of products. Heating a toluene solution of α-cumylhydrazine and phthalic anhydride at reflux gives only *N*-α-cumylaminophthalimide. When treated with sodium ethoxide, the imide affords the desired α-cumylphthalazinedione **4b** in high yield.[22] Perhydropyridazine-3,6-diones **6** were prepared by hydrogenation of the corresponding tetrahydropyridazinediones **5** at 50 psi and 80 °C with platinum–carbon catalyst[23] in the case of **6a** or, for **6b**, at 30 psi and 25 °C with the more active rhodium–carbon catalyst.

Cyclic Diacylhydrazyl Radicals. When treated with lead dioxide, α-cumyl- and *tert*-butyloxadiazolidinediones **3b** and **3c** afford, after centrifugation and decantation, orange or yellow solutions of radicals **3b**• and **3c**•, respectively. Sealed, degassed toluene solutions of radical **3c**• change from light yellow to bright orange when frozen at −196 °C, reverting to light yellow on warming above −100 °C. α-Cumyloxadiazolidinedione radical **3b**• gives rise to an EPR spectrum consisting of nine lines owing to the unequal splitting of the hydrazyl nitrogens. The hyperfine splitting (hfs) constants of this and other radicals described in this paper are summarized in Table I. *tert*-Butyl radical **3c**• has not only the same basic EPR spectrum as α-cumyl radical **3b**•, but also an additional splitting arising from the coupling of the unpaired electron to the *tert*-butyl hydrogens. Oxadiazolidinedione radicals **3b**• and **3c**• decompose within 24 h affording colorless, diamagnetic solutions containing colorless solids. Treatment of phenyloxadiazolidinedione **3a** with lead dioxide does not provide a radical detectable by EPR. However, when treated with either *tert*-butyl hypochlorite or *N*-bromosuccinimide, **3a** gives rise to a very weak EPR signal consisting of three equally intense lines as a consequence of the relatively strong coupling of the unpaired electron to one nitrogen.

When treated with lead dioxide, phthalazinediones **4a** and **4b** and α-cumylpyridazinedione **5b** afford light yellow, paramagnetic solutions of the corresponding radicals. Sealed, degassed toluene solutions of α-cumyl radicals **4b**• and **5b**• become intensely purple when frozen at −196 °C. Upon warming above −100 °C, the color returns to light yellow. α-Cumylphthalazinedione radical **4b**• gives rise to an EPR spectrum that has nine lines from the unequal coupling of the unpaired electron to the hydrazyl nitrogens. α-Cumylpyridazinedione radical **5b**• has an EPR spectrum similar to that of its phthalazinedione analogue **4b**•, but also contains an

Table I. Hyperfine Splitting Constants of Cyclic Diacylhydrazyl Radicals [a,b]

Radical	$a_{N\text{-}2(1)}$	$a_{N\text{-}1(2)}$	$a_{N\text{-}1(2)}/a_{N\text{-}2(1)}$	a_H
3a•[c]	9.50[d]			
3b•	7.50	6.50	0.87	
3c•[e,f]	7.60	6.50	0.86	0.15[g] (9 H)
4a•[e]	7.30	4.50	0.62	0.55 (5 H)
4b•	7.05	5.05	0.72	
5a•	6.75[d]	4.25[d]	0.63	
5b•	6.35	4.50	0.71	0.55 (1 H)
6b•	9.00	5.80	0.64	0.80 (2 H)

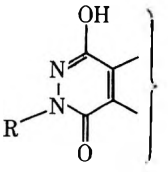
[a] ±0.05 G, unless otherwise stated. [b] In benzene solution at room temperature, unless otherwise stated. [c] This radical most probably is not a hydrazyl type radical. [d] ±015 G. [e] In toluene solution. [f] At 0 °C. [g] ±0.02 G.

additional splitting arising from the coupling of one hydrogen. The EPR spectrum of phenylphthalazinedione radical **4a**• shows, in addition to the unequal splitting of the hydrazyl nitrogens, a splitting due to the five equivalent hydrogens of the phenyl substituent. After treatment with lead dioxide, solutions of phenylpyridazinedione **5a** effervesce excessively when vacuum degassed and do not give rise to any detectable EPR signal. However, when an undegassed, unsealed mixture of **5a** and lead dioxide in benzene is observed by EPR, a weak signal consisting of nine lines appears. Within 36 h, the EPR signals of phthalazinedione radicals **4**• and pyridazinedione radicals **5**• disappear.

When treated with lead dioxide, α-cumylperhydropyridazinedione **6b** affords a light yellow solution of the corresponding radical. In addition to the basic nine-line pattern from the splitting of the hydrazyl nitrogens, the EPR spectrum of radical **6b**• reveals the coupling of two equivalent hydrogens, and a smaller unresolved splitting. The EPR signals of **6b**• disappear within 48 h. Treatment of phenylperhydropyradazinedione **6a** with lead dioxide, *tert*-butyl hypochlorite, or *N*-bromosuccinimide fails to produce any detectable EPR signal.

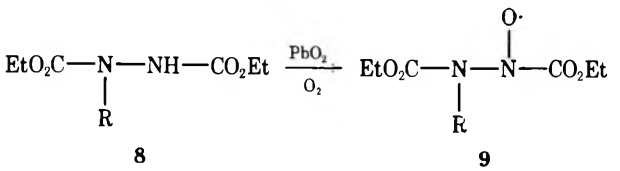
Discussion

Although the results of various studies[24] demonstrate that phthalazinediones **4** and pyridazinediones **5** exist predominantly in the monoketo, monoenol form **7**, when treated with



7

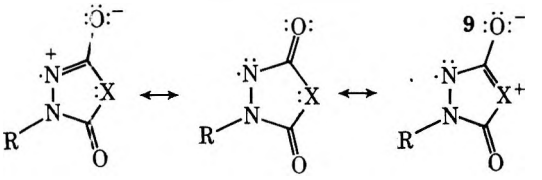
lead dioxide, these cyclic diacylhydrazines, along with perhydropyridazinedione **6b** and oxadiazolidinediones **3b** and **3c**, afford free radicals, the EPR spectra of which are characteristic of nitrogen centered, hydrazyl radicals.[25] Oxidation of phenyloxadiazolidinedione **3a** affords a free radical that has an EPR spectrum not dissimilar to those obtained from the oxidation of acyclic diacylhydrazines **8** (R = CH_3,[8] $PhCMe_2$[1]). These acyclic radicals have been shown[8] to be hydrazoxyls **9**



8 **9**

rather than the hydrazyl radicals. However, it is also possible that this radical is a nitroxide-type radical.[25]

The hydrazyl radicals described in this paper most probably have π ground states, this being the simplest rationale for the extensive spin delocalization observed. Danen et al.[26] have previously addressed themselves to the question of π vs. Σ ground states for a somewhat similar situation (i.e., *N*-alkoxy-*N*-carbethoxyamine radicals). Using essentially their argument, one infers that delocalization of the lone pair of electrons on the divalent nitrogen into the carbonyl group as in canonical form **10** has the effect of localizing the unpaired electron on that nitrogen. In urazole radicals (**11**, X = N–R′) delocalization of the lone pair on the imide nitrogen as in resonance structure **12** reduces the ability of the carbonyl group to delocalize the divalent nitrogen lone pair and thus allows delocalization of the unpaired electron.



10 **11** **12**

To the extent that both hydrazyl nitrogens are similarly hybridized, the ratio of their hyperfine splitting (hfs) constants, $a_{N\text{-}1(2)}/a_{N\text{-}2(1)}$, is suggestive of the distribution of the unpaired electron spin density over these nitrogens. The ratios for oxadiazolidinedione radicals **3b**• and **3c**• are slightly greater than for DPPH (0.83)[4] or the corresponding urazole radicals (0.81).[1] Delocalization of the unpaired electron over the hydrazyl nitrogens in α-cumylphthalazinedione and pyridazinedione radicals **4b**• and **5b**• is similar to that of the 1-phenylurazole and pyrazolidinedione radicals (0.71–0.74).[1] The distribution of spin density between the hydrazyl nitrogens in phenylphthalazinedione and pyridazinedione radicals **4a**• and **5a**• and α-cumylperhydropyridazinedione **6b**• is more disparate than in any of the other cyclic diacylhydrazyl radicals studied.

That the cyclic diacylhydrazyl radicals studied in this paper are less persistent than the analogous urazole radicals is not surprising. Three conditions are generally required for organic free radicals to be persistent: (a) steric congestion of the site formally bearing the unpaired electron, (b) substitution of hydrogen by other groups or atoms at sites where disproportionation may occur, and (c) delocalization of unpaired electron spin density.[4,10,27] In the case of urazole radicals, all these conditions are met. However, for the radicals described here, removal of the urazole imide nitrogen alters the delocalization of spin density. Because an oxygen or a carbon–carbon double bond is not as effective as a nitrogen in delocalizing its pair of electrons, resonance structure **12** does not play as significant a role in the electronic structure of oxadiazolidinedione radicals (**11**, X = O), phthalazinedione or pyridazinedione radicals (**11**, X = C=C), as it does in the urazole radicals. The resultant localization of the unpaired electron in radicals **3**•, **4**•, **5**•, and **6**• renders them less persistent. In view of the fact that phenyl substituted pyrazolidinedione radicals (**11**, R = Ph; X = CR'_2) can be isolated, it is surprising that, even when treated with a variety of oxidizing agents, phenyl-substituted perhydropyridazinedione **6a** does not form a free radical.

Experimental Section

General. Melting points were taken in open Pyrex capillary tubes using a Büchi "Schmelzpunktbestimmungs Apparat" and are uncorrected. Infrared spectra were taken on a Beckman IR-12 grating spectrophotometer. NMR spectra were obtained with Varian A-60A or HA-100 spectrometers. Chemical shifts, δ, are expressed in parts per million relative to internal tetramethylsilane. EPR spectra were

recorded with a Varian E-9 X-Band spectrometer. Mass spectra were obtained with a Varian MAT CH-5 mass spectrometer. Mass spectral data processing equipment employed was provided by NIH Grants CA 11388 and GM 16864 from the National Cancer Institute and the National Institute of General Medical Sciences, respectively. Elemental analyses were performed by the Microanalytical Laboratory of the School of Chemical Sciences, University of Illinois. All hydrazines were distilled prior to use. Other commercially available reagents and reagent grade solvents were used without further purification, unless otherwise stated.

EPR Samples. Solutions of radicals were prepared by stirring solutions of the appropriate cyclic diacylhydrazine with lead dioxide. After 15 s–5 min, the mixtures were centrifuged and the supernatant liquid was put into 4-mm o.d. quartz tubes and frozen at −196 °C. Each sample was vacuum degassed by at least three freeze–pump–thaw cycles and sealed while frozen under high vacuum. All samples were stored at −196°C until used.

2-Phenyl-1,2,3,4-tetrahydrophthalazine-1,4-dione (4a). A solution of sodium ethoxide (prepared from 2.58 g, 112 mmol, of sodium), diethyl phthalate (22.22 g, 100 mmol), and phenylhydrazine (10.81 g, 100 mmol) in absolute ethanol (100 mL) was heated at reflux for 22 h and then concentrated in vacuo. The resultant gum was dissolved in water and extracted with dichloromethane (twice) to remove unreacted starting material. Acidification of the aqueous solution with concentrated hydrochloric acid afforded, after filtration, 19.96 g of a tan solid. Recrystallization (three times) from nitromethane afforded 12.43 g (52.3 mmol, 52%) of slightly off-white needles: mp 214–216 °C [lit.[22a] mp 212 °C (EtOH)]; IR (KBr) 1650, 1602, 1577, 1565, and 1202 cm^{-1}.

Anal. Calcd for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.47; H, 4.29; N, 11.85.

***N*-α-Cumylaminophthalimide.** A solution of α-cumylhydrazine[21] (3.75 g, 25 mmol) and phthalic anhydride (3.70 g, 25 mmol) in toluene (175 mL) was heated at reflux for 20 h, the condensate being collected in a Dean-Stark trap. Removal of the solvent under reduced pressure and recrystallization of the crude solid from ethanol afforded 6.28 g (22.4 mmol, 90%) of the phthalimide as a yellow solid: mp 87–89 °C; IR (KBr) 3460 and 3300 (NH), 3065, 2990, 2975, and 2940 (CH), 1788, 1768, and 1732 (C=O), 1390 (CMe_2), 1377, 1366 $(CMe)_2$, 1112, 888, 767, and 710 cm^{-1}; NMR ($CDCl_3$) δ 1.56 [s, 6, $C(CH_3)_2$], 4.69 (s, 1, NH), 7.1–7.4 and 7.5–7.9 (m, 9, C_6H_5, C_6H_4); mass spectrum (70 eV) *m/e* (rel intensity) 280 (weak, M^+), 162 (28), 120 (10), 119 (100), 118 (24), 104 (10), 103 (6), 91 (43), 79 (9), 77 (15), 76 (10), 51 (5), and 41 (22).

Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.65; H, 5.65; N, 10.03.

2-α-Cumyl-1,2,3,4-tetrahydrophthalazine-1,4-dione (4b). A solution of sodium ethoxide (prepared from 1.24 g, 54 mmol, of sodium), *N*-α-cumylaminophthalimide (5.61 g, 20 mmol), and ethyl acetate (1.00 g, 11.4 mmol) in absolute ethanol (80 mL) was heated at reflux for 20 h and then concentrated to ca. 40 mL. After dilution with water (ca. 50 mL), acidification with concentrated hydrochloric acid, and filtration, a solid was obtained. Recrystallization from ethanol afforded 4.47 g (16.9 mmol, 80%) of phthalazinedione **4b** as a white solid which melts at 218 °C, immediately resolidifies, and does not melt again below 300 °C: IR (KBr) 3445 (OH), 3145 (NH), 3060, 3035, 3005, 2985, and 2935 (CH), 1643 (C=O), 1590, 1574, 1558, 1497, 1387 (CMe_2), 1365 (CMe_2), 1358, 1263, 1195. 1156, and 698 cm^{-1}; NMR (acetone-d_6) δ 1.87 [s, 6, $C(CH_3)]_2$, 2.86 (s, 1, OH), 7.0–7.3 and 7.68 (m, 9, C_6H_5,C_6H_4); mass spectrum (70 eV) *m/e* (rel intensity) 280 (13, M^+), 163 (28), 162 (97), 132 (10), 120 (1), 119 (100), 118 (93), 117 (18), 104 (15), 103 (11), 91 (64), 79 (12), 78 (11), 77 (19), 51 (11), and 41 (30).

Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.83; H, 5.67; N, 10.02.

1-Phenyl-1,2,5,6-tetrahydropyridazine-3,6-dione (5a) was prepared according to the method of Biquard and Grammaticakis[18] by heating a solution of maleic anhydride (9.81 g, 100 mmol) and phenylhydrazine (10.81 g, 100 mmol) in glacial acetic acid (40 mL) at reflux for 1 h. After workup and recrystallization from ethanol, 8.76 g (46.6 mmol, 47%) of pyridazinedione **5a** was obtained as white needles: mp 267.5–268.5 °C [lit.[18] mp 265 °C (EtOH)]; IR (KBr) 1763, 1601, 1573, 1500, 1483, 1456, 1265 cm^{-1}.

Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.83; H, 4.29; N, 14.89. Found: C, 64.07; H, 4.50; N, 15.09.

1-Phenylperhydropyridazine-3,6-dione (6a). A 200-mL pressure bottle wrapped with heating tape was charged with a solution of pyridazinedione **5a** (1.88 g, 10.0 mmol) in ethanol (100 mL) and platinum–carbon catalyst (100 mg). After attaching the bottle to a Parr apparatus, the hydrogen pressure was set at 50 psi. The bottle was then heated until the pressure had increased another 15 psi. After shaking for 2 days, the reactions mixture was filtered and concentrated in vacuo to afford 1.91 g of an off-white solid. Recrystallization from ethanol afforded 1.15 g (6.05 mmol, 61%) of pyridazinedione **6a** as a white solid: mp 197–198 °C [lit.[28] mp 199 °C (H_2O)]; IR (KBr) 1672 cm^{-1}.

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.72. Found: C, 63.26; H, 5.29; N, 14.94.

1-α-Cumylperhydropyridazine-3,6-dione (6b). A solution of pyridazinedione **5b**[19] (0.12 g, 0.52 mmol) in ethanol (75 mL) was shaken in a Parr apparatus with rhodium–carbon catalyst (50 mg) under an atmosphere of hydrogen (30 psi). After 24 h, the reaction mixture was filtered and concentrated at reduced pressure. Recrystallization of the crude product from ethyl acetate afforded 0.08 g (0.34 mmol, 67%) of pyridazinedione **6b** as a white solid: mp 134–136 °C; IR (KBr) 3450 and 3230 (NH), 2990 (CH), 1675 (C=O), 1400, 1186, 768, and 702 cm^{-1}; NMR (acetone-d_6) δ 1.76 [s, 6, $C(CH_3)_2$], 2.48 (s, 4, $COCH_2$), 2.77 (s, 1, CONH), and 7.1–7.6 (m, 5, C_6H_5); mass spectrum (70 eV) *m/e* (rel intensity) 232 (weak, M^+), 120 (11), 119 (100), 118 (10), 103 (5), 91 (50), 79 (7), 77 (9), 41 (16), and 28 (6).

Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.10; H, 6.84; N, 12.10.

Acknowledgments. This work has been partially supported by funds from the Alfred P. Sloan Research Foundation and the National Institutes of Health (GM 14518).

Supplementary Material Available. EPR spectra of radicals **3b·**, **3c·**, **4a·**, **4b·**, **5b·**, and **6b·** (6 pages). Ordering information is given on any current masthead page.

Registry No.—**3a·**, 61446-35-3; **3b·**, 61446-36-4; **3c·**, 61446-37-5; **4a**, 5439-98-5; **4a·**, 61446-38-6; **4b**, 61446-39-7; **4b·**, 61446-40-0; **5a**, 1698-54-0; **5a·**, 61446-41-1; **5b·**, 61446-42-2; **6a**, 61446-43-3; **6b**, 61446-44-4; **6b·**, 61446-45-5; diethyl phthalate, 84-66-2; phenylhydrazine, 100-63-0; *N*-α-cumylaminophthalimide, 61446-46-6; α-cumylhydrazine, 3178-39-0; phthalic anhydride, 85-44-9; ethyl acetate, 141-78-6; maleic anhydride, 108-31-6.

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The Use of Chiral Solvating Agents for Nuclear Magnetic Resonance Determination of Enantiomeric Purity and Absolute Configuration of Lactones. Consequences of Three-Point Interactions

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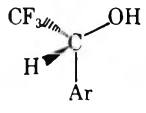
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Received October 21, 1976

Diastereomeric solvates result from the solvation of enantiomeric lactones by chiral 2,2,2-trifluoro-1-(9-anthryl)ethanol (**1**). In most instances, these solvates are of similar general structure and energy as a consequence of "two-point only" interaction. The nature of the time-averaged NMR spectral differences of these diastereomeric solvates is a reliable guide to the absolute configurations of the lactone enantiomers. Additional (i.e., "three-point") interactions require modification of the generalizations of the "two-point" model. Several lactones bearing nitrophenyl or nitrobenzyl substituents have been shown to depart from the two-point model as a consequence of π–π interaction between the nitrated aromatic substituent of the lactone and the anthryl substituent of **1**. These π–π interactions cause the diastereomeric solvates to be of different stabilities as evidenced by Eu(fod)$_3$ studies and direct chromatographic resolution of the nitrated lactone enantiomers on silica gel using solutions of chiral **1** as an eluent. ^{13}C NMR studies offer additional insight into the structures of these diastereomeric solvates.

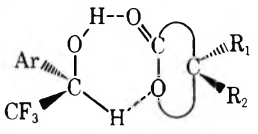
The intermediacy of short-lived molecular complexes has been invoked in such diverse areas as rationalization of reaction mechanisms, separation methods, biological activity, and physical and spectral properties. Diastereomeric complexes, produced through interactions of chiral molecules, often show considerable stereochemical dependence of their chemical, spectral, and physical properties. Such behavioral differences are not always well understood even though the practical applications of such differences are legion.

We have been concerned about the details of interaction between certain "chiral solvating agents" and a diverse series of enantiomeric solutes.[1a-j] In many cases, both enantiomeric purity and absolute stereochemistry can be determined for the solutes on the basis of such interactions. For example, we recently reported[2] that "two-point" interaction between chiral 2,2,2-trifluoro-1-(9-anthryl)ethanol (**1**) and γ-lactone enantiomers, as shown in **2a,b**, is responsible for the nonequivalence of the NMR spectra of the enantiomers. The shielding effect of the anthryl substituent causes the resonances of the R_1 substituent(s) to occur at higher field for the enantiomer incorporated into **2a** than for that incorporated into **2b**. The converse situation holds for the resonances of R_2 substituents located on the other face of the lactone. Implicit in this solvation model is the assumption that no additional interactions occur between the alcohol and the lactone. It was suggested that additional interactions might perturb the model and alter the correlation between stereochemistry and observed senses of nonequivalence. In this paper, we address ourselves to the consequences of one type of "additional interaction" between lactones and chiral carbinol **1**.

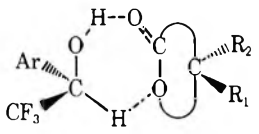


Ar = 9-anthryl

1

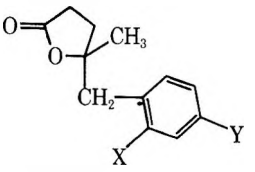


2a



2b

Diastereomeric solvates **2a** and **2b** can be considered to be of essentially equal stability if no appreciable lactone–carbinol interactions occur beyond the hydrogen bonding–carbinyl hydrogen bonding[1b] interactions depicted. Additional interactions will be stereochemically dependent and can result in differential stability of the solvates. They may even alter the structure of the solvates. Consider, for example, the diastereomeric solvates derived from (*R*)-(−)-**1** and the enantiomers of γ-benzyl-γ-methylbutyrolactone (**3**) and the o-nitro, *p*-nitro, and 2,4-dinitro analogues, **4**, **5**, and **6**. In the presence



3, X = Y = H
4, X = NO_2; Y = H
5, X = H; Y = NO_2
6, X = Y = NO_2

of a severalfold excess of (*R*)-(−)-**1**, a (−)-enriched sample of **3** shows low-field nonequivalence for the benzyl methylene hydrogens and high-field nonequivalence fo the methyl hydrogens. In accord with the model, this lactone has been assigned the (*S*)-(−) configuration. Addition of the achiral shift reagent Eu(fod)$_3$ to the preceding sample causes the lactone resonances to move downfield (Figure 1 shows this for the benzyl methylene hydrogens) as the Eu(fod)$_3$ "strips" the lactone from carbinol **1**.[3] Figure 2, a plot of nonequivalence magnitude (i.e., $\delta R - \delta S$) as a function of Eu(fod)$_3$:lactone ratio, shows a smooth attenuation of nonequivalence toward zero. This is a consequence of the similar stabilities of the two diastereomeric lactone–carbinol solvates in the absence of "additional" interactions.[3]

Repetition of these NMR experiments for (*S*)-enriched samples of nitrated lactones **4**, **5**, and **6** affords different results. First, the senses of methyl nonequivalence for these lactones are inverted and are of the same sense as that of the benzyl methylene groups. Secondly, Eu(fod)$_3$ seems less able to "disrupt" the lactone–carbinol solvates, especially in the case of the dinitro analogue, **6** (Figure 1). Thirdly, Eu(fod)$_3$ preferentially "disrupts" the (*R,S*) solvate, as evidenced (Figure 2) by the greater downfield shifts of both the methyl and benzyl methylene resonances of the *S* enantiomer than the *R* enantiomer. Again, this effect is more pronounced for dinitro **6** than for *p*-nitro **5** or *o*-nitro **4**. These curves are best explained by invoking a stereochemically dependent π–π interaction between the anthryl substituent of **1** and the nitrated benzyl substituents of the lactones. The strengths of these π–π interactions are dinitro **6** > *p*-nitro **5** > *o*-nitro **4**.[5] For steric

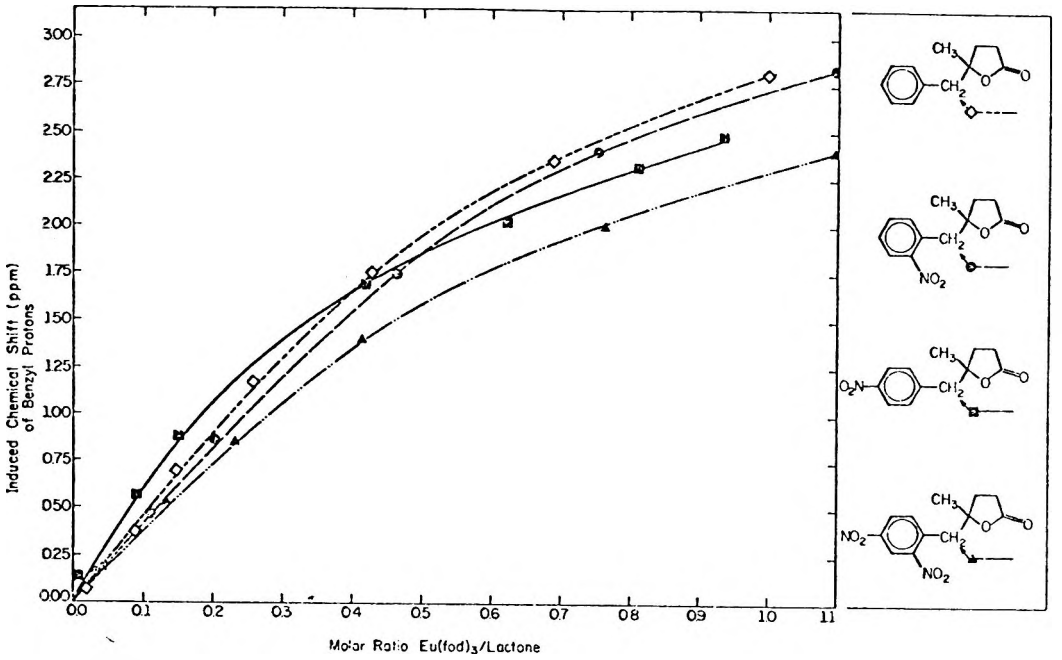


Figure 1. The influence of $Eu(fod)_3$ concentration on the (averaged) induced chemical shifts of the benzyl protons of lactones 3–6. Lactone concentrations are ca. 0.07 M; carbinol 1 concentration is ca. 0.21 M.

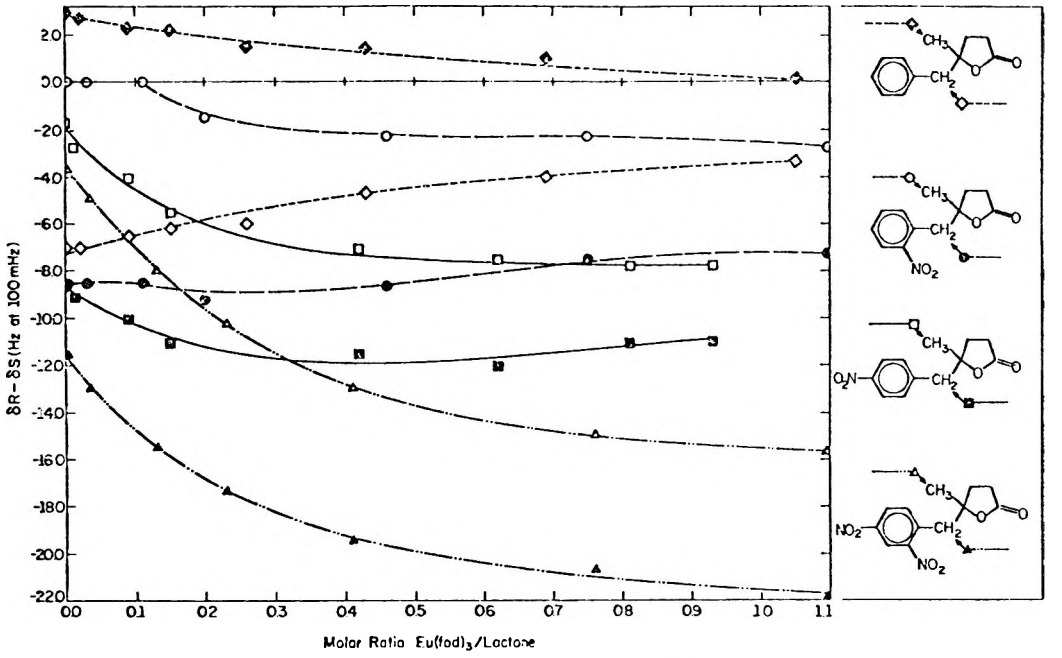


Figure 2. The influence of $Eu(fod)_3$ concentration on the senses and magnitudes of nonequivalence of the lactones 3–6. Samples used to generate these data were those described for Figure 1.

reasons, the *o*-nitro group of **4** is less apt to be coplanar with the phenyl ring and is consequently a less effective π acid. Solvates **7a,b** make it evident that the *R,R* solvate can simultaneously experience three bonding interactions whereas the *R,S* solvate can simultaneously experience but two.

As a further test of this "differential stability" concept, 30 mg of racemic **6** was chromatographed on silica using a carbon tetrachloride solution of (*R*)-(−)-**1** as eluent. The progress of the colored π complexes was followed visually and, after development, the section of the column containing this band was divided into high R_f, mid R_f, and low R_f fractions.[6] Recovery and chromatographic purification of the high and low R_f fractions afforded optically active samples of **6**, the enantiomeric compositions and absolute configurations (Table I) of which were established by NMR in the presence of (*R*)-(−)-**1**. The high R_f fraction (8.8 mg) was 50% enriched in the (*R*)-(−) enantiomer; the low R_f sample (17.4 mg), 18% enriched in the (*S*)-(+) enantiomer. This elution order is that expected if the mechanism of chromatographic resolution reflects the relative stabilities of the two diastereomeric solvates.

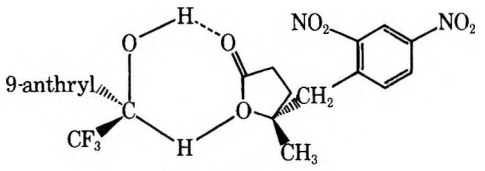
The assignment of the (*S*)-(+) configuration to **6** was independently established. After chromatographic separation of the chiral diastereomeric hydroxy amides **8**, hydrolysis of the low R_f isomer followed by cyclization leads to (*S*)-(−)-**3** in high enantiomeric purity. Nitration with nitronium tetrafluoroborate affords (*S*)-(+) samples of **4**, **5**, and **6** with moderate racemization (Scheme I). Lactones **4**, **5**, and **6** were separated chromatographically.

To gain further insight into the structures of the diaste-

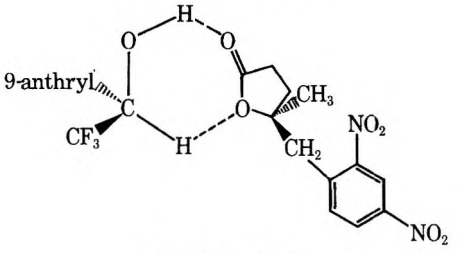
Table I. Rotational and NMR Nonequivalence Data for Lactones 6, 9, and 10 Enantiomerically Enriched by Chromatography Using (*R*)-(−)-1 as Eluent

	High R_f fraction		Low R_f fraction	
Lactone (wt chromatographed)	Wt, mg $[\alpha]^{25}_D$ ($CHCl_3$) ee[a] by NMR	Proton (amt noneq),[b] sense[c]	Wt, mg $[\alpha]_D$ ($CHCl_3$) ee[a] by NMR	Proton (amt noneq),[b] sense[c]
6 (30 mg)	8.8 −12.2°[d] (*c* 0.98) 50%	H_6 (18.0), H Benzyl (10.0), H $-CH_3$ (3.5), H	17.4 +6.7° (c 1.93) 18%	H_6 (20.0), L Benzyl (11.0), L $-CH_3$ (2.2), L
9 (30 mg)	14.2 +5.6° (*c* 1.58) 15%	H_3 (3.0), H; H_5 (18.0), H H_γ (11.0), H	8.8 −14.2° (*c* 0.98) 36%	H_3 (3.2), L H_5 (22.5), L H_6 (22.0), L H_γ (13.0), L
10[e] (49 mg)	 50%	H_3 (3.0), H; H_5 (26.0), H	24 +72.9° 50%	H_3 (3), L; H_5 (26), L

[a] Enantiomeric excess as determined by relative peak heights of enantiomeric resonances. [b] Amount of nonequivalence in hertz at 100 MHz. Variations in nonequivalence magnitudes between high and low R_f fractions reflect somewhat different sample concentrations. [c] H = highfield; L = lowfield. [d] Sample used for rotation later found to contain a trace of (*R*)-(−)-**1**. [e] This lactone was actually resolved using (*S*)-(+)-**2**. Signs of rotation and senses of nonequivalence have been inverted in the table for uniformity with the other entries.



7a *R,R* solvate



7b *R,S* solvate

reomeric solvates derived from carbinol **1** and the enantiomers of **6**, ^{13}C NMR nonequivalence studies were carried out. In the presence of a severalfold excess of (*R*)-(−)-**1**, every carbon of (*S*)-(+)-enriched **6**, except the methyl carbon, shows nonequivalence (Table II). Note that all carbon resonances shift upfield in the presence of **1** except the carbonyl and carbinyl carbons. The downfield shifts noted for the latter are consistent with a diminution of electron density at these carbons attendant with hydrogen bonding and carbinyl hydrogen bonding to the adjacent oxygens. As expected, the carbonyl carbon shows the greater effect. Upfield shifts of the remaining carbons are rationalized on the basis of diamagnetic shielding by the anthryl substituent of **1** and by its electron donation via π–π complexing to **6**. The low-field sense of nonequivalence shown by all carbons in the 2,4-dinitrobenzyl substituent is in accord with a greater degree of π–π (charge transfer) interaction in the *R,R* solvate than in the *R,S* solvate. Similarly, the high-field nonequivalence shown by the carbonyl, α, β, and γ carbons suggests a greater degree of hydrogen bonding and carbinyl hydrogen bonding for the *R,R* than for the *R,S* diastereomer.

The data presented are consistent with **7a** being representative of the time-averaged structure of the *R,R* solvate. It is not clear that **7b** is equally representative of the *R,S* solvate since, should the π–π interaction be competitive with carbinyl hydrogen bonding, structure **7c** might well compete with or dominate **7b**. Structure **7c** could well be responsible for the "inverted" sense of nonequivalence shown by the methyl group of **6**. Since **7b** is the conformation expected to provide the shielding responsible for the "normal" upfield sense of methyl nonequivalence of *S*-enriched **6**, the "absence" of **7b**

Scheme I

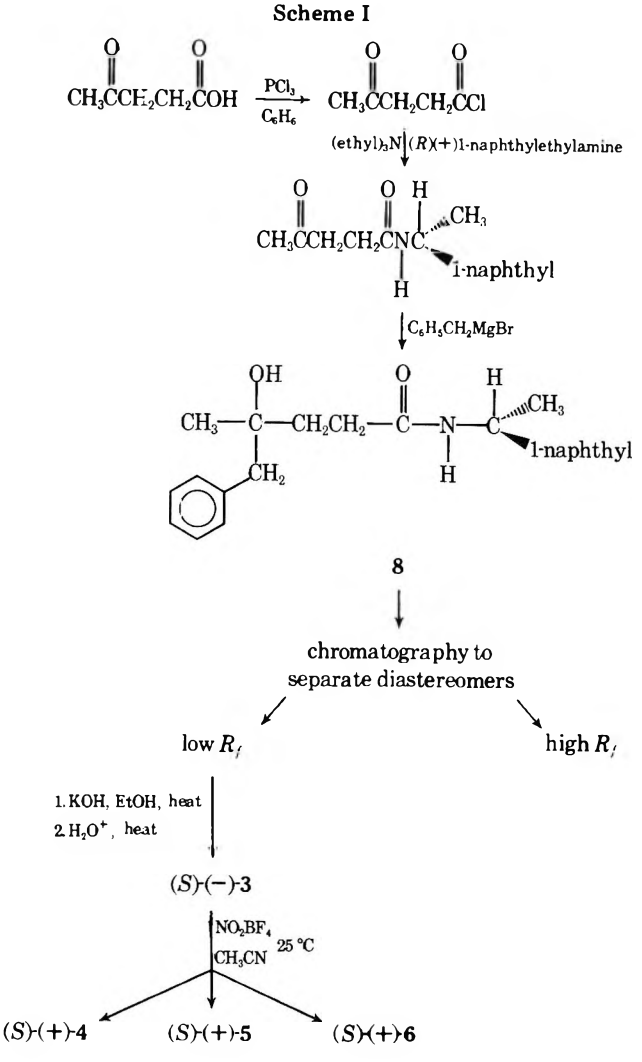
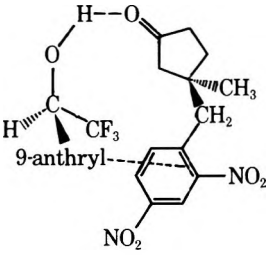


Table II. ^{13}C NMR Chemical Shifts and Nonequivalence of (*S*)-(+)-Enriched 6 in the Presence of (*R*)-(−)-1

Carbon	Without 1, ppm[a]	In the presence of (*R*)-(−)-1: ppm[a]	Δppm	Nonequivalence magnitude, Hz (sense)[b]
C=O	174.798	177.267	+2.469	8.62 (H)
α	33.315	32.744	−0.571	1.98 (H)
β	28.576	28.291	−0.285	Shoulder (H?)
γ	84.944	86.078	+1.134	4.66 (H)
$-CH_3$	25.850	24.815	−1.035	0.0
Benzyl	41.672	40.663	−1.009	4.13 (L)
Aromatic				
C-1	137.464	136.618	−0.846	4.13 (L)
C-2	150.660	149.608	−1.052	4.12 (L)
C-3	120.293	119.740	−0.553	3.05 (L)
C-4	147.278	146.407	−0.871	4.67 (L)
C-5	126.616	Not assignable		
C-6	135.466	134.623	−0.842	3.24 (L)

[a] Downfield from Me_4Si. [b] H = highfield, L = lowfield sense.

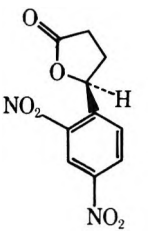
would thwart predictions predicated upon its substantial population.



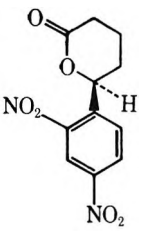
7c

Similar reasoning leads one to anticipate a stability difference in the diastereomeric solvates derived from (*R*)-(−)-1 and the enantiomers of dinitrophenyl lactones **9** and **10**. Indeed, chromatographic resolution of the enantiomers of these lactones can be effected as it was for lactone **6**. These results are summarized in Table I. It should also be noted that the senses of nonequivalence of the carbinyl hydrogens of **9** and **10** are (presumably) "inverted" since they are of the same sense as the nonequivalence of the protons on the 2,4-dinitrophenyl groups. These "inversions" appear to have the same general origin as those of lactones **5** and **6**. Thus, the differential chromatographic and spectroscopic behavior of the enantiomers of lactones **9** and **10** [in the presence of (*R*)-(−)-**1**] appear very similar to that of lactone **6**. Hence, the *S* configuration is assigned to the enantiomer preferentially included in the low R_f chromatographic fractions shown in Table I for each of these lactones.[7]

For lactones **4–6, 9,** and **10**, it was immediately apparent (from the similar senses of nonequivalence of substituents on either face of the lactone ring) that the usual lactone–carbinol solvation model was being perturbed. This is of no consequence for enantiomeric purity determinations but did raise questions concerning assignments of absolute configuration based upon the observed senses of nonequivalence. It has been demonstrated that this perturbation comes from the presence of a third lactone–carbinol interaction (π–π bonding in these instances) that is stereochemically dependent. Since knowledge of lactone structure will often allow anticipation of such "third interactions", rational interpretation of observed senses of nonequivalence will often be possible even for "abnormal solutes". In general, the observation of opposite senses of nonequivalence for substituents on opposite faces of the lactone ring will be the hallmark of the normal solvation model.



9



10

Experimental Section

General. Melting points were taken on a Buchi apparatus and are uncorrected. Optical rotations were determined at 589 nm in a Zeiss visual polarimeter using a 1.0-dm tube. ^1H NMR data were obtained with a Varian HA-100 or HR-220 spectrometer at 27 or 25 °C, respectively. Proton-decoupled carbon-13 spectra were obtained with a Varian XL-100-15 spectrometer equipped with a Digilab NMR-3 data system. The 25.2-MHz natural abundance spectra were obtained at 30 °C in the FT mode using a 32K point transform. The off-resonance proton-decoupled carbon-13 spectrum was obtained with a JEOL JNM FX-60 spectrometer in the FT mode. Microanalysis were performed by J. Nemeth and his colleagues.

The synthesis, resolution, and absolute configuration of **1** have been previously reported[2] as has an alternate synthesis of enantiomerically enriched **3**.[2]

Racemic Nitrated Lactones 4, 5, and 6. Nitration of racemic lactone **3** was effected by addition of a fourfold excess of nitronium tetrafluoroborate to the lactone (0.1 M) in dry acetonitrile at 0 °C followed by stirring for 1–2 h at 25 °C. Addition of H_2O and extraction with CH_2Cl_2 gave a mixture of *o*-nitro-, *p*-nitro-, and 2,4-dinitrophenyl substituted lactones **4, 5,** and **6** which were separated by column chromatography on silica gel with CH_2Cl_2. The elution order was **4**, followed by **5**, and then **6**. All three lactones were recrystallized from a mixture of CCl_4 and CH_2Cl_2 (5:1, v:v). Characterization data and yields are reported in Table III.

Table III

Lactone (mp, °C) yield, %	100-MHz NMR	Microanal. Calcd	Found
4 (110) 5–10	(CCl_4–$CDCl_3$ 2.1, v:v) 7.88 (m, 1), 7.65–7.30 (m, 3), 3.36 (s, 2), 2.73–1.97 (m, 4), 1.43 (s, 3)	$C_{12}H_{13}NO_4$ C, 61.27 H, 5.57 N, 5.95	C, 61.47 H, 5.72 N, 6.02
5 (110) 30	($CDCl_3$) 8.17 (d, 2, J = 8.5 Hz), 7.42 (d, 2, J = 8.5 Hz), 3.06 (s, 2), 2.63–1.97 (m, 2), 1.42 (s, 3)	$C_{12}H_{13}NO_4$ C, 61.27 H, 5.57	C, 60.99 H, 5.37
6 (93) 40	(CCl_4–$CDCl_3$ 3:1, v:v) 8.69 (d, 1, J = 2.3 Hz), 8.40 (d of d, 1, J = 2.3, 9.0 Hz), 7.75 (d, 1, J = 9.0 z), 3.43 (s, 2), 2.70–1.90 (m, 4), 1.38 (s, 3)	$C_{12}H_{12}N_2O_6$ C, 51.43 H, 4.32 N, 10.00	C, 51.63 H, 4.36 N, 10.05

Enriched Lactones 3, 4, 5, and 6. To a stirred solution of levulenic acid (23 g, 0.19 mol) in benzene (180 mL) was added phosphorus trichloride (16 g, 0.117 mol). After the initial exothermic reaction, the solution was stirred at 25 °C for 2.5 h. Evaporation of the solution under reduced pressure to 90 mL volume removed unreacted PCl_3 (bp 78 °C) and cooling and decantation separated the soluble acid chloride from the insoluble phosphorus-containing by-products. Care was taken to keep the solution cool since a previous attempt at distillation of the acid chloride had resulted in formation of α,β- and β,γ-unsaturated lactones.

The entire C_6H_6 solution of acid chloride was slowly added to a stirred and cooled (0 °C) solution of (*R*)-(+)-α-naphthylethylamine (20 g, 0.117 mol) and triethylamine (12 g, 0.119 mol) in C_6H_6 (100 mL). After the addition, the solution was allowed to warm to 25 °C and stirred for 12 h. The resulting amine hydrochloride was removed by filtration after addition of CH_2Cl_2 (400 mL). The filtrate was washed with dilute hydrochloric acid (1.5 M, 4 × 50 mL) and with dilute sodium bicarbonate (5%, 3 × 40 mL), dried ($MgSO_4$), and distilled under reduced pressure to yield 25.2 g of residue assumed to be mainly the keto amide.

A solution of benzylmagnesium bromide, prepared by addition of α-bromotoluene (32.2 g, 0.188 mol) to magnesium turnings (9.1 g, 0.376 mol) in anhydrous ether (150 mL) followed by reflux (30 min), was added to a cold (5 °C) solution of the above keto amide (13 g, 0.048 mol) in dry ether (600 mL) with stirring. A solid formed immediately. After stirring at 25 °C for 3.5 h, hydrolysis with saturated aqueous ammonium chloride (350 mL) followed by ether extraction afforded, after drying and concentration of the extracts, an orange-brown oil (22.3 g). Chromatography of this oil on silica gel with CH_2Cl_2 afforded a 3:1 mixture (14.6 g) of the desired hydroxy amides and unreacted keto amide.

Chromatography of a portion of this mixture [silica gel with CH_2Cl_2–Et_2O (4:1, v:v)] resulted in separation of all three components (keto amide and the two diastereomers). The low R_f diastereomer (2.0 g, 5.54 mmol) was hydrolyzed by heating to reflux for 10 h with KOH (4.2 g, 75 mmol) in ethanol (50 mL). Subsequent addition of H_2O (200 mL) and extraction with CH_2Cl_2 (4 × 40 mL) removed the amine and acidification (3 M HCl) followed by extraction afforded the hydroxy acid which was lactonized by azeotropic removal of H_2O with benzene.

Nitration was effected as described earlier for the racemate and results in some racemization. In one case, **3** of 61% enantiomeric purity yielded **6** of 35% enrichment. To increase the yield of the o-nitrophenyl substituted lactone, a sample of the nitration reaction mixture was removed and worked up 10 min after addition of NO_2BF_4 while the solution was still cold. This sample was added to the final product before chromatography. The dinitrated lactone obtained in this manner was used for the carbon-13 study. Optical rotations and enantiomeric purities of the samples thus obtained follow: **4**, $[\alpha]^{24}_D$ +10.70° (c c 4.60, $CHCl_3$), 34% ee; **5**, $[\alpha]^{24}_D$ +8.33° (*c* 9.72, $CHCl_3$), 31% ee; **6**, $[\alpha]^{24}_D$ +6.21° (*c* 9.50, $CHCl_3$), 31% ee. The NMR spectra of these lactones are identical with those of the racemic lactones.

Racemic γ-2,4-Dinitrophenyl-γ-butyrolactone (9). A solution of 4-phenylbutanoic acid (0.01 mol) in concentrated nitric (10 mL) and sulfuric (5 mL) acids was heated on a steam bath for 12–16 h. Cooling, followed by careful addition of H_2O (100 mL), caused precipitation of the nitrated acid which was extracted into CH_2Cl_2 (3 × 30 mL) and washed with H_2O. Evaporation of the solvent from the dried ($MgSO_4$) extract afforded 4-(2,4-dinitrophenyl)butanoic acid (>90%). γ-Bromination of the nitrated acid (5 mmol) was effected with *N*-bromosuccinimide (5 mmol) in CCl_4 (125 mL) through heating at reflux for 5 h in the presence of dibenzoyl peroxide (0.05 mmol). Succinimide precipitated on cooling and was removed by filtration. The filtrate, containing a mixture of the desired lactone, bromo acid, and unbrominated acid, was washed with 10% aqueous sodium bicarbonate to remove the acids from lactone **9**. Heating the aqueous extract converted the bromo acid salt to the hydroxy acid salt. Acidification of the aqueous solution followed by extraction with benzene and azeotropic removal of water by distillation effected lactonization. Acidic impurities were removed by extraction with 10% $NaHCO_3$. Both fractions of lactone **9** were combined and crystallized from a mixture of CCl_4 and CH_2Cl_2 (5:1, v:v): mp 109 °C; NMR ($CDCl_3$) δ 9.05 (d, 1, *J* = 2.3 Hz), 8.65 (d of d, 1, *J* = 9.0, 2.3 Hz), 8.12 (d, 1, *J* = 9.0 Hz), 6.30 (t, 1, *J* = 7.0), 3.20–1.90 (m, 4). Anal. Calcd for $C_{10}H_8N_2O_6$: C, 47.63; H, 3.20; N, 11.11. Found: C, 47.59; H, 3.32; N, 10.95.

Racemic δ-2,4-Dinitrophenyl-δ-valerolactone (10). This lactone was prepared from 5-phenylpentanoic acid in the manner described above for lactone **9**. Lactone **10** was not readily crystalline and was characterized only by 100-MHz NMR: NMR ($CDCl_3$) δ 8.82 (d, 1, *J* = 2.3 Hz), 8.55 (d of d, 1, *J* = 9.0, 2.3 Hz), 8.05 (d, 1, *J* = 9.0 Hz), 6.07 (d of d, 1), 3.00–1.50 (m, 6).

Acknowledgment. This work has been partially supported by the National Science Foundation and by the National Institutes of Health.

Registry No.—(*R*)-(−)-**1**, 53531-34-3; (±)-**3**, 61520-92-1; (*S*)-(−)-**3**, 61477-77-8; (±)-**4**, 61477-78-9; (*S*)-(+)-**4**, 61520-93-2; (±)-**5**, 61477-79-0; (*S*)-(+)-**5**, 61520-94-3; (±)-**6**, 61477-80-3; (*S*)-(+)-**6**, 61520-95-4; (*R*)-(−)-**6**, 61520-96-5; **8**, 61477-81-4; (±)-**9**, 61477-82-5; (*S*)-(−)-**9**, 61520-97-6; (*R*)-(+)-**9**, 61520-98-7; (±)-**10**, 61477-84-7; (*S*)-(+)-**10**, 61521-47-9; (*R*)-(−)-**10**, 61520-99-8; levulinic acid, 123-76-2; levulinoyl chloride, 1490-24-0; (*R*)-(+)-α-naphthylethylamine, 3886-70-2; *N*-(1-napthylethyl)levulinamide, 61477-85-8; benzyl bromide, 100-39-0; 4-phenylbutanoic acid, 1821-12-1; 5-phenylpentanoic acid, 2270-20-4.

References and Notes

(1) (a) W. H. Pirkle and M. S. Hoekstra, *J. Am. Chem. Soc.*, **98**, 1832 (1976); (b) W. H. Pirkle and J. R. Hauske, *J. Org. Chem.*, **41**, 801 (1976); (c) W. H. Pirkle and D. L. Sikkenga, *J. Chromatogr.*, **123**, 400 (1976); (d) W. H. Pirkle and M. S. Hoekstra, *J. Magn. Reson.*, **18**, 396 (1975); (e) W. H. Pirkle, S. D. Beare, and R. L. Muntz, *Tetrahedron Lett.*, 2295 (1974); (f) W. H. Pirkle and R. L. Muntz, *J. Am. Chem. Soc.*, **93**, 2817 (1971); (g) W. H. Pirkle, S. D. Beare, and R. L. Muntz, *J. Am. Chem. Soc.*, **91**, 4575 (1969); (h) W. H. Pirkle and S. D. Beare, *ibid.*, **91**, 5150 (1969); (i) W. H. Pirkle, T. G. Burlingame, and S. D. Beare, *Tetrahedron Lett.*, 5847 (1968); (j) W. H. Pirkle and S. D. Beare, *J. Am. Chem. Soc.*, **89**, 5485 (1967).

(2) W. H. Pirkle, D. L. Sikkenga, and M. S. Pavlin, *J. Org. Chem.*, **42**, 384 (1977).

(3) In a solution containing enantiomeric lactones, R and S, chiral carbinol, C, and shift reagent, L, a *partial* accounting of the ensuing interactions is as follows:

$$R + C \underset{}{\overset{k_1}{\rightleftharpoons}} RC$$

$$S + C \overset{k_2}{\rightleftharpoons} SC$$

$$R + L \overset{k_3}{\rightleftharpoons} RL$$

$$S + L \overset{k_3}{\rightleftharpoons} SL$$

$$R + C + L \overset{k_4}{\rightleftharpoons} RLC$$

$$S + C + L \overset{k_5}{\rightleftharpoons} SLC$$

There are at least four mechanisms which might contribute to the time-averaged NMR nonequivalence shown by R and S: (a) the spectrum of RC ≠ SC; (b) [RL] ≠ [SL], i.e., $k_1 \neq k_2$; (c) the spectrum of RLC ≠ SLC; (d) [RLC] ≠ [SLC], i.e., $k_4 \neq k_5$. A more detailed explanation of a similar situation dealing with enantiomeric sulfoxides has been presented.[4]

(4) W. H. Pirkle and D. L. Sikkenga, *J. Org. Chem.*, **40**, 3430 (1975).

(5) The curves shown in Figure 2 are qualitatively similar in shape to those observed for several ring-substituted phenyl methyl sulfoxides in ref 4. The observation that higher concentrations of $Eu(fod)_3$ are required to produce the maximum perturbation in the spectrum of **6** than for **5** or **4** presumably indicates the greater magnitudes of k_1 and k_2 in the case of **6**. A smaller value for k_3 would afford a similar observation. $Eu(fod)_3$ competition experiments show that k_3 is smaller for lactone **6** than for **3**.

(6) A more detailed account of the chromatographic procedure is given in ref 1c.

(7) Similar arguments have been used to assign absolute configurations to methyl 2,4-dinitrophenyl sulfoxide and methyl *p*-nitrophenyl sulfoxide.[1c,4]

Azadiene Chemistry. 3. Polycyclic Amines from 2,3,4,5,5-Pentachloro-1-azacyclopentadiene in Diels–Alder Reaction[1]

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Received October 12, 1976

The title azadiene has been shown to undergo typical Diels–Alder reaction to yield polycyclic amine adducts. These cycloadducts include the bridgehead aza analogues of the commercial insecticides aldrin and dieldrin as well as several 5-substituted 1-azanorbornenes. Structural analysis of these polycyclic amine adducts is achieved via NMR spectral analyses using decoupling, shift reagent, and computer simulation techniques. Thus, azaaldrin is assigned structure **2**, azadieldrin **3**, and the equilibration of **2** with isomer **2b** via retrograde Diels–Alder reaction has been demonstrated. Reactions of the azadiene with monosubstituted olefins are both stereo- and regiospecific, yielding only the endo-5-substituted 1-azanorbornenes. The rates of the reactions of norbornadiene and styrene with the azadiene and hexachlorocyclopentadiene are compared and their relative reactivity discussed.

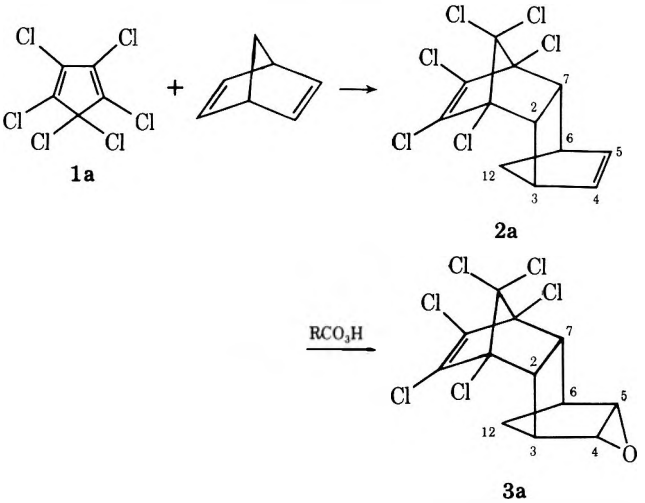
The enormous preparative importance of the Diels–Alder reaction is based on the range of variations of both the dienes and dienophiles. Dienes containing one heteroatom for the synthesis of heterocyclic compounds are uncommon, except for the 1-oxadienes such as acrolein.[2] The 1-azadiene, as a Diels–Alder diene, is conspicuously absent in the recent literature. The unreactive nature of this diene system was shown by Snyder et al.,[3] who reported that certain conjugated anils (–N=C–C=C–CH–) reacted with maleic anhydride via the enamine form (–NHC=C–C=C–) to yield an amino-substituted cyclohexane adduct, and that *N*-cinnamylideneaniline did not react since it has no γ hydrogen to tautomerize. In a review article[4] on the Diels–Alder synthesis with heteroatomic addends, there are ten references cited concerning the unsuccessful attempts to synthesize pyridine derivatives using anils as dienes. A few successful examples are also known where the azadiene is part of an extensive π system.[2] More recently, it has been observed that *N*-cinnamylideneaniline reacts with ketene to form the normal [4 + 2] dihydropyridone adduct.[5] However, reaction of *N*-cinnamylidenemethylamine with *N*-methylmaleimide was found to proceed in a non-Diels–Alder manner to yield a 1:2 adduct.[6] It therefore appears that the course of cycloaddition reactions with a 1-azadiene may be determined by the choice of diene, dienophile, and reaction conditions.

For a variety of synthetic goals to prepare polycyclic amines with bridgehead nitrogen, a one-step synthesis starting from cyclic 1-azadienes in Diels–Alder reaction would be particularly useful. As part of our continuing program[1] to study the reactivities and properties of α- and β-pyrrolenines (1- and 2-azadienes, respectively, in the cyclic form), we have discovered that 2,3,4,5,5-pentachloro-1-azacyclopentadiene (pentachloro-α-pyrrolenine, **1**)[7] reacts in typical Diels–Alder manner to yield polycyclic amine adducts. Thus, we have prepared polycyclic amines which are bridgehead aza analogues of the commercial insecticides aldrin and dieldrin as well as several 5-substituted 1-azanorbornenes. This paper describes the structural analysis of these polycyclic amines and the reactivity, stereospecificity, and regiospecificity of the cyclic azadiene **1** in the Diels–Alder reaction.

Results and Discussion

Synthesis and Structure of Azaaldrin (2) and Azadieldrin (3). An example of the preparative significance of the Diels–Alder reaction can be seen in the once popular insecticides aldrin (**2a**) and dieldrin (**3a**). Heating hexachlorocyclopentadiene (**1a**) in excess norbornadiene at 90 °C produces aldrin (**2a**)[8] in quantitative yield and peracid oxidation of **2a** forms the monoepoxide dieldrin (**3a**)[9] as shown in Scheme I. Structure **2a** was established for aldrin by a x-ray

Scheme I



crystallographic analysis,[10] and the exo configuration of the epoxide ring in **3a** was assigned on the basis of NMR studies.[11,12] By patterning on Scheme I, 2,3,4,5,5-pentachloro-1-azacyclopentadiene (**1**) was heated in excess norbornadiene at 90 °C for 24 h to yield an adduct (~80% yield after recrystallization) which analyzed correctly for $C_{11}H_8NCl_5$ as azaaldrin. Its IR spectrum (KBr) ν_{C-H} 3050, 2990, 2900, δ_{C-H} 1475, 720, $\nu_{C=C}$ 1615, and ν_{C-N} 1150 cm^{-1}, is almost superimposable on that of aldrin (**2a**). Of the four structural candidates for azaaldrin shown in Scheme II, viz., endo-exo (2β,3β,6β,7β,8α) **2**, exo-endo (2α,3β,6β,7α,8α) **2b**, endo-endo (2β,3α,6α,7β,8α) **2c**, and exo-exo (2α,3α,6α,7α,8α) **2d**, the Diels–Alder "endo" adduct **2** is favored by analogy to aldrin.[10] Also shown in Scheme II is the exo epoxidation of **2** to yield azadieldrin **3** in a *m*-chloroperbenzoic acid–methylene chloride mixture at 25 °C. The structural assignments of **2** and **3** are substantiated by NMR studies. In Table IA are tabulated the ^1H NMR spectra of aldrin (**2a**), azaaldrin (**2**), dieldrin (**3a**), and azadieldrin (**3**), and Table IB shows the ^{13}C NMR spectra of the same. The spectral assignments for aldrin and dieldrin are in accordance with literature.[11,12] Similarly, the assigned proton and carbon chemical shifts for the aza analogues are compatible with structures **2** and **3**.

Confirmation of the above NMR assignments was sought by analyzing the characteristic patterns due to the two C-12 methylene protons of **2** and **3** (syn and anti relative to the 4,5 double bond or epoxide). It was reported by several groups[11] that in aldrin (**2a**) H-12 anti can be decoupled from the vinyl protons to resolve one of the pairs of broadened doublets into a doublet of triplets which are attributed to the coupling of H-12 anti to H-3 and H-6. Also, the broadened doublet of H-12

Table I. NMR Spectra of Azaaldrin, Azadieldrin, and the Carbocycle Analogues

Hydrogen or carbon	δ ($CDCl_3$, Me_4Si = 0), J Hz			
	Aldrin (2a)	Azaaldrin (2)	Dieldrin (3a)	Azadieldrin (3)
	A. ^1H NMR Spectra			
2	2.68 s	2.88 d, 8	2.67 m	2.88 d, 7
3	2.87 s[a]	3.12 s[a]	2.70 s[a]	2.87 s[a]
4	6.30 m	6.28 m	3.12 s[a]	3.14 d, 3.5
5	6.30 m	6.28 m	3.12 s[a]	3.09 d, 3.5
6	2.87 s[a]	2.90 s[a]	2.70 s[a]	2.66 s[a]
7	2.68 s	2.68 d, 8	2.67 m	2.67 d, 7
12 syn	1.28 d, 11	1.27 d, 12	1.14 d, 13	1.23 d, 12
12 anti	1.63 d, 11	2.02 d, 12	0.97 d, 13	1.48 d, 12
	B. ^{13}C NMR Spectra			
2	54.50 d, 150	54.19 d, 150	53.56 d, 140	53.31 d, 150
3	40.82 d, 150	41.34 d, 145	36.98 d, 145	37.30 d, 145
4	141.04 d, 175	140.81 d, 175	51.09 d, 195	50.89 d, 200
5	141.04 d, 175	140.81 d, 175	51.09 d, 195	50.49 d, 200
6	40.82 d, 150	40.81 d, 145	36.98 d, 145	36.90 d, 145
7	54.50 d, 150	53.30 d, 150	53.56 d, 140	52.04 d, 150
12	40.69 t, 130	41.50 t, 140	20.41 t, 140	21.00 t, 140

[a] Broad singlet.

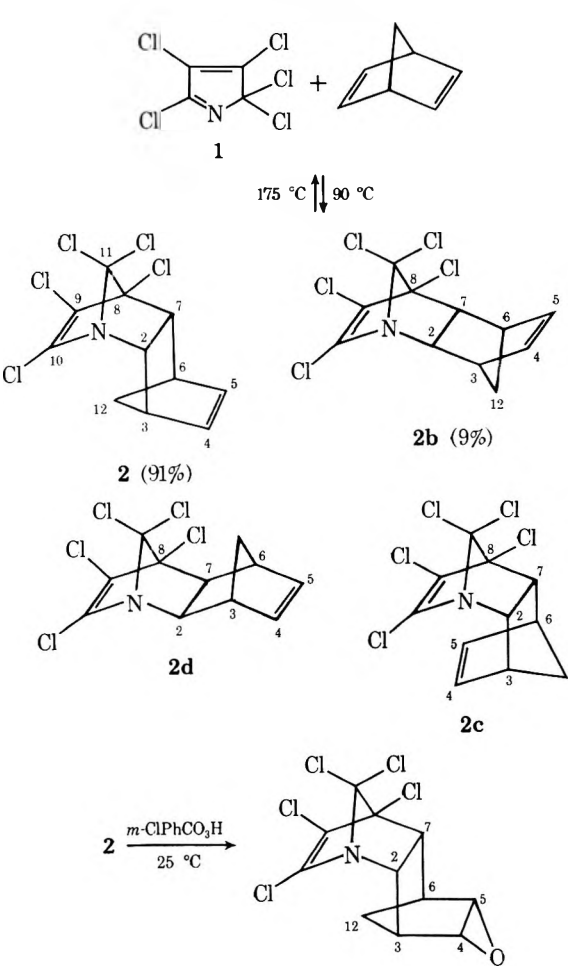
anti of dieldrin (**3a**) can be resolved by decoupling the long-range W-shape coupling between H-12 anti and H-4, H-5 of the epoxide ring.[11] The decoupled spectra clearly identify the H-12 anti doublet in each case. (See paragraph at end of paper regarding supplementary material.) The great resemblance of these decoupled partial spectra for **2** and **2a** as well as for **3** and **3a** gives support to the structural assignments of **2** and **3**. The apparent anomaly of H-12 anti of dieldrin (**3a**) appearing at higher field than H-12 syn, while the reverse is true in azadieldrin (**3**), is explained as follows. The upfield shift of the C-12 methylene hydrogens in **3a** compared to those in **2a**, Δδ anti 0.66 ppm and Δδ syn 0.14 ppm, can be attributed to steric compression of these hydrogens by the exo epoxide in **3a**.[11b] Similar upfield shifts in azadieldrin (**3**) are Δδ anti 0.55 ppm and Δδ syn 0.04 ppm. The apparent reversal of H-12 anti and H-12 syn in **3a** but not in **3** can be traced to the original separation of these two resonances in **2** of 0.75 ppm but only 0.35 ppm in **2a**.

Although treatment of azaaldrin (**2**) with the europium shift reagent did not produce any shift in the ^1H NMR spectrum, addition of $Eu(fod)_3$ to azadieldrin (**3**) did. A plot of the proton chemical shifts of **3** vs. equivalents of $Eu(fod)_3$ gave the following slopes: H-12 syn (29.4), H-4,5 (16.2), H-3 (15.2), H-6 (15.0), H-12 anti (12.7), H-2 (10.8) and H-7 (10.5). (See paragraph at end of paper regarding supplementary material.) These data are compatible with structure **3** with the europium atom attached to the oxygen lone pair anti to H-4,5 which is sterically most accessible.

Equilibration of Azaaldrin (2) with Isoazaaldrin (2b). For many cyclopentadiene–cyclic dienophile combinations, the endo adduct is the kinetically controlled product, and the exo isomer sometimes the thermodynamically more stable one.[13] We have scrutinized the crude reaction mixture from which azaaldrin was isolated by means of GLC analysis. The chromatogram revealed two peaks (t_R 17.4 and 18.5 min) in a 91:9 ratio. Azaaldrin (**2**), after recrystallization from acetone–water, showed only the shorter retention time peak. Preparatory high-pressure liquid chromatography allowed the collection of the minor product, which analyzed correctly for $C_{11}H_8NCl_5$. This adduct is therefore isoazaaldrin, an isomer of azaaldrin (**2**). The same analytical techniques, when applied to the Diels–Alder reaction mixture of aldrin, showed no other products but aldrin itself.

Among the three theoretically possible adducts other than **2** shown in Scheme II, the exo-exo adduct **2d** is sterically unlikely, while the endo-endo adduct **2c** is the aza analogue of isodrin. The latter is not formed in the aldrin synthesis and is known to cyclize to a caged compound upon irradiation.[14] When isoazaaldrin was irradiated under conditions sufficient to cause cyclization of isodrin in <10 min (high-pressure

Scheme II

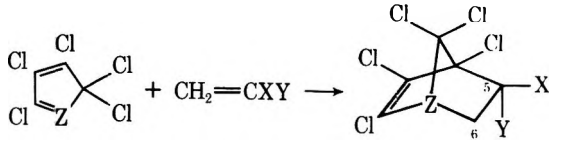


mercury lamp with Pyrex filter using acetone as medium), no reaction was observed even after 1 h. This leaves **2b** as the most plausible candidate for isoazaaldrin. The ^{1}H NMR spectrum, δ 1.38 (d, 2 H, J = 7 Hz, H-12), 2.71 (d, 1 H, J = 7 Hz, H-7), 2.85 (s, 1 H, H-6), 2.90 (d, 1 H, J = 7 Hz, H-2), 3.15 (s, 1 H, H-3), 6.38 (m, 2 H, H-4,5), is consistent with the assignment of **2b.** Particularly, the vinyl resonance is of diagnostic value. Comparing isodrin to aldrin, $\Delta\delta$ H-4,5 0.30 ppm upfield, the vinyl hydrogens in isodrin at δ 6.00[14] are shielded by the stacking dichlorovinyl moiety. However, the same comparison for isoazaaldrin and azaaldrin shows that H-4,5 in isoazaaldrin are deshielded by 0.1 ppm; hence the latter compound is incompatible with structure **2c.**

Azaaldrin (**2**) was found to be stable when heated at its melting point at 99 °C. However, pyrolysis of **2** in a sealed tube at 175 °C for 24 h led to 12% decomposition to nonvolatiles, and the remainder showed the same two peaks for **2** and **2b** on the gas chromatogram in the same 91:9 ratio as did the original reaction mixture. This indicates that an equilibrium was reached between the more stable endo-exo adduct **2** and its exo-endo isomer **2b.** This thermal conversion of **2** to **2b** is analogous to the isomerization of some strained endo Diels–Alder adducts to the exo isomers via a retrograde Diels–Alder reaction.[13] Thus, the dissociation of **2** to the azadiene **1** and norbornadiene was followed by forward Diels–Alder reaction to re-form **2** and **2b** in the same ratio. The remarkably low degree of polymerization when **2** was subjected to prolonged pyrolysis and the reversibility shown by the equilibration between **2** and **2b** indicate a normal diene character for the cyclic azadiene **1** in Diels–Alder reaction.

Synthesis of 5-Substituted 2,3,4,7,7-Pentachloro-1-azanorbornenes. Both regiospecificity and endo stereospecificity in the Diels–Alder reaction of 2,3,4,5,5-pentachloro-1-azacyclopentadiene (**1**) with unsymmetrical dienophiles are apparent from the reactions summarized in Scheme III. Thus, reactions of **1** with vinyl chloride, styrene, isobutylene, and α-methylstyrene led to the exclusive formation of the 5-substituted adducts, **4, 5, 6,** and **7,** respectively. Although the yields of these adducts are 9–62%, chromatographic analysis (gas–liquid phase and high-pressure liquid) of the reaction mixtures did not show other product peaks with reasonable retention times. Cycloaddition of **1** with ethylene itself to yield pentachloro-1-azanorbornene (**8**) was also carried out as a point of reference. The corresponding carbocyclic analogues **4a, 5a, 6a, 7a,** and **8a** as adducts of hexachlorocyclopentadiene are known,[15–18] and they were prepared for NMR comparisons. Comparison of the ^{1}H NMR spectra of the four 5-substituted norbornene pairs shows $\Delta\delta$ (N–CCl) range for H-5 exo −1.2 to −4.8 Hz, H-6 exo +7.2 to +10.2 Hz, and H-6 endo +11.4 to +12.6 Hz, and that the nitrogen atom induced shifts are consistently deshielding for the 6-methylene hydrogens but slightly shielding for the 5-methine hydrogen. (See paragraph at end of paper regarding supplementary material.) In order to ascertain that the 5 substituents are not contributing to these $\Delta\delta$ values, the proton spectra of the ethylene adducts **8** and **8a** are compared. The spectrum of the azanorbornene **8** showed a tightly coupled ABCD pattern, and was analyzed using the iterative computer program LAOCN3 executed on a DEC 1080 computer. (See paragraph at end of paper regarding supplementary material.) The average probable error of the parameter sets in this simulation is 0.061. The AA′BB′ spectrum of the carbocycle analogue **8a** was reported by Fay et al.[19] Thus, the $\Delta\delta$(N–CCl) values for **8** and **8a** are H-5 exo −0.96 Hz, H-5 endo, −2.76 Hz, H-6 exo +7.6 Hz, and H-6 endo +11.5 Hz, quite comparable to those of the 5-substituted pairs. It appears that the downfield shifts of the C-6 methylene protons may be attributable to the predominance of the inductive withdrawing effect of the bridgehead nitrogen, while the difference in induced shifts for H-6 exo and H-6 endo may be the result of changing anisotropies. It has been shown that the diamagnetic shielding by a nitrogen lone pair is the cause of chemical shift differences between certain axial and equatorial protons in a number of polycyclic amines.[20] Otherwise, bond rehybridizations due to shorter C–N bond compared to C–C bond[21] and electrostatic field effects of the lone pair are also perturbing factors in induced shifts. The small upfield shifts observed for the C-5 hydrogens may be due to a combination of these factors, although their relative contributions have not been sorted out. The consistent trend of these nitrogen-induced shifts therefore lends strong support to the structural assignments of the 5-substituted 1-azanorbornenes shown in Scheme III.

Scheme III



			Z = N	Z = CCl	
(i)	X = H; Y = Cl	110 °C, 53%	4	4a	(ref 15)
(ii)	X = H Y = Ph	135 °C, 62%	5	5a	(ref 16)
(iii)	X = Y = Me	100 °C, 34%	6	6a	(ref 17)
(iv)	X = Me; Y = Ph	110 °C, 9%	7	7a	(ref 17)
(v)	X = Y = H	95 °C, 26%	8	8a	(ref 18)

A comparison of the methylene resonances of the isobutylene adduct **6** with those of the α-methylstyrene adduct **7** (cf. supplementary material) demonstrates the endo preference of the cycloadducts. While $\Delta\delta$ of H-6 exo is only 0.11 ppm, $\Delta\delta$ of H-6 endo is 1.18 ppm. The large downfield shift of H-6 endo of **7** is best accounted for by the endo benzene ring. Also, the methylene peaks of the exo-phenyl epimer of the carbocycle **7a** at δ 3.495 (H-6 exo) and 2.125 (H-6 endo) as reported by Mark[17] are drastically different from those of **7,** thereby confirming the endo phenyl configuration in **7.** Furthermore, the europium shift behavior of this 1-azanorbornene is worthy of note. While azaaldrin (**2**) was not shifted at all by several shift reagents, addition of 0.3 equiv of Eu(fod)$_3$ to **7** led to induced shifts of 7 and 5 Hz for H-6 endo and H-6 exo, respectively. The slopes of the linear curves relating induced shifts to equivalents of europium are 23 for the endo and 17 for the exo hydrogen. The greater change for the endo hydrogen seems to indicate that the steric bulk of Eu(fod)$_3$ and the norbornenyl bridgehead nitrogen require the shift reagent to approach **7** from the less hindered endo face of the molecule rather than along the axis of the nitrogen lone pair. Such behavior has been reported for other sterically hindered heteroatom–shift reagent complexes.[22] The small absolute magnitude of the induced shifts reflects weak complex formation due to the large steric requirement of both the shift reagent and the substrate.

Relative Reactivity of Pentachloro-1-azacyclopentadiene (1) and Hexachlorocyclopentadiene (1a). Alder[23] classified hexachlorocyclopentadiene (**1a**) as "the diene with the highest possible addition ability", implying an inverse electron demand on the dienophile. Mark[24] reported that reactions of **1a** with a number of electron-deficient trans-1,2-disubstituted ethylene derivatives gave appreciable amounts of the cis adducts via stepwise reactions, while

Table II. Rates of Diels–Alder Reaction of 1 and 1a at 90 °C[a]

Diene	Dienophile	k, s^{-1}	Rel rates
1a	Norbornadiene	1.04×10^{-4}	2.16
1	Norbornadiene	4.82×10^{-5}	1
1a	Styrene	4.36×10^{-4}	7.87
1	Styrene	5.54×10^{-5}	1

[a] Diene:dienophile 1:4; disappearance of dienes and formation of products were followed by GLC and peak areas plotted as ln A^0/A vs. time. The pseudo-first-order rate constants were determined by a least-squares curve fit program.

electron-rich trans-1,2-disubstituted dienophiles, such as *trans*-2-butene, added stereospecifically and concertedly. However, attempted reactions of 1 with a variety of trans-disubstituted dienophiles such as *trans*-β-methylstyrene, methyl crotonate, and *trans*-1,2-dichloroethylene gave no adducts, indicating the decreased reactivity of 1 relative to **1a**. No reaction was observed for 1 with either maleic anhydride or *N*-phenylmaleimide at temperatures to 175 °C. More electron-rich cis-disubstituted olefins such as norbornadiene or monosubstituted olefins as shown in Scheme III reacted with 1 to yield Diels–Alder adducts, albeit slower than the corresponding reactions with **1a**. Using norbornadiene and styrene as the dienophiles, these two diene systems are compared quantitatively as shown in Table II. Given the assumption that these reactions are frontier orbital controlled,[25] it can be inferred from the rate ratios of 2.16 and 7.87 (**1a**:1) that either the LUMO of 1 is of higher energy than the LUMO of **1a** or that the atomic coefficients in the LUMO of 1 are uniformly smaller than those in the LUMO of **1a**.

Experimental Section

^{1}H NMR spectra were obtained using a Varian A-60A spectrometer or a Perkin-Elmer R-12 spectrometer. The 100-MHz proton spectrum of 8 was obtained on a JEOL FX-100 spectrometer, courtesy of JEOL Analytical Instruments, Inc., Cranford, N.J. ^{13}C NMR spectra were determined on a Varian CFT-20 spectrometer, courtesy of University of Kentucky, Lexington, Ky. NMR samples were prepared as 0.5 M solutions in $CDCl_3$ containing 1% tetramethylsilane [δ (Me_4Si = 0)]. IR spectra were run on a Beckman IR-12. GLC analyses were performed on a Hewlett-Packard 5750 B chromatograph with dual flame ionization detector. All analyses were done on a 6 ft × 0.25 in. aluminum column packed with 20% SE-30 on Chromosorb W AW DMCS and at 30 ml/min of nitrogen, T_I = 270 °C, T_D = 240 °C, T_C = 170 °C (unless otherwise noted). High-pressure liquid chromatography was done on a Waters Associates instrument (M6000 pump, U6K injector) using a μ-porasil column, chloroform as solvent, and 254-nm UV detector. Melting points are uncorrected. Combustion analyses were performed by either Midwest Microlab, Ltd., Indianapolis, Ind., or M-H-W Laboratories, Garden City, Mich.

(2β,3β,6β,7β,8α)-8,9,10,11,11-Pentachloro-1-azatetracyclo-[6.2.1.1^{3,6}.0^{2,7}]dodeca-4,9-diene (Azaaldrin, 2). To 6.5 g (27 mmol) of pentachloro-1-azacyclopentadiene (1)[7] was added 9.1 g (108 mmol, 4 equiv) of bicyclo[2.2.1]hepta-2,5-diene, and the mixture was refluxed for 24 h. The dark brown reaction mixture containing the product, T_R 17.5 min, 91%, and an isomer, T_R 18.5 min, 9%, was evaporated, and the residue chromatographed on 100 g of silica gel in hexane. The eluent was evaporated, and the light orange residue was recrystallized from acetone–water to yield 6.83 g (76.3%) of white, crystalline product: mp 97–99 °C; NMR as shown in Table I.

Anal. Calcd for $C_{11}H_8NCl_5$: C, 39.81; H, 2.41; N, 4.22. Found: C, 39.99; H, 2.22; N, 4.06.

The isomer (isoazaaldrin, **2b**) was isolated from the reaction mixture by high-pressure liquid chromatography using two 18 × 0.25 in. preparative columns packed with 14 g each of Porasil A (35–75 μ) in series, eluted with chloroform at 6 mL/min. The eluent was evaporated and the residue crystallized from ethanol–water yielding a white, crystalline product: mp 105–107 °C; NMR described in text.

Anal. Calcd for $C_{11}H_8NCl_5$: C, 39.81; H, 2.41; N, 4.22. Found: C, 40.22; H, 2.37; N, 4.37.

(2β,3β,6β,7β,8α)-*exo*-4,5-Epoxy-8,9,10,11,11-pentachloro-1-azatetracyclo[6.2.1.1^{3,6}.0^{2,7}]dodec-9-ene (3). To 6 g (18 mmol) of (2β,3β,6β,7β,8α)-8,9,10,11,11-pentachloro-1-azatetracyclo[6.2.1.1^{3,6}.0^{2,7}]-dodeca-4,9-diene (azaaldrin, **2**) in 50 mL of methylene chloride was added 3.90 g (21 mmol, 1.25 equiv) of *m*-chloroperbenzoic acid. The homogeneous solution was allowed to stand for 5 days at 22–24 °C. The solution was extracted with 3 × 50 mL of 5% $NaHSO_3$, 6 × 50 mL of 5% $NaHCO_3$, and 2 × 50 mL of water. The methylene chloride layer was dried and evaporated, and the solid residue recrystallized from ethanol–water to yield 5.9 g (94.4%) of white, crystalline **3**: mp 158.5–160 °C; IR (KBr) 2990, 2960, 2900 (C–H stretch), 1475 (C–H bend), 1575 (Cl–C=C–Cl stretch), 1150 cm^{-1} (C–N stretch); NMR as shown in Table I.

Anal. Calcd for $C_{11}H_8NOCl_5$: C, 37.98; H, 2.30; N, 4.02. Found: C, 38.24; H, 2.21; N, 3.82.

2,3,4,5-*endo*,7,7-Hexachloro-1-azabicyclo[2.2.1]hept-2-ene (4). Pentachloro-1-azacyclopentadiene (1,[7] 1.17 g, 4.9 mmol) and vinyl chloride (0.62 g, 9.9 mmol) were dissolved in 5.6 mL of toluene and the solution was heated under nitrogen in a sealed tube at 110 °C for 96 h. The brown reaction mixture was decolorized and the toluene removed in vacuo. The yellow residue was recrystallized from ethanol–water to yield 0.78 g (53%) of white, crystalline **4**: mp 88–90 °C; NMR as shown in Table II.

Anal. Calcd for $C_6H_3NCl_6$: C, 23.84; H, 0.99; N, 4.64. Found: C, 23.80; H, 1.02; N, 4.56.

***endo*-5-Phenyl-2,3,4,7,7-pentachloro-1-azabicyclo[2.2.1]hept-2-ene (5).** A mixture of 4.92 g of pentachloro-1-azacyclopentadiene (1, 20.5 mmol) and 2.14 g (20.5 mmol) of styrene was heated at 135 °C for 24 h. The dark brown reaction mixture was molecularly distilled at 130 °C (2 mmHg) to afford 4.403 g (62%) of a clear, pale yellow liquid which solidified on standing overnight at −20 °C: mp 56–60 °C; NMR δ 2.68 (q, 1 H, J_{AB} = −14 Hz), 3.02 (q, 1 H, J_{BX} = 9.4 Hz), 3.90 (q, 1 H, J_{AX} = 4.6 Hz), 7.10–7.50 (m, 5 H).

Anal. Calcd for $C_{12}H_8NCl_5$: C, 41.96; H, 2.35; N, 4.08. Found: C, 41.78; H, 2.56; N, 3.95.

5,5-Dimethyl-2,3,4,7,7-pentachloro-1-azabicyclo[2.2.1]hept-2-ene (6). To an excess (~0.5 g, 9 mmol) of isobutylene condensed at −78 °C in an 8-mm i.d. heavy-walled glass tube was added 0.492 g (2.05 mmol) of pentachloro-1-azacyclopentadiene (**1**).[7] The tube was sealed under reduced pressure and heated at 100 °C for 72 h. The tube was opened and evaporated, and the liquid which remained was dissolved in 1 mL of a 19:1 isooctane–chloroform mixture and chromatographed on 50 g of silica gel in the above solvent system. The 50:50 isooctane–chloroform eluent containing the product was decolorized, filtered, and evaporated to provide 0.206 g (34%) of a white solid: mp 95–99 °C; NMR δ 1.12 (s, 3 H), 1.51 (s, 3 H), 2.17 (d, 1 H, J = −14.0 Hz), 2.68 (d, 1 H, J = −14.0 Hz).

Anal. Calcd for $C_8H_8NCl_5$: C, 32.53; H, 2.73; N, 4.74. Found: C, 32.71; H, 2.73; N, 4.67.

***exo*-5-Methyl-*endo*-5-phenyl-2,3,4,7,7-pentachloro-1-azabicyclo[2.2.1]hept-2-ene (7).** A solution of pentachloro-1-azacyclopentadiene (1, 2.46 g, 10.3 mmol) and α-methylstyrene (1.21 g, 10.3 mmol) in 20 mL of freshly distilled toluene was heated at reflux for 42 h. The solvent was evaporated, the residue dissolved in 1 mL of distilled hexane, and the solution chromatographed on 50 g of silica gel. The eluent containing the product was filtered and evaporated to provide 0.341 g (9.3%) of a white solid: mp 75–79 °C; NMR δ 1.96 (s, 3 H), 3.35 (d, 1 H, J = −14 Hz), 2.79 (d, 1 H, J = −14 Hz), and 7.20–7.60 (m, 5 H).

Anal. Calcd for $C_{13}H_{10}NCl_5$: C, 43.72; H, 2.82; N, 3.91. Found: C, 43.71; H, 2.91; N, 3.92.

2,3,4,7,7-Pentachloro-1-azabicyclo[2.2.1]hept-2-ene (8). To 12 mmol of freshly distilled 1,2-dimethoxyethane saturated with ethylene was added 2.13 g (89 mmol) of pentachloro-1-azacyclopentadiene (**1**).[7] The solution was sealed in a heavy-walled glass tube, and the mixture was heated at 95 °C for 70 h. The tube was opened and evaporated, and the brown residual liquid was chromatographed on 50 g of silica gel. Elution with chloroform–hexane (7:3) afforded a fraction containing the product. This was decolorized, filtered, and evaporated to provide a white solid (0.672 g, 26%). Sublimation of this material provided an analytical sample of the adduct: mp 66–71 °C; NMR as shown in Table II.

Anal. Calcd for $C_6H_4NCl_5$: C, 26.95; H, 1.51; N, 5.24. Found: C, 26.82; H, 1.96; N, 5.10.

Acknowledgment. This investigation was supported in part by NIH Grant GM 19212, for which we are grateful. The authors wish to thank Professor Stanford Smith and Mr. John Layton, Department of Chemistry, University of Kentucky,

for running the ^{13}C NMR spectra and the simulation plot of the proton spectrum of 8. We also thank Mr. Koji Goto of JEOL Analytical Instruments for running the 100-MHz proton spectrum of 8.

Registry No.—**1**, 57802-40-1; **2**, 61473-88-9; **2b**, 61473-89-0; **3**, 61473-90-3; **4**, 61394-83-0; **5**, 61394-84-1; **6**, 61394-85-2; **7**, 61394-86-3; **8**, 61394-87-4; bicyclo[2.2.1]hepta-2,5-diene, 121-46-0; *m*-chloroperbenzoic acid, 937-14-4; vinyl chloride, 75-01-4; styrene, 100-42-5; isobutylene, 115-11-7; α-methylstyrene, 98-83-9; ethylene, 74-85-1.

Supplementary Material Available. Normal and decoupled ^1H NMR spectra of **2**, **2a**, **3**, and **3a** in the C-12 methylene region, a plot of chemical shift of 3 protons vs. equivalents of $Eu(fod)_3$, the 100-Hz ^1H NMR of 8 and the simulated spectrum of 8, and ^1H NMR data for the compounds **4**–**8** and **4a**–**8a** (4 pages). Ordering information is given on any current masthead page.

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Cyclophanes. 10.[1] Synthesis and Conformational Behavior of [2.2](2,5)Pyrrolophanes[2]

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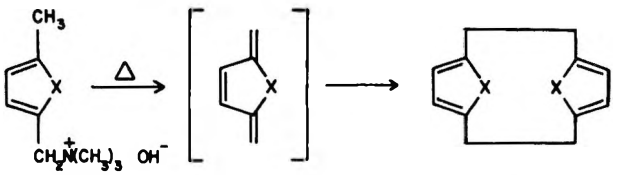
Received October 18, 1976

Attempted synthesis of [2.2](2,5)pyrrolophanes by 1,6-Hofmann elimination proved unsuccessful and led only to dipyrrolmethanes. [2.2](2,5)Pyrroloparacyclophane (**11a**), [2.2](2,5)pyrrolo(1,4)naphthalenophane (**12a**), and [2.2](2,5)pyrrolo(2,5)furanophane (**13a**) were prepared by Paal–Knorr cyclization of 3,6-diketo[8]paracyclophane (**10a**), 3,6-diketo[8](1,4)naphthalenophane (**10b**), and 3,6-diketo[8](2,5)furanophane (**10c**), respectively, with ammonia. Preparation of the analogous *N*-methyl derivatives **11b**, **12b**, and **13b** by Paal–Knorr cyclization using methylamine was successful only for the synthesis of *N*-methyl[2.2](2,5)pyrroloparacyclophane (**11b**). *N*-Methyl[2.2](2,5)pyrrolophane (**17a**) and *N*-benzyl[2.2](2,5)pyrrolophane (**17b**) were also synthesized by Paal–Knorr cyclization of 1,4,7,10-cyclododecatetraone by successive treatment with the appropriate alkylamine and ammonia. Reductive cleavage of the benzyl group in **17b** with sodium afforded the parent [2.2](2,5)pyrrolophane (**1**). The spectral properties and structural assignment of the above pyrrolophanes are discussed. Variable temperature NMR studies on the above pyrrolophanes indicated that all aromatic rings in the above phanes are conformationally rigid on the NMR time scale with the exception of the pyrrole ring in **11a**. In this pyrrolophane the barrier to pyrrole ring rotation is 17 kcal/mol.

In the past two and one-half decades a substantial literature has accumulated concerning the synthesis and properties of cyclophanes.[4] The syntheses of [2.2]cyclophanes containing heteroaromatic nuclei have been extensively recorded and among some of the common heteroaromatic groups which have been incorporated into the cyclophane macrocycle are furan,[5] thiophene,[5a,6] pyridine,[7] and pyridazine.[7a,8] However, conspicuously absent from these ranks are those containing the pyrrole moiety.[9] Indeed, except for the recent synthesis of *N,N'*-dimethyl[2.2](2,5)pyrrolophane (**2**)[10] the literature is devoid of reports concerning [2.2]pyrrolophanes. Of special interest is the parent phane, [2.2](2,5)pyrrolophane (**1**). On the basis of relative properties, general chemical behavior, and stability,[11] pyrrole, like the analogous furan and thiophene ring systems, ought to exist as a stable aromatic entity within a [2.2]cyclophane macrocycle. Additionally, in view of the contemporary interest in rotational behavior of aromatic moieties within [2.2]cyclophanes,[12] the dynamic behavior of [2.2](2,5)pyrrolophanes, as compared with [2.2](2,5)furanophanes, [2.2](2,5)thiophenophanes, [2.2](2,6)pyridinophanes, and other [2.2]metaphanes, would prove of interest in defining the relative steric bulk and intramolecular interactions of an N–H and N⁻ grouping as compared with O:, S:, N:, and C–H groupings during the rotational process in which these groups pass through the cavity of the cyclophane macrocycle. In view of the above we undertook the synthesis of a number of pyrrolophanes.

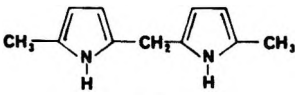
Hofmann Pyrolytic Route. Previous successful use of a 1,6-Hofmann elimination reaction on the appropriate quaternary ammonium hydroxide for the synthesis of **3**[5a] and **4**[5a] (see Scheme I) prompted us to attempt the synthesis of **2** by this method. A procedure quite analogous to that traditionally

Scheme I



5 a X=O
b X=S
c X=N-H

1 X=N-H
2 X=N-CH$_3$
3 X=O
4 X=S

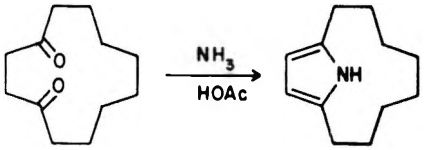


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followed was used with the modification of strict exclusion of light and oxygen. However, pyrolysis of quaternary ammonium hydroxide **5c** afforded one major product in low yield, dipyrrylmethane **6**, but none of the expected pyrrolophane was observed.

Paal–Knorr Cyclization Route. This successful synthetic approach to the [2.2](2,5)pyrrolophanes is based on work of Nozaki[9b] and Wasserman[10a] in which the former synthesized [8](2,5)pyrrolophane (**7**) by cyclization of 1,4-cyclododecadione with ammonia (see Scheme II) and the latter synthesized *N*-methyl-3,6-diketo[8]pyrrolophane (**8**) and *N,N'*-

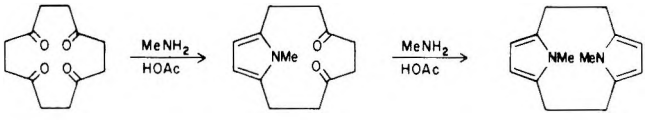
Scheme II



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dimethyl[2.2](2,5)pyrrolophane (**2**) by cyclization of 1,4,7,10-cyclododecatetraone with methylamine (see Scheme III). Since the requisite 1,4-diketone synthon necessary for

Scheme III

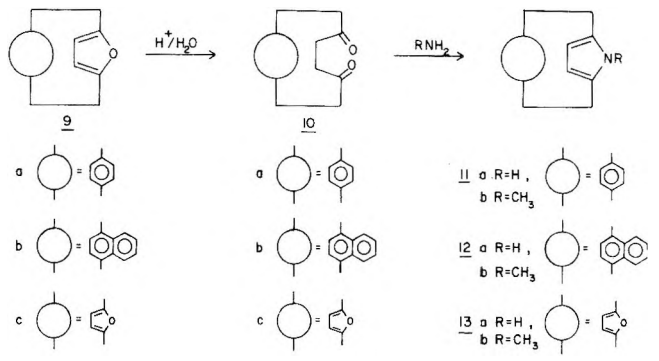


15 8 2

cyclization was potentially available from the furan containing phanes by hydrolysis, a series of mixed [2.2](2,5)pyrrolophanes was synthesized initially.

A. Pyrrolophanes from 3,6-Diketo[8]phanes. In general, the synthetic scheme (see Scheme IV) involved generating the

Scheme IV



9 10

11 a R=H, b R=CH$_3$
12 a R=H, b R=CH$_3$
13 a R=H, b R=CH$_3$

γ-diketone **10** from the appropriate furanophane **9** by acid hydrolysis in the absence of light and oxygen. The crystalline diketones were then cyclized to the pyrrolophanes by treatment with ammonia via a Paal–Knorr reaction.[11a] Thus 3,6-diketo[8](1,4)naphthalenophane (**10b**) and 3,6-diketo[8](2,5)furanophane (**10c**) were synthesized in 71 and 68% yield, respectively, as had been done previously by Cram[5b] for 3,6-diketo[8]paracyclophane (**10a**), by refluxing **9b** and **9c**, respectively, for 18 h at 105 °C and 17 h at 55 °C in an acetic acid/water/sulfuric acid medium.

Treatment of **10a, 10b,** and **10c** with ammonia in acetic acid at 80 °C in the dark under nitrogen followed by workup and chromatography afforded pyrrolophanes **11a, 12a,** and **13a** in 55, 86, and 67% yields, respectively.

The reaction of diones **10** with the more bulky methylamine was successful only for the preparation of *N*-methyl[2.2](2,5)pyrroloparacyclophane (**11b**) and as expected the reaction required elevated temperatures. Thus, when **10a** was treated with methylamine in acetic acid at 105 °C, **11b** was formed in 53% yield. While the reaction of methylamine with **10b** and **10c** was also carried out at higher temperatures only starting materials were recovered. The reason for the nonreactivity of **10b** and **10c** toward methylamine is not fully understood but is probably due, in the former, to the increased interaction of the *N*-methyl group with the outer fused portion of the naphthalene ring during the attack of the amine on the carbonyl. This steric interaction would be even more important during ring closure. What is surprising is that this does not force the formation of a *syn*-*N*-methyl[2.2](2,5)pyrrolo(1,4)naphthalenophane from **10b** and that the reaction does not take place with **10c**. That **10a** reacts while **10b** and **10c** do not may be indicative of an attractive or stabilizing influence by the benzene ring during the formation of the pyrrole ring.

As was expected, reaction of **10a, 10b,** and **10c** with the exceptionally bulky *tert*-butylamine afforded only starting material.

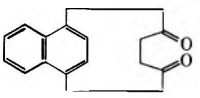
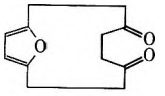
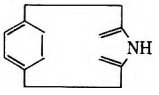
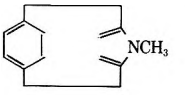
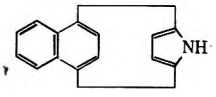
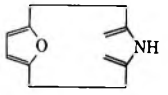
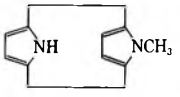
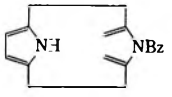
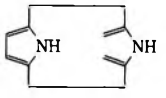
Characterization of 3,6-diketo[8]cyclophanes **10b** and **10c** followed from spectral analysis (see Table I) and the spectral data for **10b** and **10c** are consistent with the structures proposed. Of particular interest are the NMR spectra[13] of **10b** and **10c**, which indicate unrestricted conformational mobility of the furan ring in **10c** and the aliphatic chain in **10c** and **10b**, and restricted mobility of the naphthalene ring in **10b**.[14]

The assignment of structures to **11a,b, 12a,** and **13a** is based on spectroscopic analysis.[5b,c,10] All four pyrrolophanes exhibit mass spectral patterns which are typical for the cyclophane structure, i.e., a parent peak and major peaks corresponding to fragmentation of the molecule by cleavage of the two ethylene bridges. The band usually associated with transannular π–π interactions (244 nm) in the ultraviolet spectra of [2.2]cyclophanes[15] is only observed for **12a**; however, this band is sometimes not observed in [2.2]cyclophanes containing a five-membered heterocyclic nucleus.[5c] The presence of the pyrrole hydrogen is indicated by the sharp absorption at ca. 3400 cm^{-1} in the infrared spectra of all but **11b**.

The NMR spectra of **11a,b, 12a,** and **13a** conclusively prove the cyclophane structure of these compounds. The benzenoid protons in **11a** and **11b** appear as an AA'XX' multiplet suggesting that the two rings are frozen parallel to one another, thus allowing one side of the benzene ring to encounter a greater portion of the shielding effects of the pyrrole ring. This is in sharp contrast to [2.2](2,5)furanoparacyclophane **9a**, which exhibits, in its room temperature spectrum, a singlet for the benzenoid protons[5b,13] due to the rapid rotation of the furan nucleus.

Of greatest interest, and a fact which lends support to the above structures, is the chemical shift of the pyrrole hydrogen. The chemical shift for this proton in 2,5-dimethylpyrrole is τ 2.52.[16] In pyrrolophanes **13a, 11a,** and **12a**, respectively, this

Table I. Physical and Spectral Properties of [2.2](2,5)Pyrrolophanes

Compd	Structure	Mp, °C[a] (crystn solvent)	Yield,[b] %	NMR, τ[c]	IR, cm^{-1}[d]	UV, λ_{max}, nm (log ε)[e]	MS[f]
10b		158–159 (EtOH/H_2O)	71	2.2 (AA′BB′, 4 H) 2.83 (s, 2 H) 6.6 (m, 4 H) 7.55 (m, 4 H) 8.67 (m, 4 H)	1680 (C=O)	231 (4.65) 297.5 (3.70)	266, 168 144, 100
10c		109–110 (H_2O)	68	4.2 (s, 2 H) 7.45 (s, 4 H) 7.45 (AA′BB′, 8 H)	1700 (C=O)	222 (3.56) 292 (sh) (1.94)	206, 108 107, 99
11a		197–198 (hexane)	55	3.28 (AA′XX′, 4 H) 4.55 (d, 2 H, J = 2.5 Hz) 5.00 (broad s, 1 H) 7.4 (m, 8 H)	3400 (N–H)	219 (4.3) 269 (sh) (2.98) 286 (sh) (2.79)	197, 104 93
11b		212–214 (EtOH/H_2O)	53	3.46 (AA′XX′, 4 H) 4.4 (s, 2 H) 7.15 (m, 8 H) 7.5 (s, 3 H)		204.5 (3.99) 226.5 (3.89) 269 (sh) (2.75) 279 (sh) (2.61)	211, 107 104
12a		111–112 (EtOH/H_2O)	83	2.3 (AA′BB′, 4 H) 3.5 (s, 2 H) 4.5 (d, 2 H, J = 3.0 Hz) 6.2 (broad s, 1 H) 6.4 (m, 2 H) 7.5 (m, 6 H)	3450 (N–H)	226.5 (4.28) 243 (sh) (4.13) 301 (3.43)	247, 144 93
13a		131–132 (EtOH/H_2O)	65	3.6 (broad s, 1 H) 3.95 (s, 2 H) 4.05 (d, 2 H, J = 3.0 Hz) 7.35 (m, 8 H)	3408 (N–H)	222 (4.00)	187, 93 94
17a		78–79[g]	43	3.4 (broad s, 1 H) 3.71 (s, 2 H) 4.15 (d, 2 H, J = 2.9 Hz) 6.98 (s, 3 H) 7.15 (m, 8 H)	3450 (N–H)	204 (4.22) 219 (4.04) 240 (3.91)	200 107 93 92
17b		84–85[g]	17	3.45 (broad s, 1 H) 2.7–3 (m, 5 H) 3.8 (s, 2 H) 4.1 (d, 2 H, J = 2.6 Hz) 5.42 (s, 2 H) 7.27 (m, 8 H)	3450 (N–H)	206 (4.10) 240 (3.76) 263 (3.11) 270 (2.94)	276 183 182 168 93 91
1		163–164[g]	87	3.58 (broad s, 2 H) 4.16 (d, 4 H, J = 2.5 Hz) 7.43 (AA′BB′, 8 H)	3450 (N–H)	218 (3.98) 254 (3.19)	186 185 94 93

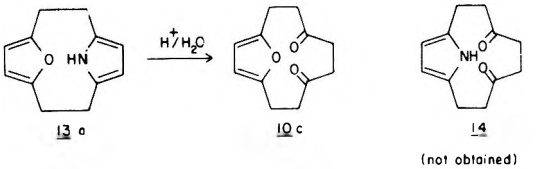
[a] Uncorrected. [b] Isolated. [c] $CDCl_3$/1% Me_4Si. [d] KBr. [e] EtOH (absolute). [f] m/e. [g] Sublimed.

absorption appears at τ 3.6, 5.0, and 6.3.[17] Additionally, the chemical shift of the *N*-methyl group in **11b** appears 0.72 ppm upfield from that observed in 1,2,5-trimethylpyrrole.[18] These data clearly indicate that the substituent on the nitrogen is positioned above an aromatic plane and enjoys the increasing anisotropic shielding influence of the aromatic nuclei.[19,20] This property is typical and consistent with the cyclophane structures proposed.

Finally, the appearance of the β-pyrrole protons in **11a,b** and **12a** at chemical shifts nearly identical with those in 2,5-dimethylpyrrole and 1,2,5-trimethylpyrrole[21] indicates a minimum of transannular shielding by the parallel aromatic ring. In addition, the pyrrole protons in **13a** appear at a chemical shift similar to those in *N,N′*-dimethyl[2.2](2,5)-pyrrolophane previously assigned an anti configuration by Wasserman and Bailey.[10] These facts, coupled with the above noted significant upfield shifts of the nitrogen substituent, demonstrate that **12a** and **13a** exist in the more stable anti conformation.[5c]

B. Pyrrolophanes from 1,4,7,10-Cyclododecatetraone (15). Initially it was supposed that **1** would be available from **13a** by selective hydrolysis of the more reactive furan ring[11b,22] followed by Paal–Knorr cyclization of 3,6-diketo[8](2,5)pyrrolophane (**14**) (see Scheme V). However treatment of **13a**

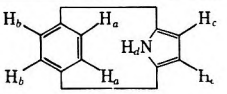
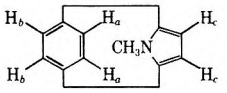
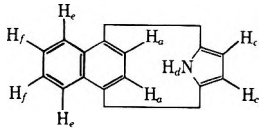
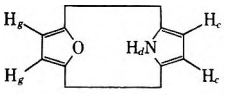
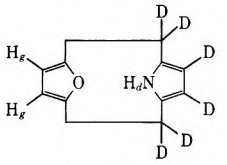
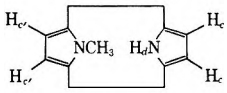
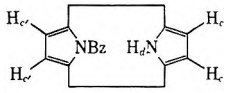
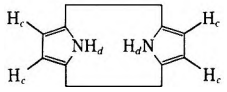
Scheme V



with 10% sulfuric acid in acetic acid for 16 h at 65 °C afforded only **10c**.

In addition, in light of the successful Paal–Knorr cyclizations described above, we attempted a synthesis of **1** by the reaction of tetraone **15** with ammonia but were unsuccessful.[23] *N*-Methyl[2.2](2,5)pyrrolophane (**17a**), *N*-benzyl[2.2](2,5)-

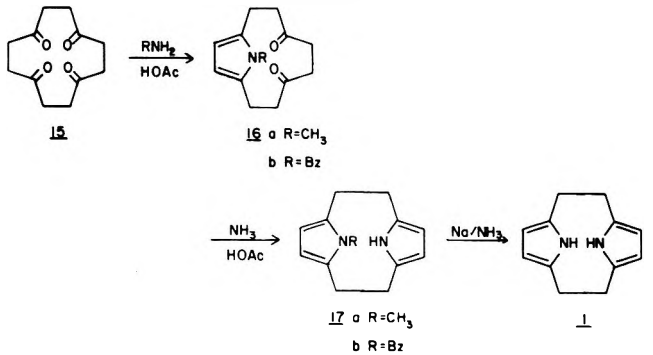
Table II. Chemical Shifts (τ) and Assignments for Protons in [2.2](2,5)Pyrrolophanes

Compd	Structure	a	b	c	d	e	f	g	Bridge
11a		3.29	2.85	4.55	5.0				7.40[a]
11b		3.88	3.05	4.40					7.15[a] 7.5 (NCH_3)
12a		3.50		4.50	6.2	1.95	2.36		6.25[a] and 7.50[a]
13a				4.05	3.6			3.95	7.35[a]
13a-d_6					3.6			3.9	7.3[a]
17a				c 4.15 c′ 3.71	3.4				7.15[a] 6.98 (NCH_3)
17b				c 4.1 c′ 3.8	3.45				7.27[a]
1				4.16	3.58				7.43[a]

[a] Multiplet center.

pyrrolophane (**17b**), and the parent pyrrolophane **1** were, however, successfully prepared from tetraone **15** as described in Scheme VI. Thus, **15** was treated in glacial acetic acid with

Scheme VI



methylamine for 10 min, affording dione **16a**.[10] The dione was not isolated but treated in situ with ammonia. Chromatography of the reaction mixture followed by sublimation afforded pyrrolophane **17a** in 43% yield.

Analogously, **15** was treated successively with benzylamine and ammonia and afforded a 17% yield of **17b** after chromatography and sublimation. Reductive cleavage of the benzyl group by sodium in liquid ammonia afforded the parent [2.2](2,5)pyrrolophane **1** in 87% yield after sublimation. Compounds **17a, 17b,** and **1** were characterized spectrally and the pertinent data are summarized in Table I.

Compounds **17a, 17b,** and **1**, respectively, exhibit the simple recognizable mass spectral characteristics of [2.2]cyclophanes showing a molecular ion for the phane (*m/e:* **17a,** 200; **17b,** 276; **1,** 186), and ions corresponding to the two fragments arising from, and indicative of, the cleavage of the ethylene bridges (*m/e:* **17a,** 107 and 93; **17b,** 183 and 93; **1,** 93). In addition compound **17b** exhibits a strong peak at *m/e* 91 associated with the loss of the benzyl group. The infrared spectra of the three compounds confirm the presence of a nitrogen–hydrogen bond, exhibiting, in each, an absorption at 3450 cm^{-1} characteristic of the N–H stretch. The ultraviolet absorption spectra of these compounds are not unusual. Compound **17b** exhibits two shoulders at 270 and 263 nm confirming the presence of the benzenoid group. All three compounds show absorptions, in the 240–250-nm region, usually associated with transannular π–π interactions.[15] The degree (if any) that these interactions enhance this absorption is not immediately evident since pyrrole nuclei normally absorb in this region, albeit with a much lower extinction coefficient.

The NMR spectra of the three cyclophanes were most significant and informative in elucidating their structures. Each compound exhibited broad absorptions at τ 3.4–3.6, indicative of the nitrogen-bound pyrrole proton. The chemical shift of these protons is similar to that observed in [2.2]-(2,5)furano(2,5)pyrrolophane **13a** (τ 3.6), illustrative of the similar anisotropic shielding effects of both the furan and pyrrole rings. The chemical shift of the β protons on the N-unsubstituted pyrrole nuclei in **17a, 17b,** and **1** is observed at about τ 4.1 and the peaks are split into doublets by the pyrrole N–H. These chemical shifts and coupling constants are similar to those found in **13a** (τ 4.05, J = 3.0 Hz). The analogous β protons on the N-substituted pyrrole rings in **17a** and **17b,** on the other hand, are found as sharp singlets at τ 3.7–3.8 and are positioned near the chemical shift of the β-pyrrole protons in **2** (τ 3.9).[10] Each compound also shows a complex absorption pattern at τ 7.3 for the eight protons on the ethylene bridges.

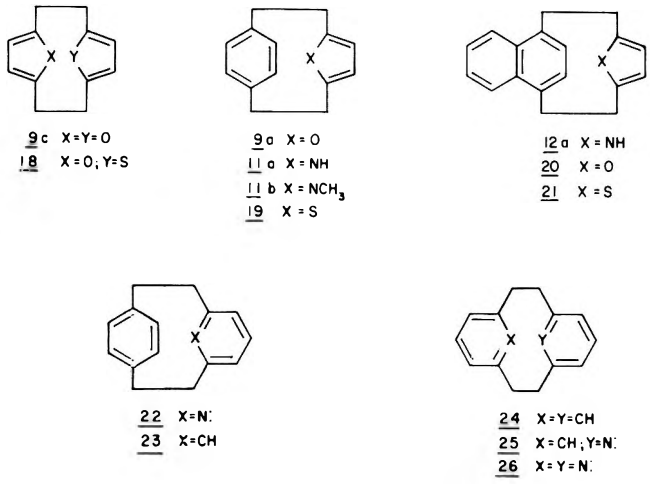


Figure 1.

Again, the shifts are similar to those found in **2** (τ 7.16)[10] and **13a** (τ 7.35). Additionally, **17a** exhibits a single absorption at τ 7 for the N-methyl protons, similar to that found in **2** (τ 6.95),[10a] and **17b** shows a singlet at τ 5.42 and a multiplet at τ 2.85 for the methylene and benzenoid protons of the benzyl group, respectively. The above data are entirely consistent with the assigned structures of **17a, 17b,** and **1.**

Conformational Behavior of Pyrrolophanes. The conformational behavior of numerous [2.2]cyclophanes has been studied internationally in various groups by variable temperature NMR spectroscopy. It has been demonstrated that the size of the cavity of the cyclophane macrocycle and the steric bulk of the groups passing through this cavity play a major role in determining the barrier to rotation of various aromatic groups.[6a,b,7a,b,8,13,25,26] For instance, cyclophanes (see Figure 1) **18**,[6a] **19**,[6c] **20**,[5c,6b] **21**,[6b] **24**,[25f] and **25**[6a] are rigid on the NMR time scale (E_{act} > 27 kcal/mol) while **9a**,[13] **9c**,[7a] **22**,[7c] **23**,[25a,26] and **26**[7a] are mobile, with coalescence temperatures (T_c, °C) and activation energies (E_{act}, kcal/mol) of −40, 11.1; 63, 16.8; −43.5, 10.7; 157, 20.6; and 13.5, 14.8, respectively. Because rotational behavior of the pyrrole nuclei in cyclophanes was not known, a variable temperature NMR study was carried out on the pyrrolophanes synthesized above.

The chemical shift data (ambient temperature) for the various protons in pyrrolophanes **11a, 11b, 12a, 13a, 17a, 17b,** and **1** are given in Table II.

At room temperature, the protons on the benzene nuclei in both compounds **11a** and **11b** appear as a well-separated AA′XX′ multiplet, similar to that observed for **9a** at low temperatures, providing strong evidence for a frozen conformation for both **11a** and **11b.** Upon raising the sample temperature, **11a** exhibits a broadening and coalescence (T_c = 105 °C) of the multiplets associated with protons a and b until at 190 °C a sharp singlet at a point halfway between the original two multiplets is observed. This behavior is completely in accord with an averaging of the environment of these benzenoid protons by rapid flipping of the heterocyclic nucleus. At the above T_c the process requires a $\Delta G^{\ddagger}$ of ca. 17 kcal/mol.[27] This energy barrier is thus greater than that associated with either **22** or **9a,** but, as might be expected from the size of the N atom and the length of the N–H bond, less than that for **23.** The protons on the ethylene bridges, which give rise to an ABCD multiplet at ambient temperatures, show a corresponding spectral change and appear as a symmetrical AA′BB′ multiplet at 190 °C.

The variable temperature NMR behavior of **11b** was also examined. The NMR spectrum of **11b,** however, remained unchanged from ambient temperature to 190 °C, indicating a greater energy barrier for flipping. No broadening of the multiplets due to the benzenoid protons was observed up to

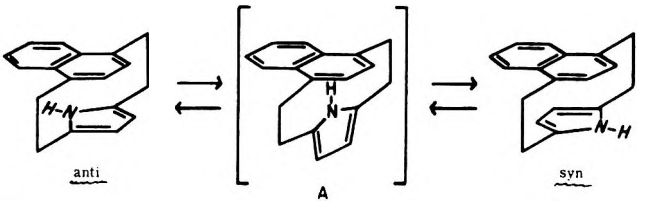


Figure 2.

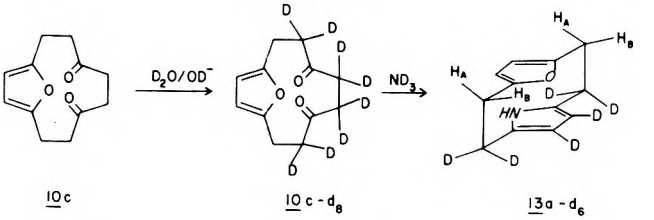
190 °C, suggesting an activation energy in excess of 27 kcal/mol,[7a,25a,26] an expectedly high barrier in view of the steric bulk of the methyl group.

A priori, it might be reasoned that **12a** should exhibit rotational behavior similar to that shown by **22, 23, 9a,** or **11a.** However, while the barriers to flipping in these compounds are for the most part due to the bulky size of the atoms or group of atoms passing through the cavity during the inversion process, there is an added interaction in **12a** which can contribute to the energy barrier in converting the anti to the syn conformation (see Figure 2). Inspection of models shows that the syn conformer is indeed more energetic due to an added transannular π–π interaction. The barrier to rotation would, therefore, be somewhat perturbed as compared with that of **11a,** depending upon the magnitude of this π–π interaction.

It was found that the aromatic region of the NMR spectrum of **12a** remained unchanged from room temperature to 190 °C. Apparently, despite the capability of the N–H to pass through an aromatic π cloud (as demonstrated from the data on compound **11a**), the syn conformer of **12a,** being relatively energy rich, is not populated to an appreciable extent. Thus, an averaged spectrum, nearly identical with that of the anti conformation, is obtained. While the above NMR data are not rich in conformational information, they do indicate that other influences,[28] aside from steric bulk, effect the flipping in these cyclophanes, and that the syn and anti conformations are substantially different in energy. It should be noted that compound **21** has been isolated by Misumi[6b] in both syn and anti forms but attempted thermal interconversion (similar to those described in Figure 2 for **12a**) resulted in decomposition. Thus, the barrier to rotation in **21** is high enough so that both forms are isolable but is too high for thermal interconversion without bond fragmentation (i.e., decomposition occurs prior to thiophene ring inversion). In contrast only the anti form of **12a** has been isolated, which indicates either a low syn to anti flipping barrier of the pyrrole ring or more likely a continued increase in energy due to greater π–π interaction as rotation continues from A to the syn form[1c] (see Figure 2).

The conformational behavior of **13a** between −35 and 190 °C was not easily interpreted from its NMR spectrum since the multiplet for the bridge protons is very narrow and it was very difficult to observe line broadening. The study was therefore carried out on the hexadeuterio analogue of **13a** (prepared as described in Scheme VII) to reduce the com-

Scheme VII



plexity of the absorption pattern for the protons α to the furan ring.

The NMR spectrum of **13a**-d_6 at 60 MHz exhibits a deuterium broadened AB quartet (in contrast to the complicated

ABCD pattern in **13a**) for the bridge protons α to the furan ring. The deuterium decoupled 100-MHz spectrum of **13a-d_6** shows the AB quartet more clearly. The separation between the A and B resonances is calculated[29] to be 12.7 Hz based on the coupling constant (J_{AB}) of 13.6 Hz as obtained from the deuterium decoupled spectrum. This deuterium decoupled spectrum remains unchanged upon heating the sample to 190 °C. For a minimum detectable line broadening of 0.5 Hz, the above data represent a rate constant for conformational flipping of the furan ring in **13a-d_6** of $<1\ s^{-1}$ with an associated Arrhenius energy of activation greater than 27 kcal/mol. The data demonstrate that the furan ring is not flipping and since the steric bulk of the N–H group of the pyrrole ring has been shown above to be higher than that of the oxygen of the furan ring, it implies that the pyrrole ring is also conformationally rigid.

This system is analogous to the conformationally rigid [2.2](2,6)pyridinometacyclophane (**25**)[6a] and indicates the similar steric bulk of C–H–:N and N–H–:O groups as these groups attempt to pass through the cavity in their respective cyclophanes.

The multiplicity of the bridge protons in **1** (AA'BB') indicates that, unlike the corresponding furan rings in [2.2](2,5)furanophane (**9c**),[7a] the pyrrole rings are not flipping. This conformational rigidity was predicted in light of the high activation energy (>27 kcal/mol) observed for the analogous cyclophane **13a**. Attempts, however, to detect the rotational process by variable temperature NMR techniques and to rigorously substantiate the above prediction proved fruitless owing to the decomposition of **1** at high temperatures. On the other hand, high-temperature NMR experiments on **17a** demonstrated conclusively that the pyrrole rings are not rotating at temperatures up to 190 °C and that the barrier to rotation is >27 kcal/mol. Though variable temperature NMR spectra were not obtained for **17b**, it seems likely that the results would be similar to that obtained for **17a**, i.e. the pyrrole rings are rigid on the NMR time scale.

Our present efforts are being directed toward the synthesis of [*n*.2.2]pyrrolophanes[10b] and the effect that removal of the proton from the nitrogen in these [2.2]pyrrolophanes will have on the rotational behavior of the pyrrole nucleus.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Boiling points are uncorrected. Infrared spectra were taken on a Perkin-Elmer Model 735 grating spectrophotometer and a Perkin-Elmer Infracord Model 137 spectrophotometer and were calibrated with the 1601-cm^{-1} band of polystyrene. Nuclear magnetic resonance spectra were taken on Varian Model A-60A, Perkin-Elmer Model R-24, Perkin-Elmer Model R-32, and Bruker Model WH-90 spectrometers. Deuterium decoupled NMR spectra of **13a** were recorded on a Varian Model HA-100 spectrometer. Chemical shifts are reported in parts per million on a τ scale, using Me_4Si as an internal standard. Ultraviolet spectra were taken on Perkin-Elmer-Coleman Model 124 and Perkin-Elmer Model 202 spectrophotometers. Mass spectra were obtained using an A.E.I. Model MS-12 mass spectrometer. Microanalyses were performed by Chemalytics, Inc., Tempe, Ariz., and Galbraith Laboratories, Knoxville, Tenn.

[2.2](2,5)Pyrroloparacyclophane (11a). A three-neck flask, equipped with a condenser, serum cap, and glass stopper, was charged with glacial acetic acid (50 mL, purged with nitrogen for 15 min) and 3,6-diketo[8]paracyclophane (0.7 g, 3 mmol). The flask was wrapped in aluminum foil to exclude light and heated under nitrogen in an oil bath (80 °C) for 10 min. Precondensed liquid ammonia was distilled into the mixture via a disposable pipet placed through the serum cap and the nitrogen inlet at the top of the condenser was replaced with a drying tube (Drierite). The ammonia was allowed to bubble into the heated and stirred solution for 30 min. By this time the mixture had usually solidified. It was cooled in ice and made basic (pH 10) with ammonium hydroxide (concentrated). The light-yellow solution was extracted with chloroform (4 × 25 mL). The organic layer was washed several times with water until the wash was neutral and dried over anhydrous sodium sulfate. Removal of solvent in vacuo yielded a yellow-white solid. This was purified by chromatography on silica gel (elution with chloroform). Recrystallization from hexane afforded silky white needles of **11a** (0.35 g, 55%): mp 197–198 °C; NMR ($CDCl_3$) τ 3.28 (AA'XX', 4 H), 4.55 (d, 2 H, J = 2.5 Hz), 5.0 (broad s, 1 H), 7.4 (m, 8 H); IR (KBr) 3400 (N–H), 2900, 1390, 1025, 874, 800, 765, 720 cm^{-1}; UV (EtOH) λ (log ϵ) 286 nm sh (2.79), 269 sh (2.98), 219 (4.0); MS *m/e* 197 (M^+), 104, 93.

Anal. Calcd for $C_{14}H_{15}N$ (mol wt 197.28): C, 85.24; H, 7.66; N, 7.10. Found: C, 85.15; H, 7.91; N, 7.21.

***N*-Methyl[2.2](2,5)pyrroloparacyclophane (11b).** A flask equipped with a condenser, serum cap, and glass stopper was charged with glacial acetic acid (10 mL, purged with nitrogen for 15 min) and 3,6-diketo[8]paracyclophane (0.25 g, 0.0012 mol). The flask was wrapped in aluminum foil to exclude light and heated under nitrogen in an oil bath (105 °C) for 10 min. Precondensed methylamine was bubbled into the hot acid solution for 90 min via a disposable pipet placed through the serum cap and the nitrogen inlet was replaced with a drying tube (Drierite). The orange reaction mixture was cooled, made basic (pH 10) with ammonium hydroxide (concentrated), and extracted with chloroform (4 × 25 mL). The light, orange organic layer was washed with water until the wash was neutral and dried over anhydrous sodium sulfate. Chromatography of the residue, after solvent removal on alumina with methylene chloride as eluent, afforded a yellow-white solid. Recrystallization from ethanol/water gave colorless, crystalline **11b** (0.15 g, 53%): mp 212–214 °C; NMR ($CDCl_3$) τ 3.46 (AA'XX', 4 H), 4.4 (s, 2 H), 7.15 (m, 8 H), 7.5 (s, 3 H); IR (KBr) 3000, 1280, 1080, 870, 755, 720 cm^{-1}; UV (EtOH) λ (log ϵ) 279 nm sh (2.61), 269 sh (2.75), 226.5 (3.89), 204.5 (3.99); MS *m/e* 211 (M^+), 107, 104.

Anal. Calcd for $C_{15}H_{17}N$ (mol wt 211.31): C, 69.89; H, 6.84; N, 5.66. Found: C, 69.65; H, 6.82; N, 5.69.

3,6-Diketo[8](1,4)naphthalenophane (10b). A liquid mixture of glacial acetic acid (4.3 mL), water (2.2 mL), and 10% sulfuric acid (3 drops) was placed in a flask and purged with nitrogen for 15 min. To this solution was added [2.2](2,5)furano(1,4)naphthalenophane (0.467 g, 1.9 mmol). The flask was covered with aluminum foil to exclude light and was heated under nitrogen with magnetic stirring in an oil bath (105 °C) for 18 h. The resulting mixture, after cooling, was poured into water (10 mL) and the cloudy solution extracted with methylene chloride (4 × 20 mL). The light-yellow organic layer was washed with water (2 × 15 mL), a saturated solution of sodium bicarbonate (2 × 15 mL), and a saturated solution of sodium chloride (2 × 15 mL), and dried over anhydrous sodium sulfate. Removal of solvent in vacuo gave 0.43 g (88%) of crude white solid. Recrystallization from ethanol (95%) afforded 3,6-diketo[8](1,4)naphthalenophane (**10b**, 0.36 g 71%): mp 159–160 °C; NMR ($CDCl_3$) τ 2.2 (AA'BB', 4 H), 2.83 (s, 2 H), 6.6 (m, 4 H), 7.55 (m, 4 H), 8.67 (m, 4 H); IR (KBr) 2950, 1680 (C=O), 814, 765 cm^{-1}; UV (EtOH) λ (log ϵ) 297.5 nm (3.70), 231 (4.35); MS *m/e* 266 (M^+), 168, 144, 100.

Anal. Calcd for $C_{18}H_{18}O_2$ (mol wt 266.34): C, 81.17; H, 6.81. Found: C, 81.05; H, 6.86.

[2.2](2,5)Pyrrolo(1,4)naphthalenophane (12a). A flask, equipped with a condenser, serum cap, and glass stopper, was charged with glacial acetic acid (10 mL) and purged with nitrogen (15 min) and to the acid was added 3,6-diketo[8](1,4)naphthalenophane (75 mg, 0.28 mmol). The flask was wrapped in foil to exclude light and heated in an oil bath (80 °C) for 10 min. Precondensed ammonia was bubbled into the solution (30 min) through the serum cap via a disposable pipet and the nitrogen inlet tube at the top of the condenser was replaced with a drying tube (Drierite). The yellow-orange solution was cooled in ice, made basic (pH 10) with ammonium hydroxide (concentrated), and extracted with chloroform (4 × 15 mL). The orange organic layer was washed several times with water, until the wash was neutral, and dried over anhydrous sodium sulfate. Removal of solvent in vacuo afforded an orange, solid residue. Purification by chromatography on silica gel, eluting with chloroform, gave **12a** (0.06 g, 86%). Recrystallization from ethanol/water afforded white needles: mp 111–112 °C; NMR ($CDCl_3$) τ 2.3 (AA'XX', 4 H), 3.5 (s, 2 H), 4.5 (d, 2 H, J = 3.0 Hz), 6.2 (broad s, 1 H), 6.4 (m, 2 H), 7.5 (m, 6 H); IR (KBr) 3450 (N–H), 2950, 1170, 1010, 758, 705 cm^{-1}; UV (EtOH) λ (log ϵ) 301 nm (3.43), 243 sh (4.13), 226.5 (4.28); MS *m/e* 247 (M^+), 144, 93.

Anal. Calcd for $C_{18}H_{17}N$ (mol wt 247.34): C, 87.41; H, 6.93; N, 5.66. Found: C, 87.20; H, 6.73; N, 5.69.

3,6-Diketo[8](2,5)furanophane (10c). A flask charged with a liquid mixture of glacial acetic acid (54 mL), water (27 mL), and 10% sulfuric acid (1.2 mL) was purged with nitrogen (15 min) and to the solution was added [2.2](2,5)furanophane (4.43 g, 0.0235 mol). The flask was covered with aluminum foil to exclude light and heated in

an oil bath (70–80 °C) under nitrogen for 18 h. The resulting light-yellow mixture was poured into water (100 mL) and extracted with methylene chloride (4 × 50 mL). The yellow organic layer was washed with water (2 × 20 mL), a saturated solution of sodium bicarbonate (2 × 20 mL), and a saturated solution of sodium chloride (2 × 20 mL) and dried over anhydrous sodium sulfate. Removal of the solvent in vacuo gave a white-yellow powder (4.0 g, 82.5%). Recrystallization from water afforded 3,6-diketo[8](2,5)furanophane **10c** (3.4 g, 68%), as colorless crystals: mp 109–110 °C; NMR ($CDCl_3$) τ 4.2 (s, 2 H), 7.45 (s, 4 H), 7.45 (AA'BB', 8 H); IR (KBr) 2940, 1700 (C=O), 1420, 1160, 1015, 805 cm^{-1}; UV (EtOH) λ (log ϵ) 292 nm sh (1.94), 222 (3.56); MS *m/e* 206 (M^+), 108, 107, 99.

Anal. Calcd for $C_{12}H_{14}O_3$ (mol wt 206.24): C, 69.89; H, 6.84. Found: C, 69.65; H, 6.82.

[2.2](2,5)Furano(2,5)pyrrolophane (13a). A flask equipped with a condenser, serum cap, and glass stopper was charged with glacial acetic acid (15 mL) and purged with nitrogen for 15 min. To this solution was added 3,6-diketo[8](2,5)furanophane (0.260 g, 1.3 mmol). The flask was wrapped in aluminum foil to exclude light and placed in an oil bath (80 °C) for 15 min. Precondensed ammonia was distilled into the solution (30 min) through the serum cap via a disposable pipet and the nitrogen inlet tube at the top of the condenser was replaced with a drying tube (Drierite). The reaction mixture was cooled in ice and made basic (pH 10) with ammonium hydroxide (concentrated). It was extracted with chloroform (4 × 20 mL) and the yellow organic layer washed several times with water until the wash was neutral and dried over anhydrous sodium sulfate. Removal of solvent in vacuo gave solid yellow product, 0.25 g. This solid was purified by chromatography on silica gel, eluting with chloroform, and recrystallized from ethanol–water affording colorless needles of **13a** (0.15 g, 67%), mp 131–132 °C. The crystals were light sensitive: NMR ($CDCl_3$) τ 3.6 (broad s, 1 H), 3.95 (s, 2 H), 4.05 (d, 2 H, J = 3.0 Hz), 7.35 (m, 8 H); IR (KBr) 3408 (N–H), 2920, 1170, 1010, 750 cm^{-1}; UV (EtOH) λ (log ϵ) 222 nm (4.0); MS *m/e* 187 (M^+), 94, 93.

Anal. Calcd for $C_{12}H_{13}NO$ (mol wt 187.24): C, 76.98; H, 7.00; N, 7.48. Found: C, 76.91; H, 7.05; N, 7.37.

***N*-Methyl[2.2](2,5)pyrrolophane (17a).** Methylamine (precondensed) was bubbled into a stirred and heated solution of 1,4,7,10-cyclododecatetraone (110 mg, 0.49 mmol) in glacial acetic acid (10 mL, purged with nitrogen for 15 min) in the dark for 10 min. The reaction system was purged with nitrogen and ammonia (precondensed) was distilled into the solution for 20 min. The "solid" brown-red reaction mixture was made basic (pH 10) with ammonium hydroxide (concentrated) and extracted with chloroform (5 × 15 mL). The brown organic layer was washed with water until the washings were neutral, dried over anhydrous sodium sulfate, and concentrated in vacuo to a brown residue. Preparative chromatography (silica gel/chloroform, R_f 0.72) afforded a light yellow, crystalline product. Sublimation afforded *N*-methyl[2.2](2,5)pyrrolophane (**17a**, 23 mg, 43%): NMR ($CDCl_3$) τ 3.71 (s, 2 H), 4.15 (d, 2 H, J = 2.9 Hz), 6.98 (s, 3 H), 7.15 (m, 8 H); IR (KBr) 3450 (N–H), 2950, 1170, 1010, 780, 760 cm^{-1}; UV (EtOH) λ (log ϵ) 240 nm (3.91), 219 (4.04), 204 (4.22); MS *m/e* 200 (M^+), 107, 93, 92.

Anal. Calcd for $C_{13}H_{16}N_2$ (mol wt 200.27): C, 77.96; H, 8.05; N, 13.99. Found: C, 77.83; H, 8.08; N, 13.73.

***N*-Benzyl[2.2](2,5)pyrrolophane (17b).** Benzylamine (135 mg, 1.26 mmol, distilled from sodium) was added to a heated solution (85 °C) of 1,4,7,10-cyclododecatetraone (100 mg, 0.45 mmol) in glacial acetic (10 mL) (purged with nitrogen for 15 min) under nitrogen and in the dark. After the reaction mixture had been heated and stirred for 1 h,[30] ammonia (precondensed) was bubbled into the light-orange solution for 30 min. The brown reaction mixture was cooled and made basic (pH 10) with ammonium hydroxide (concentrated). The mixture was extracted with chloroform (5 × 15 mL) and the organic layer was washed with water until the wash was neutral. The combined organic layers were dried over anhydrous sodium sulfate and the solvent was removed in vacuo affording a red-brown oil. Purification by preparative chromatography (silica gel/chloroform, R_f 0.63) and sublimation yielded the white, crystalline *N*-benzyl[2.2](2,5)pyrrolophane (**17b**, 20 mg, 17%): mp 84–85 °C; NMR ($CDCl_3$) τ 2.7–3.0 (m, 5 H), 3.8 (s, 2 H), 4.1 (d, 2 H, J = 2.6 Hz), 5.42 (s, 2 H), 7.27 (m, 8 H); IR (KBr) 3450 (N–H), 3000, 1410, 1170, 755, 745, 705 cm^{-1}; UV (EtOH) λ (log ϵ) 270 nm (2.94), 263 (3.11), 240 (3.76), 206 (4.10); MS *m/e* 276 (M^+), 183, 182, 168, 93, 91.

Anal. Calcd for $C_{19}H_{20}N_2$ (mol wt 276.36): C, 82.57; H, 7.29; N, 10.14. Found: C, 82.51; H, 7.41; N, 9.97.

[2.2](2,5)Pyrrolophane (1). *N*-Benzyl[2.2](2,5)pyrrolophane (**17b**, 13 mg, 0.0471 mmol) was dissolved in tetrahydrofuran (2 mL, distilled from sodium). This solution was placed in a dry flask under nitrogen and precondensed ammonia was distilled from sodium into the flask. After about 15 mL had been condensed, the distillation was stopped and sodium (20 mg) was added in small portions. The dark blue reaction mixture was stirred for 1 h. The ammonia was allowed to evaporate from the reaction mixture. The last traces of ammonia and tetrahydrofuran were removed in vacuo leaving a residual white solid. Addition of water (10 mL) yielded a suspension, which was extracted with chloroform (4 × 10 mL). The organic layer was washed with water (1 × 10 mL) and dried over anhydrous sodium sulfate and the solvent removed in vacuo to afford a light yellow solid. Sublimation yielded white powdery [2.2](2,5)pyrrolophane 1 (7.5 mg, 87%), mp 163–165 °C dec. The compound decomposes slowly in light and air: NMR ($CDCl_3$) τ 3.58 (broad s, 2 H), 4.16 (d, 4 H, J = 2.5 Hz), 7.12–7.74 (AA'BB', 8 H); IR (KBr) 3450 (N–H), 2970, 1175, 1040, 765, 708 cm^{-1}; UV (EtOH) λ (log ϵ) 254 nm (3.19), 218 (3.98); MS *m/e* 186 (M^+), 185, 94, 93.

Anal. Calcd for $C_{12}H_{14}N_2$ (mol wt 186.24): C, 77.38; H, 7.58; N, 15.04. Found: C, 77.35; H, 7.76; N, 15.31.

2,2,4,5,7,7-Hexadeuterio[2.2](2,5)furano(2,5)pyrrolophane (13a-d_6). 3,6-Diketo[8]furanophane (**10c**, 0.5 g, 2.4 mmol) in dioxane (5 mL, distilled from $LiAlH_4$) and D_2O (6 mL, 99.8%, Stohler) was stirred for 16 h in the dark in the presence of a trace of sodium. The reaction mixture was extracted with $CHCl_3$ (3 × 10 mL) and the extracts washed with saturated NaCl (20 mL) and dried over $MgSO_4$. Evaporation of solvent left crystalline diketone **10c**-d_8 (0.440 g, 2.1 mmol, 85%): NMR ($CDCl_3$) τ 4.16 (s, 2 H), 7.09 (broad s, 4 H).

A solution of **10c**-d_8 (300 mg, 1.4 mmol) in acetic acid-d_1 (7 mL, 99%, Stohler) was purged with nitrogen for 30 min and then ammonia-d_3 (99%, Stohler) was bubbled into the stirred solution at 80 °C in the dark. The solution was then cooled and basified to pH 10 with NH_4OH (concentrated). The solution was extracted with $CHCl_3$ (3 × 25 mL) and the extracts washed with water until neutral and then dried over Na_2SO_4. Evaporation of solvent afforded **13a**-d_6 (245 mg, 1.3 mmol, 91%). Recrystallization from 95% EtOH gave white, crystalline material: mp 130–132 °C; NMR ($CDCl_3$) τ 3.6 (broad s, 1 H), 3.91 (s, 2 H), 7.3 (deuterium broadened AB q, 4 H); MS *m/e* 193 (M^+), 99, 94. Analysis of the mass spectrum shows >70% hexadeuteration and >90% hexa- and pentadeuteration in the bridge positions α to the pyrrole ring. The effect of the pentadeuterated isomers on the NMR spectrum is negligible.

Acknowledgments. We thank Professor Ernest Grunwald (Brandeis University) for helpful discussions and Larry Costa and James A. Simms (Massachusetts Institute of Technology) for help in obtaining the 100-MHz deuterium decoupled NMR spectra. We also thank the National Science Foundation (GU-3852), the National Institutes of Health (Biomedical Science Support Grant RR-7044-07), and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work.

Registry No.—**1**, 56634-48-1; **10b**, 51460-19-6; **10c**, 51460-20-9; **10c**-d_8, 61394-88-5; **11a**, 51053-69-1; **11b**, 51012-07-8; **12a**, 51012-08-9; **13a**, 51041-05-5; **13a**-d_6, 61394-89-6; **17a**, 56634-47-0; **17b**, 61394-90-9; 3,6-diketo[8]paracyclophane, 5297-49-4; [2.2](2,5)furano(1,4)-naphthalenophane, 25108-53-6; [2.2](2,5)furanophane, 5088-46-0; 1,4,7,10-cyclododecatetraone, 25887-95-0; methylamine, 74-89-5; benzylamine, 100-46-9; D_2O, 7789-20-0; ammonia-d_3, 13550-49-7.

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(1) For previous papers in this series see (a) R. Luhowy and P. M. Keehn, *J. Am. Chem. Soc.*, in press; (b) J. O'Connor and P. M. Keehn, *ibid.*, **98**, 8446 (1976); (c) S. M. Rosenfeld, C. Shana, and P. M. Keehn, *Tetrahedron*, in press; (d) J. F. Haley, Jr., and P. M. Keehn, *Chem. Lett.*, 999 (1976); (e) R. Luhowy and P. M. Keehn, *Tetrahedron Lett.*, 1043 (1976); (f) J. F. Haley, Jr., and P. M. Keehn, *ibid.*, 1675 (1975); (g) S. M. Rosenfeld and P. M. Keehn, *J. Chem. Soc., Chem. Commun.*, 119 (1974); (h) *Tetrahedron Lett.*, 4021 (1973); (i) J. F. Haley, Jr., and P. M. Keehn, *ibid.*, 4017 (1973).

(2) This paper is based on the Ph.D. Thesis of James F. Haley, Jr., Brandeis University, Waltham, Mass., 1975. The material was communicated in part (see ref 1f–i) and was presented at the XXV IUPAC Congress, Jerusalem, Israel, June 1975.

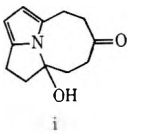
(3) To whom correspondence should be addressed.

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(23) When **15** was heated (70 °C) in acetic acid with the addition of ammonia for 30 min, workup and chromatographic separation afforded compound i in low yield, whose structure is tentatively assigned on the basis of the



i

following spectral data: NMR ($CDCl_3$) τ 4.2 (AB q, 2 H, J = 3.1 Hz), 7.5 (m, 13 H); IR (KBr) 3280 (OH), 1690 cm^{-1} (C=O); MS *m/e* 205 (M^+), 204, 106, 92.
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Synthesis of Bicyclo[2.2.2]octenes and Bicyclo[3.2.2]nonenes by π-Cyclization

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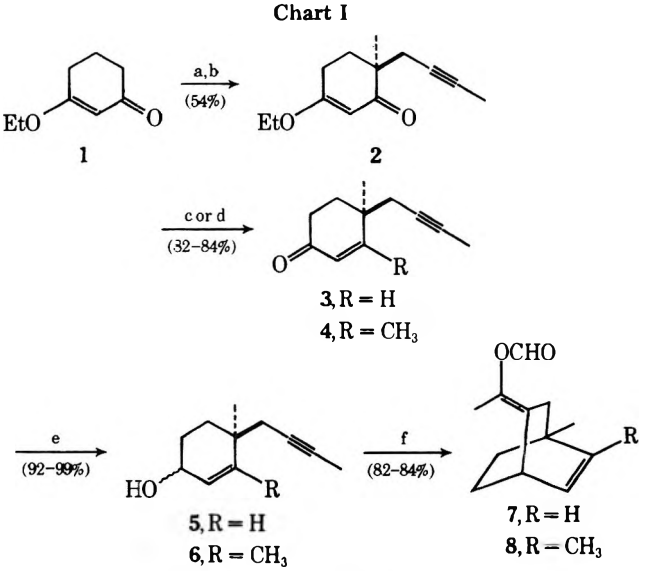
Received September 20, 1976

The (2-butynyl)cyclohexenols **5**, **6**, and **12** undergo cyclization to bicyclic enol formates **7**, **8**, and **13**, respectively, upon treatment with formic acid at room temperature. The trimethylsilylpropynyl analogue **17** cyclizes in the alternative sense to yield, after hydrolysis and protodesilylation, the bicyclo[3.2.2]nonenone **18**.

π-Cyclization (the interaction of a carbon–carbon multiple bond with a neighboring cationic center) has become an important method for the creation of carbocycles. The most extensive and definitive work in the area is that of Johnson and co-workers and concerns mainly the application of π-cyclization to the synthesis of steroids.[1,2] We have now found that π-cyclization provides a convenient synthesis of bicyclo[2.2.2]octenes and bicyclo[3.2.2]nonenes.

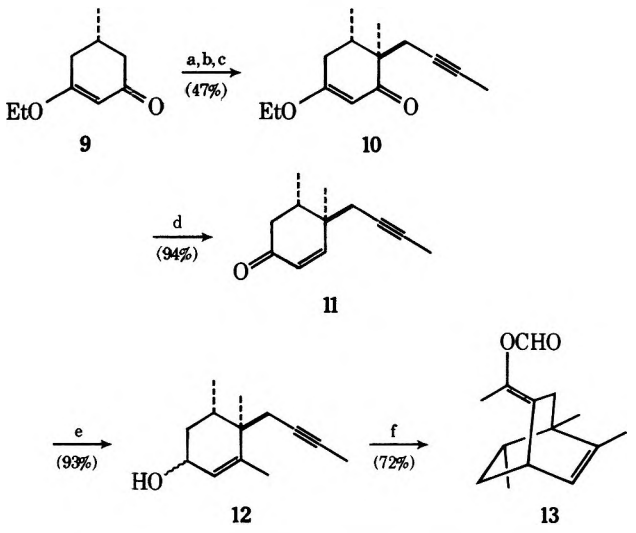
The method is typified by the synthesis of enol formates **7** and **8** (Chart I). Successive alkylation of enol ether **1**[3] by methyl iodide and 1-bromo-2-butyne[4] affords enol ether **2**, which may be reduced or treated with methyllithium to yield, after acid workup, enones **3** or **4**. Reduction of these materials affords allylic alcohols **5** and **6**. When these allylic alcohols are dissolved in 98% formic acid and kept at room temperature for 2 h, bicyclic enol formates **7** and **8** are produced in good yield (33–38% overall from enone **1**). The structures assigned are consistent with elemental compositions, infrared spectra, and both proton and carbon nuclear magnetic resonance spectra of the two compounds. Only one stereoisomer is produced in each case. Although the geometry of the double bond is unknown, it is probably *E*, as depicted in Chart I (anti addition).

Chart I



a, lithium diisopropylamide (LDA), THF, −78 °C, CH_3I; b, LDA, THF, −78 °C, $CH_3C{\equiv}CCH_2Br$; c, $LiAlH_4$, ether, H_3O^+; d, CH_3Li, H_3O^+; e, $LiAlH_4$; f, HCO_2H, 25 °C

Chart II

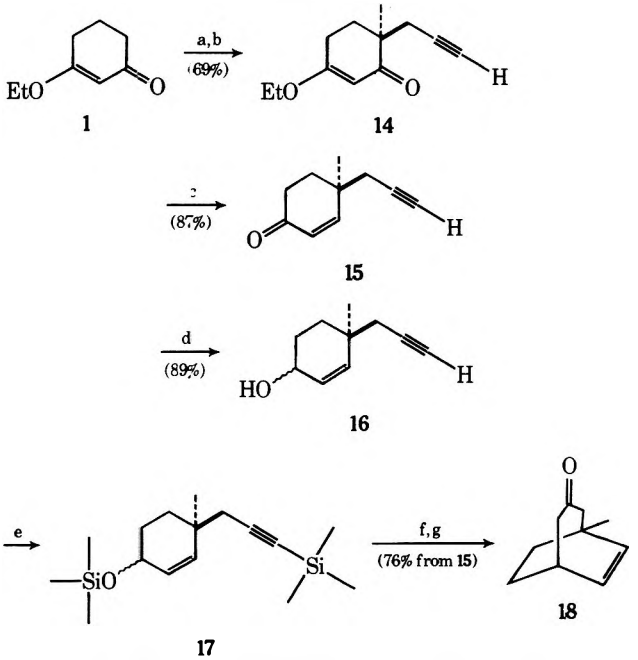


a, LDA, THF, −78°C, CH_3I; b, LDA, THF, −78°C, $CH_3C{\equiv}CCH_2Br$; c, recrystallize; d, CH_3Li; e, $LiAlH_4$; f, HCO_2H, 25 °C

To further explore the scope of this method of forming bicyclo[2.2.2]octenes, we have converted the methylated enol ether **9**[5] into compound **13** (Chart II). Successive alkylations of **9** yield a mixture of stereoisomers in which isomer **10** predominates and may be obtained in a pure state by recrystallization.

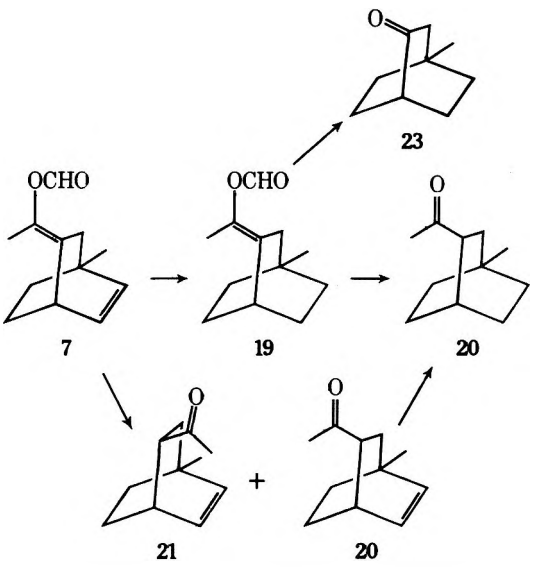
By a simple modification, the method provides a synthesis of the bicyclo[3.2.2]nonenone **18** in 41% overall yield (Chart III). In this case, cyclization of the allylic cation probably occurs at the terminus of the propargyl chain so as to avoid placing a positive charge adjacent to the electropositive silicon atom.

Chart III



a, LDA, THF, −78°C, CH_3I; b, LDA, THF, −78°C, $HC{\equiv}CCH_2Br$; c, $LiAlH_4$, H_3O^+; d, $LiAlH_4$; e, *n*-BuLi, $(CH_3)_3SiCl$; f, HCO_2H, 25 °C; g, KOH, CH_3OH, H_2O

The difunctional compounds produced in these reactions may have synthetic utility. For example, catalytic hydrogenation of **7** (10% Pd/C in C_2H_5OH) affords enol formate **19**. The enol formate double bond is quite resistant to reduction. Hydrolysis of **19** yields methyl ketone **20**. The same methyl ketone is produced by reversing the order of the two operations. Hydrolysis of **7** affords a 3:1 mixture of two unsaturated ketones (**21** and **22**). Hydrogenation of this mixture yields **20**. Ozonization of enol formate **19** yields bicyclo[2.2.2]octanone **23**.



Experimental Section[6]

Alkylation of Enones 1 and 9. These compounds were alkylated by the procedure of Danheiser and Stork.[3] After introduction of the first alkyl group, the product was distilled and alkylated again with the second alkyl halide. The following compounds were prepared.

3-Ethoxy-6-(2-butynyl)-6-methylcyclohex-2-enone (2). Enol ether **1** was alkylated first with 1-bromo-2-butyne and then with methyl iodide to provide **2** in 45% yield or in the reverse order to provide **2** in 54% yield. The product is a clear liquid with bp 95–100 °C (0.05–0.08 Torr): ^1H NMR 1.07 (3, s), 1.37 (3, t, J = 7 Hz), 1.77 (3, t, J = 1.5), 3.95 (2, q, J = 7 Hz), 5.13 ppm (1, s).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.55; H, 8.69. HRMS: Found, 206.1311.

3-Ethoxy-6-(2-propynyl)-6-methylcyclohex-2-enone (14). Enol ether **1** was alkylated first with methyl iodide and then with propargyl bromide to provide **14** in 54% yield. The product is a clear liquid with bp 70 °C (0.01 Torr): ^1H NMR 1.11 (3, s), 1.37 (3, t, J = 7 Hz), 3.92 (2, q, J = 7 Hz), 5.12 ppm (1, s).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.80; H, 8.44. HRMS: Found, 192.1131.

(5*S*,6*R*)-3-Ethoxy-6-(2-butynyl)-5,6-dimethylcyclohex-2-enone (10).[7] This material was prepared by successive alkylations of enol ether **9** with methyl iodide and 1-bromo-2-butyne.[8] The distilled product [bp 120 °C (0.03 Torr)], obtained in 59% yield, is contaminated by approximately 20% of the diastereomer having trans methyl groups. The pure cis product (mp 76–77 °C) is obtained by recrystallization from light petroleum ether: ^1H NMR (360 MHz, 1% in $CDCl_3$) 0.91 (3, s), 0.97 (3, d, J = 6.4 Hz), 1.32 (3, t, J = 7.2 Hz), 1.70 (3, t, J = 2.4 Hz), 2.06 (1, dq, J = 16.4 and 2.4 Hz), 2.22 (1, ddd, J = 1.5, 10, and 17.5 Hz), 2.37 (1, dd, J = 5 and 17.5 Hz), 2.53 (1, ddq, J = 5, 6.4, and 10 Hz), 2.77 (1, dq, J = 2.4 and 16.4 Hz), 3.86 (2, m, diastereotopic OCH_2CH_3), 5.26 ppm (1, d, J = 1.5 Hz).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.51; H, 9.17. HRMS: Found, 220.1457.

By reversing the order in which the two alkyl groups are introduced, a product consisting of 90% trans isomer and 10% cis isomer (**10**) is obtained in 44% yield.[9] Recrystallization from *n*-butyl alcohol affords pure trans isomer: mp 85–87 °C; ^1H NMR 1.00 (3, d, J = 6 Hz), 1.17 (3, s), 1.37 (3, t, J = 7 Hz), 1.75 (3, t, J = 2 Hz), 3.88 (2, q, J = 7 Hz), 5.07 ppm (1, s).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.06; H, 9.13.

4-(2-Butynyl)-4-methylcyclohex-2-enone (3). A solution of 15.45 g (75 mmol) of enol ether **2** in 150 mL of ether is cooled to 0 °C in an ice bath and 2.85 g of $LiAlH_4$ is added. After 2 h at 25 °C, the reaction is worked up by successive additions of 3 mL of water, 3 mL of 15% aqueous NaOH, and 9 mL of water. The ether solution is filtered. After drying and evaporation, the crude enone is obtained as a yellow oil. Distillation of this material gives 9.95 g (82%) of pure enone **3**: bp 75 °C (0.1 Torr); IR 1677 cm^{-1}; ^1H NMR 1.23 (3, s), 1.78

(3, t, J = 2 Hz), 5.78 (1, d, J = 10 Hz), 6.70 ppm (1, d, J = 10 Hz).

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.15; H, 8.56. HRMS: Found, 162.1035.

4-Methyl-4-(2-propynyl)cyclohex-2-enone (15). Enone **15** is prepared from enol ether **14** by the same procedure as that used for the preparation of enone **3**: IR 3300, 2120, 1678 cm^{-1}; ^1H NMR 1.27 (3, s), 5.83 (1, d, J = 10 Hz), 6.73 ppm (1, d, J = 10 Hz).

Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 80.79; H, 8.08. HRMS: Found, 148.0869.

4-(2-Butynyl)-3,4-dimethylcyclohex-2-enone (4). To a solution of 2.06 g (10 mmol) of enol ether **2** in 50 mL of dry ether at −10 °C is added 10 mL of 2 M methyllithium in ether. The solution is allowed to warm to room temperature over a 1.5-h period and is then washed with 100 mL of 15% aqueous HCl. After a normal workup, 1.48 g of enone **4** is obtained as a pale yellow liquid (84%): IR 1672, 1618 cm^{-1}; ^1H NMR 1.20 (3, s), 1.77 (3, t, J = 2 Hz), 1.92 (3, d, J = 1.2 Hz), 5.70 ppm (1, broad s). This compound was not further purified, but was directly converted into enol formate **8**.

(4*R*,5*S*)-4-(2-Butynyl)-3,4,5-trimethylcyclohex-2-enone (11).[7] Enone **11** is prepared from enol ether **10** by the same procedure as that used for the preparation of enone **4**. The material is obtained as an analytically pure off-white solid, mp 77–80 °C, in 98% yield: ^1H NMR 0.97 (3, d, J = 7 Hz), 1.00 (3, s), 1.73 (3, t, J = 2 Hz), 1.83 (3, d, J = 1 Hz), 5.73 ppm (1, broad s).

Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.88; H, 9.43. HRMS: Found, 190.1403.

Conversion of Enones 3, 4, and 11 into Bicyclo[2.2.2]octenes. The first step of this two-stage conversion is reduction of the enone with lithium aluminum hydride in ether. The enone to be reduced (8 mmol) is dissolved in 30 mL of dry ether, cooled to −10 °C, and 8 mmol of $LiAlH_4$ is added. The solution is stirred magnetically and allowed to warm to room temperature over a 1-h period. After being worked up in the normal manner (see procedure for preparation of compound **3**), the allylic alcohol is obtained, usually as a clear or pale yellow oil. ^1H NMR analysis reveals that all of the allylic alcohols are diastereomeric mixtures. In general, these materials were not subjected to combustion analysis or mass spectroscopy, but were used in crude form for subsequent cyclization.

The following cyclization procedure is typical.

(*E*)-5-(1-Formyloxyethylidine)-1-methylbicyclo[2.2.2]oct-2-ene (7). A solution of 8.95 g of allylic alcohol **5** in 200 mL of 97% formic acid is stirred at room temperature for 2 h. The solution is carefully poured into 250 mL of ice-cold 50% aqueous NaOH. The resulting mixture is extracted with ether and the resulting ether solution dried and evaporated to obtain bicyclic enol formate **7** as a dark oil. Kugelrohr distillation affords 8.68 g of **7** as a clear liquid (82%).

The enol formate produced by this workup procedure is typically contaminated with 5–15% of a 1:1 mixture of methyl ketones **21** and **22**, which are formed by base-catalyzed hydrolysis of **7**. This problem may be minimized by using anhydrous formic acid and evaporating the solvent after cyclization. However, even this modification still yields a product which is contaminated by a few percent of hydrolyzed material, perhaps as a result of the equivalent of water which is produced in the reaction. For example, a solution of 250 mg of allylic alcohol **5** in 5 mL of light petroleum ether is diluted with 25 mL of anhydrous formic acid (distilled from boric anhydride) and kept at room temperature for 2 h. The solvent is removed by evaporation at 0.5 Torr to afford 270 mg (93%) of nearly pure enol formate **7**, which is purified by distillation [bp 60–65 °C (0.01 Torr)]: IR 1733, 1149 cm^{-1}; ^1H NMR 1.16 (3, s), 1.87 (3, t, J = 1.5 Hz), 3.23 (1, broad d, J = 6.5 Hz), 5.97 (1, dd, J = 1.5 and 8.5 Hz), 6.23 (1, dd, J = 6.5 and 8.5 Hz), 7.92 ppm (1, s); ^{13}C NMR 15.57, 24.50, 26.73, 32.22, 33.94, 34.77, 39.03, 128.45, 131.23, 134.95, 139.32, 158.78 ppm.

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.27; H, 8.53. HRMS: Found, 192.1153.

The following compounds were also prepared.

(*E*)-5-(1-Formyloxyethylidine)-1,2-dimethylbicyclo[2.2.2]-oct-2-ene (8). The product as obtained is contaminated with varying amounts of hydrolyzed material (vide supra). An analytical specimen was obtained by preparative GLC (5 ft × 0.25 in. Carbowax at 170 °C, He flow 30 mL min^{-1}, retention time 7.0 min): ^1H NMR 1.13 (3, s), 1.73 (3, d, J = 1.5 Hz), 1.87 (3, t, J = 1.5 Hz), 3.13 (1, m), 5.87 (1, broad d, J = 6 Hz), 7.87 ppm (1, s); ^{13}C NMR 15.46, 17.02, 22.22, 26.61, 32.45, 34.23, 37.16, 39.07, 124.93, 128.63, 134.42, 144.66, 158.94 ppm.

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.39; H, 8.58. HRMS: Found, 206.1339.

(*E*)-(1*R*,7*S*)-5-(1-Formyloxyethylidine)-1,2,7-trimethylbicyclo[2.2.2]oct-2-ene (13).[7] The analytical sample was obtained by preparative GLC (5 ft × 0.25 in. Carbowax at 170 °C, He flow 30 mL min^{-1}, retention time 7.8 min): ^1H NMR 0.97 (3, d, J = 7 Hz), 1.12 (3, s), 7.90 ppm (1, s).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.70; H, 8.96. HRMS: Found, 220.1441.

1-Methylbicyclo[3.2.2]non-6-en-2-one (18). Enone **15** is reduced by the same method as that outlined previously for the reduction of enones **3**, **4**, and **11**; allylic alcohol **16** is isolated in 87% yield. A solution of 2.67 g (17.8 mmol) of this material in 150 mL of dry ether is cooled to −70 °C and treated with 25 mL (50 mmol) of 2 M n-butyllithium. The resulting heterogeneous mixture is allowed to warm to room temperature over a 2-h period. Trimethylsilyl chloride (6.85 g, 63 mmol) is added and the mixture is kept at room temperature overnight. The mixture is filtered through a fine filter paper (Whatman 40) and evaporated to obtain 4.16 g (80%) of compound **17**. This material is dissolved in a mixture of 150 mL of 97% formic acid and 15 mL of ether, then kept at room temperature for 5 h. After a normal workup, 2.45 g of dark oil is obtained. ^1H NMR analysis shows that this material is an enol formate and contains trimethylsilyl resonances. It is dissolved in 100 mL of methanol and 50 mL of 1 M aqueous KOH is added. After 5 h at room temperature, the solution is evaporated to a gummy semisolid which is partitioned between 10% HCl and ether. After drying and evaporation, the ether layer affords 1.66 g (76%) of enone **18** as a dark liquid. GLC analysis (0.25 in. × 5 ft OV-101 at 130 °C) reveals that the product is homogeneous. An analytical specimen was obtained by preparative GLC: IR 1704 cm^{-1}; ^1H NMR 1.14 (3, s), 6.00 (1, d, J = 9 Hz), 6.30 ppm (1, dd, J = 7 and 9 Hz).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 80.10; H, 9.41. HRMS: Found, 150.1082 (49.22% relative to m/e 93).

(*E*)-3-(1-Formyloxyethylidine)-1-methylbicyclo[2.2.2]octane (19). To a solution of 0.5 g of bicyclic enol formate **7** in 30 mL of ethanol is added 50 mg of 10% palladium on carbon. The mixture is stirred at atmospheric pressure with hydrogen gas for 2 h. The catalyst is removed by filtration to obtain 440 mg (87%) of enol formate **19** as a clear liquid. The analytical sample was obtained by preparative GLC (5 ft × 0.25 in. Carbowax): ^1H NMR 0.87 (3, s), 1.72 (3, s), 2.37 ppm (1, broad t).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.91; H, 9.13. HRMS: Found, 194.1320.

4-Methylbicyclo[2.2.2]octan-2-one (23). A solution of 0.5 g of enol formate **19** dissolved in 15 mL of methanol and 15 mL of methylene chloride is cooled to −78 °C and ozone (generated with a Welshbach Ozonator) is passed through until the solution turns blue. After adding 2 mL of dimethyl sulfide, the solution is warmed to room temperature and stirred for 1 h. The mixture is concentrated on a rotary evaporator and the residue partitioned between pentane and water. Evaporation of the dried pentane layer affords 340 mg (96%) of ketone **23** as a light yellow liquid: IR 1724 cm^{-1}; ^1H NMR 0.98 (3, s), 2.00 (2, s), 2.17 ppm (1, broad t).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.17; H, 9.81. HRMS: Found, 138.1029.

3-Acetyl-1-methylbicyclo[2.2.2]octane (20). Enol formate **19** (1.65 g) is added to 25 mL of 0.35 M KOH in methanol. After 2 h, the mixture is neutralized with concentrated HCl. The mixture is concentrated under reduced pressure to a yellow oil which is taken up in ether, dried over $MgSO_4$, and filtered. Removal of the ether affords 1.46 g of ketone **20** as a pale yellow liquid: IR 1709 cm^{-1}; ^1H NMR 0.80 (3, s), 1.87 ppm.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.53; H, 10.84. Found: C, 79.43; H, 10.69. HRMS: Found, 166.1386.

(4*S*,5*S*)-5-Acetyl-1-methylbicyclo[2.2.2]oct-2-ene (21) and (4*S*,5*R*)-5-Acetyl-1-methylbicyclo[2.2.2]oct-2-ene (22).[7] Hydrolysis of enol formate **7**, by essentially the same procedure as that given above for the hydrolysis of **19**, affords a 3:1 mixture of ketones **21** and **22** in 95% yield. The two isomers have retention times on GLC (6 ft × 0.25 in. Carbowax at 120 °C) of 2.7 and 3.4 min, respectively. The major product (retention time 3.4 min) was collected by preparative GLC for analysis: IR 1710 cm^{-1}; ^1H NMR 1.17 (3, s), 2.00 (3, s), 6.00 ppm (2, m).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.35; H, 9.75. HRMS: Found, 164.1200.

The minor component (retention time 2.7 min) was not isolated in a pure state. From the mixture of **21** and **22**, it may be deduced that the minor isomer has ^1H NMR signals at 1.17 (3, s) and 2.10 ppm (3, s). Atmospheric hydrogenation of the mixture over 10% Pd/C in ethanol affords ketone **20**, identical spectrally with the material prepared previously.

Acknowledgments. This work was supported by grants from the National Science Foundation (Grant GP-31321X) and the National Institutes of Health (Grant CA-12617). We thank Dr. Woodrow Conover of the Stanford Magnetic Res-

onance Laboratory for instructing us in the use of the HX-360 spectrometer.

Registry No.—**1**, 5323-87-5; **2**, 61484-02-4; **3**, 61484-03-5; **4**, 61484-04-6; *cis*-**5**, 61484-05-7; *trans*-**5**, 61484-06-8; *cis*-**6**, 61484-07-9; *trans*-**6**, 61505-79-1; **7**, 61484-08-0; **8**, 61484-09-1; **9**, 61484-10-4; *cis*-**10**, 61484-11-5; *trans*-**10**, 61484-12-6; **11**, 61484-13-7; **12** isomer A, 61505-42-8; **12** isomer B, 61484-14-8; **13**, 61484-15-9; **14**, 61484-16-0; **15**, 61484-17-1; *cis*-**16**, 61484-18-2; *trans*-**16**, 61484-19-3; *cis*-**17**, 61484-20-6; *trans*-**17**, 61484-21-7; **18**, 61484-22-8; **19**, 61484-23-9; **20**, 61484-24-0; **21**, 61484-25-1; **22**, 61521-26-4; **23**, 40291-46-1; 1-bromo-2-butyne, 3355-28-0; methyl iodide, 74-88-4; propargyl bromide, 106-96-7; formic acid, 64-18-6; trimethylsilyl chloride, 75-77-4; ozone, 10028-15-6.

References and Notes

(1) See W. S. Johnson K. Wiedhaup, S. F. Brady, and G. L. Olson, *J. Am. Chem. Soc.*, **96**, 3979 (1974), and previous papers in the series.
(2) For applications of π-cyclization to the synthesis of other types of systems, see, inter alia, (a) R. A. Volkmann, G. C. Andrews, and W. S. Johnson, *J. Am. Chem. Soc.*, **97**, 4777 (1975); (b) S. Murayama, D. Chan, and M. Brown, *Tetrahedron Lett.*, 3715 (1968); (c) J. A. Marshall, G. L. Bundy, and W. I. Fanta, *J. Org. Chem.*, **33**, 3913 (1968).
(3) R. L. Danheiser and G. Stork, *J. Org. Chem.*, **38**, 1775 (1973).
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(5) J. P. Blanchard and H. L. Goering, *J. Am. Chem. Soc.*, **73**, 5863 (1951).
(6) Infrared spectra (IR) were measured as neat films on a Perkin-Elmer 137 infrared spectrometer. Proton magnetic resonance spectra (^{1}H NMR) were measured in CCl_4 on a Varian T-60 or a Bruker HX-360 nuclear magnetic resonance spectrometer. Chemical shifts are reported in parts per million downfield from internal tetramethylsilane (δ) and are followed in parentheses by the integrated area, multiplicity, and coupling constant in hertz. Carbon magnetic resonance spectra (^{13}C NMR) were measured in $CDCl_3$ on a Nicolet TT-23 nuclear magnetic resonance spectrometer operating at 25.14 MHz. Chemical shifts are referenced to $CDCl_3$ and are reported in parts per million downfield from tetramethylsilane (central peak of $CDCl_3$ triplet = 1936 Hz).
(7) These products are racemic. The name given is that of the enantiomer depicted in the text.
(8) This experiment was first carried out by Phillip Nies.
(9) This experiment was first carried out by Mario Curzi.

Intramolecular 1,3-Dipolar Cycloadditions of Nitrile Imines Bearing an Alkenyl Substituent

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Received September 28, 1976

Two series of nitrile imines bearing an alkenyl substituent were generated in situ from the corresponding 1-chlorohydrazones by treatment with triethylamine in aromatic hydrocarbon solvents. The intramolecular 1,3-dipolar cycloaddition, leading to fused ring 2-pyrazolines, was the exclusive or the predominant reaction with few exceptions. Retention of stereochemistry was observed in the case of 1,2-disubstituted ethylenic functions.

1,3-Dipolar cycloadditions are well known for their utility in heterocyclic syntheses as well as for the interesting mechanistic questions which they raise. In recent years, intramolecular examples have been reported to give fused or bridged ring heterocycles.[2] In these cases, observations have often been in contrast with the usual intermolecular patterns, particularly regarding orientation.

In this context, we now report an extensive study on the behavior of nitrile imines containing a carbon–carbon double bond potentially able to behave as a dipolarophile. In order to investigate electronic and steric effects on these intramolecular reactions, the nitrile imines **4a–e** and **10a–c** were studied (Charts I and II).

Chart I

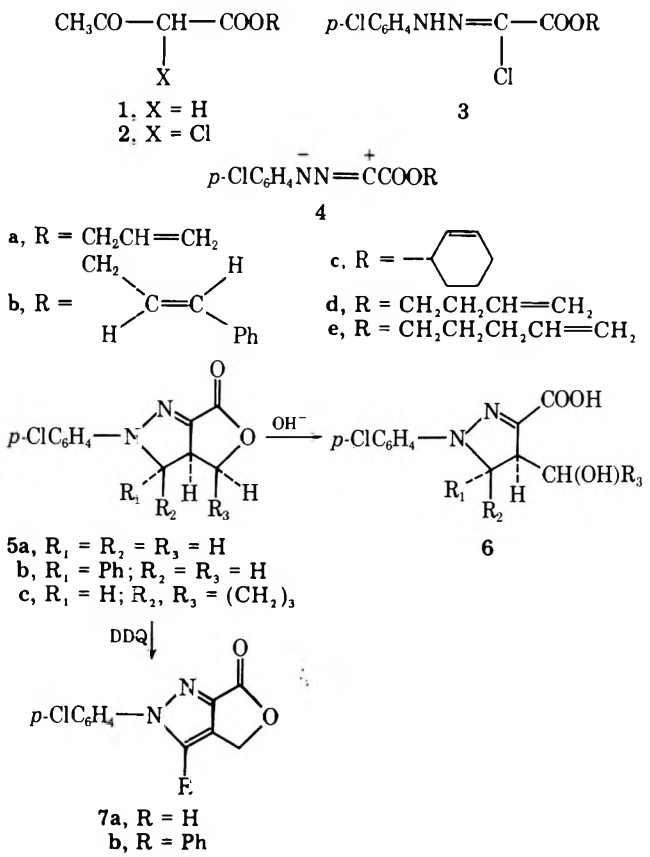


Chart II

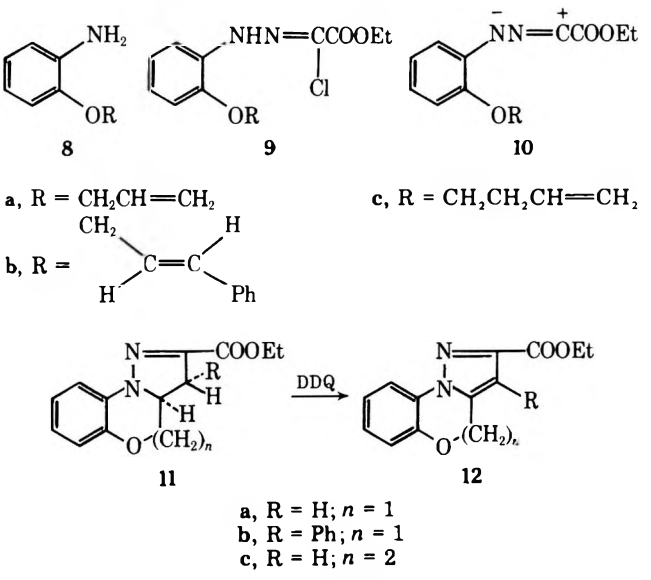


Table I. Preparation of Intermediates 1, 2, 3, and 9[a]

Compd	Yield, %	Mp or bp, °C (mm)	Recrystn solvent
1d	55	89–90 (25)	
1e	63	74–75 (3)	
2a[4]	75	45–48 (2)	
2b	81	*b*	
2c	79	*c*	
2d	73	67–69 (2)	
2e	65	78–80 (2)	
3a	67	127	Ethanol
3b	47	144	Ethanol
3c	51	138	Ethanol
3d	49	96	Ethanol
3e	65	84	*n*-Hexane
9a	30[d]	42	*n*-Pentane
9b	38[d]	95	Diisopropyl ether
9c	29[d]	34	*n*-Pentane

[a] Satisfactory elemental analyses were obtained for the compounds listed with the exception of **2b,c**. [b] Undistilled oil of ca. 90% purity by NMR analysis; attempted distillation in vacuo caused extensive decomposition. [c] Undistilled oil of purity better than 95% (NMR). [d] By chromatography on a silica gel column.

Results and Discussion

Following the common procedure for the preparation of this class of compounds,[3] nitrile imines **4a–e** and **10a–c** were obtained from the corresponding 1-chlorohydrazones **3a–e** and **9a–c**. These intermediates were in turn available as follows.

The treatment of the alkenyl acetoacetates **1a–e** with sulfuryl chloride afforded the corresponding 2-chloroacetoacetates **2a–e**, which gave **3a–e** through the coupling reaction with 4-chlorobenzenediazonium chloride. Analogously, compounds **9a–c** were prepared by diazotization of the ortho-substituted anilines **8a–c** and subsequent coupling with ethyl 2-chloroacetoacetate. Table I collects yields and physical data. (See paragraph at end of paper regarding supplementary material.)

The above 1-chlorohydrazones were treated with a large excess of triethylamine in aromatic hydrocarbon solvents, as reported in Table II. Temperatures were chosen in accord with the differing substrate reactivities, while the reaction times were determined by periodical TLC analyses. Products and yields are indicated in Table II. In the case of **3d** and **3e**, the reaction gave an intractable, tarry mixture; an attempt to isolate characterizable products after a short reaction time was also unsuccessful.

The product structures were determined from elemental analyses and IR and NMR spectra (see Table III and Experimental Section). Mass spectra are available for **14a,b**.

The DDQ oxidation of **5a,b** and **11a–c** led to the corresponding pyrazoles **7a,b** and **12a–c**, thus providing chemical support to the assigned structures.[5] Compounds **7a,b**[6] and **12a,b**[7] had already been prepared by analogous intramolecular cycloadditions of the alkyne derivatives corresponding to **4a,b** and **10a,b**. Also, the lactones **5a–c** readily underwent alkaline hydrolysis to afford the hydroxy acids **6a–c**.

The stereochemistry of the above products was assigned on the basis of the following observations.

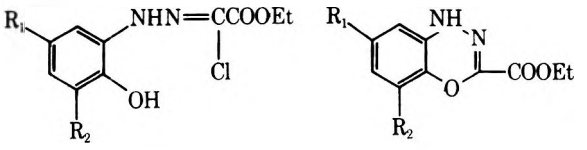
The NMR spectrum of **5b** shows for the pyrazolinic proton in the 5 position a doublet with J = 11.5 Hz. The literature data for the 2-pyrazolines[8] reveal that the vicinal coupling constants of the hydrogens in the 4 and 5 positions are in the range 2.3–10.5 Hz for J_{trans} and 8.5–14 Hz for J_{cis}, with great dependence on the substituents. Thus, the above value may suggest prima facie a cis configuration; such a stereochemistry, however, has to be ruled out for the lactone **5b**, since the hydroxy acid **6b** derived from it has $J_{4,5}$ = 5.5 Hz, which corresponds unequivocally to trans coupling. As the molecular models indicate, the above anomalous value may be related to the torsional strain involved in the fused ring structure **5**.

For the tricyclic compound **5c**, the examination of molecular models shows that only one configuration can be adopted in which the three hydrogens in the bridgehead positions are situated cis to each other; the observed values of the coupling constants are 8.5 and 11 Hz. Compound **11b** presents for the pyrazolinic protons J = 9 Hz, which is more consistent with a trans structure than with a cis one.

The results now reported reveal that the intramolecular 1,3-cycloaddition is the exclusive or predominant reaction of **4a–c** and **11a–c**, while it does not occur in the case of **4d,e**. Since the ethylenic function of **4d,e** is electronically similar to that of **10c**, the lack of intramolecular cycloaddition by the former substrates may be attributable to unfavorable molecular geometries for the intramolecular approach of the reactive centers. Such an approach, on the other hand, is probably facilitated in the case of **10c** by the ortho relationship of the substituents.[9]

The intramolecular cycloadditions of **4b,c** and **10b** are particularly interesting since they involve 1,2-disubstituted double bonds of known stereochemistry. The structure of the products reveals cis stereospecificity, which is in line with the previous findings for intermolecular cycloadditions of nitrile imines with 1,2-disubstituted ethylenes.[10]

The side process leading to the isomeric 1,3,4-benzoxadiazines **14a** and **14b** remains to be considered. These products could arise from the preliminary Claisen-type rearrangement of **9b** to the isomeric phenols **13a** and **13b**, according to the known behavior of aryl allyl ethers.[11] Owing to the presence of triethylamine, the corresponding phenoxide ions should be actually present, from which the final products may well be formed through the intramolecular nucleophilic displacement of the halogen. Control experiments showed that (1) **9b** rearranges in boiling toluene to produce only phenol **13a**, (2) the latter compound readily reacts with triethylamine to afford **14a**. Further work is in progress to provide mechanistic evidence for this interesting side reaction.



13 14

a, R_1 = $CH_2CH{=}CHPh$; R_2 = H;
b, R_1 = H; R_2 = $CH(Ph)CH{=}CH_2$

Experimental Section

Melting points were taken on a Büchi apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 377 spectrophotometer. NMR spectra were usually obtained on a Varian A-60A instrument with Me_4Si as internal standard; a Varian HA-100 instrument was used for compounds **11a–c** and **14a,b**. Mass spectra were determined on a Hitachi Model RMU-6L apparatus.

Compounds **1a,b**,[12] **1c**,[13] **8a**,[14] **8b**,[15] and **8c**[16] were prepared by literature methods. Compounds **1d,e** were synthesized according to the procedure described for **1b**.[12]

Preparation of Alkenyl 2-Chloroacetoacetates (2). General Procedure. A solution of sulfuryl chloride (72 mmol) in dry chloroform (20 mL) was slowly added (2 h) to a solution of **1** (60 mmol) in dry chloroform (80 mL). During the addition, the temperature was kept at 0 °C and dry nitrogen was bubbled through the reaction mixture. After 2 h at room temperature, chloroform was added and the organic solution was washed with aqueous $NaHCO_3$ and dried over $MgSO_4$. The solvent was removed to give **2** in a crude state. Distillation in vacuo was carried out in the case of **2a,d,e**. See Table I.

Preparation of Alkenyl 2-Chloro-2-(4-chlorophenylhydra-

Table II. Treatment of 1-Chlorohydrazones 3 and 9 with Triethylamine[a]

Compd	Solvent[b]	Time, h	Product(s)	Yield, %	Isolation procedure[c]
3a	Benzene	7	2-Aryl-6-oxo-2,3,3a,6-tetrahydro-4*H*-furo[3,4-c]pyrazole (**5a**)[d]	69	A
3b	Toluene	3	2-Aryl-6-oxo-3-phenyl-2,3,3a,6-tetrahydro-4*H*-furo[3,4-c]pyrazole (**5b**)[d]	73	A
3c	Benzene	2	4-Aryl-2-oxo-2,4,4a,5,6,7,7a,7b-octahydrofuro[4,3,2-c,*d*]indazole (**5c**)[d]	73	A
3d	Toluene	80	*e*		
3e	Xylene	90	*e*		
9a	Benzene	40	2-Carbethoxy-3,3a-dihydro-4*H*-pyrazolo[5,1-c][1,4]benzoxazine (**11a**)	85	A
9b	Toluene	108	2-Carbethoxy-3-phenyl-3,3a-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]benzoxazine (**11b**)	36	B
			2-Carbethoxy-6-(1-phenylpropen-3-yl)-4*H*-1,3,4-benzoxadiazine (**14a**)	12	B
			2-Carbethoxy-8-(3-phenylpropen-3-yl)-4*H*-1,3,4-benzoxadiazine (**14b**)	10	B
9c	Toluene	64	2-Carbethoxy-3,3a,4,5-tetrahydropyrazolo[5,1-*d*][1,5]benzoxazepine (**11c**)	45	B

[a] Concentrations were 0.01 M for the 1-chlorohydrazones and 0.05 M for triethylamine. [b] At refluxing. [c] A = crystallization with diisopropyl ether; B = chromatography on silica gel column with benzene–ethyl acetate (9:1) as eluent. [d] Aryl = 4-chlorophenyl. [e] Tarry mixture.

Table III. Physical and Spectral Data of 2-Pyrazoline Derivatives[a]

Compd	Mp, °C (recrystn solvent)	ν_{CO} (Nujol), cm^{-1}	NMR spectrum, δ (*J*, Hz)
5a	130[b] (CCl_4)	1760	$CDCl_3$: 3.7–4.9 (5 H, m, CH_2CHCH_2), 6.9–7.4 (4 H, m, Ar)
5b	175[b] (*n*-hexane–benzene)	1760	$CDCl_3$: 3.7–4.9 (3 H, m, CH_2CH), 5.35 (1 H, d, J = 11.5, CHN), 6.8–7.5 (9 H, m, Ar)
5c	140[b] (*n*-hexane–benzene)	1765	$CDCl_3$: 1.2–2.3 [6 H, m, $(CH_2)_3$], 4.09 (1 H, dd, J = 8.5 and 11, CHCHCH), 4.7–5.2 (2 H, m, CHCHCH), 6.9–7.4 (4 H, m, Ar)
6a	167[b] (acetone)	1670	C_3D_6O: 3.7–4.3 (5 H, m, CH_2CHCH_2), 4.7 (2 H, broad s, two OH), 7.0–7.4 (4 H, m, Ar)
6b	193[b] (benzene)	1665	C_3D_6O: 3.2–3.6 (1 H, m, $CHCH_2$), 3.97 (2 H, d, J = 5, CH_2), 4.8 (2 H, broad s, two OH), 5.56 (1 H, d, J = 5.5, CHPh), 7.0–7.4 (9 H, m, Ar)
6c	180[b] (acetone)	1670	Me_2SO-d_6: 1.1–2.2 [6 H, m, $(CH_2)_3$], 3.50 (1 H, dd, J = 5 and 11, CHCHCH), 4.0–4.8 (2 H, m, CHCHCH), 6.9–7.4 (4 H, m, Ar), 8.0 (2 H, broad s, two OH)
11a	101[c] (*n*-hexane)	1725	$CDCl_3$: 1.35 (3 H, t, CH_3), 2.90, 3.27 (2 H, AB part of ABX system, J_{AB} = 18, J_{AX} = 6.5, J_{BX} = 11.5, CH_2CHN), 3.4–4.5 (5 H, m, $CHCH_2O$ and CH_2CH_3), 6.8–7.6 (4 H, m, Ar)
11b	115[c] (*n*-hexane–benzene)	1715	$CDCl_3$: 1.20 (3 H, t, CH_3), 3.69 (1 H, d, J = 9, CHPh), 4.0–4.4 (5 H, m, $CHCH_2O$ and CH_2CH_3), 6.8–7.7 (9 H, m, Ar)
11c	122[d] (diisopropyl ether)	1725	$CDCl_3$: 1.37 (3 H, t, CH_3), 2.1–2.4 (2 H, m, CH_2CH_2O), 2.84 (1 H, dd, J = 13 and 17, one proton of pyrazoline CH_2), 3.3–4.6 (6 H, m, two CH_2O and two pyrazoline protons), 6.9–7.6 (4 H, m, Ar)

[a] All the compounds listed gave correct elemental analyses. [b] Yellow crystals. [c] Pale yellow crystals. [d] Colorless crystals.

zono)acetates (3). General Procedure. A cold aqueous solution of 4-chlorobenzenediazonium chloride (15 mmol) was added dropwise to a solution of 2 (15 mmol) and sodium acetate (30 mmol) in 80% aqueous methanol (60 mL) under vigorous stirring and ice cooling. The mixture was stirred overnight at room temperature. The solid material was collected by filtration, washed several times with water, and recrystallized from ethanol to give pure **3**. See Table I.

Preparation of Ethyl 2-[2-(Alkenyloxy)phenylhydrazono]-2-chloroacetates (9). General Procedure. A solution of $NaNO_2$ (10 mmol) in water (5 mL) was added to a solution of amine **8** (10 mmol) in 0.5 N HCl (60 mL) under stirring and ice cooling. The mixture was then adjusted to pH 4 by sodium acetate and ethyl 2-chloroacetoacetate (10 mmol) was added dropwise at 0–5 °C. After 1 h at room temperature, the mixture was extracted with ether and the organic solution was dried over $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column with benzene as eluent to afford pure **9**. See Table I.

Treatment of 1-Chlorohydrazones 3 and 9 with Triethylamine. General Procedure. A solution of 1-chlorohydrazone **3** or **9** (15 mmol) and triethylamine (75 mmol) in dry solvent (1.5 L) was heated under reflux as provided in Table II. The mixture was then washed with aqueous HCl, dried over $MgSO_4$, and evaporated. The residue furnished the products indicated in Table II. In the case of **9b**, the column chromatography gave three products in the following order of elution: **11b**, **14a**, and **14b**. Physical and spectral data of **5a–c** and **11a–c** are collected in Table III. The following data are available for **14a,b**.

Compound **14a**: yellow crystals, mp 157 °C (*n*-hexane–benzene); IR (Nujol) 3300 (NH) and 1710 cm^{-1} (CO); NMR (C_6D_6) δ 0.92 (3 H, t, CH_2CH_3), 3.06 (2 H, d, J = 6 Hz, CH_2CH=), 3.96 (2 H, q, CH_2CH_3), 5.83 (1 H, d, J = 2 Hz, Ar), 6.10 (1 H, dt, J = 16 and 6 Hz, CH_2CH=), 6.2–6.6 (4 H, m, PhCH=, NH, and Ar), 7.0–7.3 (5 H, m, Ar); mass spectrum *m/e* (rel intensity) 322 (100), 294 (15), 222 (4), 206 (5), 194 (13), 178 (6), 132 (11), 117 (6). Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.67; H, 5.58; N, 8.63.

Compound **14b**: yellow crystals, mp 119 °C (*n*-hexane–benzene); IR (Nujol) 3300 (NH) and 1720 cm^{-1} (CO); NMR (C_6D_6) δ 0.91 (3 H, t, CH_2CH_3), 3.92 (2 H, q, CH_2CH_3), 5.03 (1 H, dt, J = 9 and 1 Hz, CHPh), 5.1–5.2 (2 H, m, CH_2=), 5.70 (1 H, dd, J = 7 and 2 Hz, Ar), 5.95 (1 H, broad s, NH), 6.0–6.7 (3 H, m, CH= and Ar), 6.9–7.4 (5 H, m, Ar); mass spectrum *m/e* (rel intensity) 322 (100), 294 (7), 222 (16), 206 (13), 194 (16), 178 (10), 117 (14). Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63 N, 8.69. Found: C, 70.69; H, 5.89; N, 8.50.

Alkaline Hydrolysis of 5a–c. General Procedure. Lactone **5** (2 mmol) was treated with 2.5 N NaOH in 50% aqueous ethanol (30 mL). After 30 min of refluxing, the solution was allowed to cool, acidified by concentrated HCl, and partly evaporated under reduced pressure. The solid material was collected by filtration and recrystallized to afford hydroxy acid **6** in 70–80% yield. See Table III.

Oxidation of 5a–c and 11a–c by DDQ. Typical Procedure. A mixture of **11c** (1.4 mmol) and DDQ (4.2 mmol) in benzene (60 mL) was heated under reflux for 16 h. The solid material was filtered off and the solution was evaporated to dryness. The residue was chromatographed on a silica gel column with 1:1 diethyl ether–petroleum

ether as eluent to give **12c** in 61% yield: mp 78–79 °C (*n*-hexane); NMR ($CDCl_3$) δ 1.40 (3 H, t, CH_2CH_3), 3.06 (2 H, t, CH_2CH_2O), 4.2–4.7 (4 H, m, CH_2CH_3 and CH_2CH_2O), 6.77 (1 H, s, CH=), 7.1–7.4 (3 H, m, Ar), 7.75–8.05 (1 H, m, Ar). Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46; N, 10.85. Found: C, 65.19; H, 5.50; N, 10.68.

Rearrangement of 9b. A solution of **9b** (1.3 g) in dry toluene (250 mL) was heated under reflux for 60 h. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column. Elution with benzene–ethyl acetate (85:15) gave unchanged **9b** (0.40 g) followed by **13a** (0.49 g); mp 107–109 °C (*n*-hexane); IR (Nujol) 3250–3350 (NH and OH) and 1700 cm^{-1} (CO); NMR ($CDCl_3$) δ 1.32 (3 H, t, CH_2CH_3), 3.40 (2 H, d, J = 6 Hz, CH_2CH=), 4.29 (2 H, q, CH_2CH_3), 6.1–7.3 (10 H, overlapping signals, Ar and CH=CH), 7.6 (1 H, broad s, OH), 8.4 (1 H, broad s, NH). Anal. Calcd for $C_{19}H_{19}ClN_2O_3$: C, 63.59; H, 5.34; N, 7.81. Found: C, 63.29; H, 5.55; N, 7.57.

Treatment of 13a with Triethylamine. A solution of **13a** (0.26 g) and triethylamine (0.50 g) in dry toluene (70 mL) was heated under reflux for 30 min. The mixture was washed with aqueous HCl, dried over $MgSO_4$, and evaporated. The residue was taken up with diisopropyl ether and filtered to afford practically pure **14a** (0.18 g) (NMR analysis).

Registry No.—**1a**, 1118-84-9; **1b**, 61363-91-5; **1c**, 61363-92-6; **1d**, 61363-93-7; **1e**, 61363-94-8; **2a**, 21045-82-9; **2b**, 61363-95-9; **2c**, 61394-29-4; **2d**, 61363-96-0; **2e**, 61363-97-1; **3a**, 61363-98-2; **3b**, 61363-99-3; **3c**, 61364-00-9; **3d**, 61364-01-0; **3e**, 61364-02-1; **5a**, 61364-03-2; **5b**, 61364-04-3; **5c**, 61364-05-4; **6a**, 61364-06-5; **6b**, 61364-07-6; **6c**, 61364-08-7; **8a**, 27096-64-6; **8b**, 61364-09-8; **8c**, 56182-23-1; **9a**, 61364-10-1; **9b**, 61364-11-2; **9c**, 61364-12-3; **11a**, 61364-13-4; **11b**, 61364-14-5; **11c**, 61364-15-6; **12c**, 61364-16-7; **13a**, 61364-17-8; **14a**, 61364-18-9; **14b**, 61364-19-0; sulfuryl chloride, 7791-25-5; 4-chlorobenzenediazonium chloride, 2028-74-2; ethyl 2-chloroacetoacetate, 609-15-4; triethylamine, 121-44-8.

Supplementary Material Available. Full NMR data for compounds **1**, **2**, **3**, and **9** (2 pages). Ordering information is given on any current masthead page.

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(1) Author to whom correspondence should be addressed.
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Hydroboration. 45. New, Convenient Preparations of Representative Borane Reagents Utilizing Borane–Methyl Sulfide

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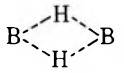
Received October 28, 1976

Convenient preparations for several highly useful borane reagents, such as thexyl-, disiamyl-, dicyclohexyl-, catechol-, diisopinocampheylborane, 9-borabicyclo[3.3.1]nonane, and 1,6-diboracyclodecane, utilizing the readily available, relatively stable reagent, borane–methyl sulfide (BMS), are described. The reactions of BMS with the respective olefins or with catechol proceed smoothly at room temperature in various solvents, such as tetrahydrofuran (THF), ethyl ether (EE), dichloromethane, and pentane. In some cases, the reaction involving the neat reagents at 0 °C can also be utilized. Methyl sulfide can be readily removed from the products. However, the presence of methyl sulfide does not interfere with typical applications of borane reagents, such as thexyl-, disiamyl-, dicyclohexyl-, and diisopinocampheylborane, normally utilized in situ, without isolation. This feature was examined by carrying out representative hydroborations with these reagents prepared from BMS and then subjecting the resulting organoboranes to subsequent representative transformations. In the case of stable and isolable reagents, such as 9-BBN, catecholborane, and 1,6-diboracyclodecane, methyl sulfide can be readily removed, along with the solvents, by distillation. A detailed study was made of the preparation of pure diisopinocampheylborane from (+)-α-pinene and BMS in various solvents, both at room temperature and at 0 °C. The applicability of this reagent thus produced in asymmetric synthesis was established by the hydroboration of *cis*-2-butene, followed by oxidation, to yield (*R*)-(−)-2-butanol in optical purities of 88–97%.

Both hydroboration and selective reduction based on organoborane derivatives are proving highly useful in organic synthesis.[2] Partially substituted borane reagents,[3] such as thexylborane, disiamylborane, dicyclohexylborane, diisopinocampheylborane (IPC_2BH), 9-borabicyclo[3.3.1]nonane (9-BBN), 1,3,2-benzodioxaborole (catecholborane), and 1,6-diboracyclodecane, are finding an increasing role in these applications.

Thexylborane is a highly versatile reagent,[4] especially valuable for the synthesis of unsymmetrical ketones and in the new annelation reactions leading to pure (100%) transfused bicyclic ketones. Disiamylborane and dicyclohexylborane are highly hindered dialkylboranes possessing better regioselectivity than borane itself.[2,5,6] These hindered reagents are used especially for the monohydroboration of alkynes to the vinylborane stage.[7] Catecholborane is a mild hydroborating[8] and reducing[9] agent, whose chemistry has recently been reviewed.[10] Unlike other dialkylboranes, 9-BBN is exceptionally stable toward disproportionation. Under nitrogen, it is indefinitely stable at room temperature. Its favorable physical properties and unusual stability have made 9-BBN the only commercially available dialkylborane.[11] It is both an exceptionally regioselective hydroborating agent[2,12] and a useful agent for the selective reductions of organic functional

groups.[13] Diisopinocampheylborane (IPC_2BH) is both a chiral hydroborating and reducing agent,[14] extensively used for the asymmetric synthesis of optically active alcohols,[15–17] iodides,[18] and amines[19] from achiral olefins, and amino acids[20] from achiral nitriles. The cyanoborohydride obtained from IPC_2BH has been used for stereoselective reductions in the prostaglandin synthesis.[21] However, 1,6-diboracyclodecane is unique[22] in that it does not hydroborate olefins; it is stable to air, water, and alcohols at room temperature, and is apparently the first molecule containing a transannular hydrogen bridge:



A large number of interesting derivatives can be prepared by the symmetrical and unsymmetrical cleavage of the BH_2B bridge.[23,24]

Until recently, all of these mono- and disubstituted boranes were prepared from borane–tetrahydrofuran (BH_3·THF)[2] or sodium borohydride–boron trifluoride in diglyme (BH_3·DG).[2] However, borane–methyl sulfide[11,25] is a more convenient reagent for the following reasons: (1) BH_3·THF must be stored at 0 °C. Even then, THF is gradually cleaved and the cleavage can become significant upon long storage. But BMS is indefinitely stable at 0 °C and can even be kept at room temperature without detectable change. (2) Reactions with BH_3·THF or BH_3·DG limit the choice of solvents to THF and DG, respectively. Both of these solvents are relatively expensive, and require both careful purification and storage in the absence of oxygen. They are readily miscible with both polar and nonpolar solvents; consequently, they can offer difficulty in their separation from the desired products. On the other hand, BMS permits the use of a wide variety of solvents, such as ethyl ether, dichloromethane, benzene, pentane, hexane, etc. (3) While BH_3·THF is available only as a 1 M solution, BMS is available in highly concentrated form. The commercially available neat liquid is nearly 10 M in BH_3, and considerably more stable than BH_3·THF, offering special advantages in shipping, handling, and storing. (4) The odor of dimethyl sulfide, which might be considered to be a disadvantage, actually proves to be an advantage. The odor serves as a sensitive warning of poor techniques, which should be avoided in working with boranes.

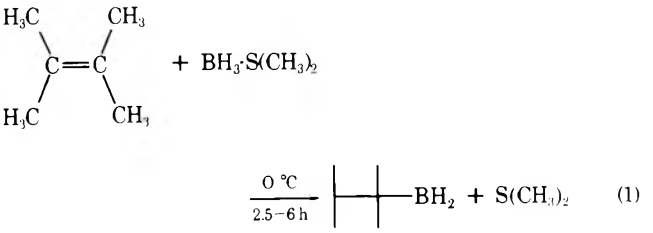
Because of these advantages, BMS is finding increasing application in hydroboration[25–27] and in selective reductions.[25,28,29] Unfortunately, thus far there have been no attempts to develop procedures for the preparation of the frequently applied borane reagents from BMS. We describe here both kinetic studies and convenient preparative methods for thexyl-, dicyclohexyl-, disiamyl-, catecholborane, IPC_2BH, 9-BBN, and 1,6-diboracyclodecane from BMS and the corresponding olefins or catechol in representative aprotic solvents of varied polarity, e.g., THF, ether, dichloromethane, and pentane, at both room temperature and at 0 °C. In addition, in some cases, the desired reagent can be synthesized easily merely by mixing the neat reactants in the stoichiometric quantity.

Methyl sulfide coordinates quite weakly with the monoalkyl-, dialkyl-, and dialkoxyboranes prepared in this study. Consequently, its presence in the reaction mixture does not interfere with the utilization of these reagents for subsequent applications.[29a] This was demonstrated for dicyclohexyl-, disiamyl-, thexyl-, and diisopinocampheylborane, which were used for representative application in situ. In the procedures involving the isolation of 9-BBN, catecholborane, and 1,6-diboracyclodecane, methyl sulfide (bp 38 °C) readily distills off with the solvent, leaving the pure reagent.

Results and Discussion

In the present study, particular importance was given to exploring the preparation of commonly used, substituted borane reagents from BMS in different solvents at two different temperatures. THF, EE, dichloromethane, and pentane were chosen as representative solvents for hydroboration at both room temperature and 0 °C. In the past, preparations and applications of these reagents were mainly studied at 0 °C, in THF or DG. In accordance with the previous reports,[29] we also observed that BMS reacts moderately slower than BH_3·THF. However, the difference in rates offered no major difficulty. Individual reagents are discussed below.

Thexylborane. The hydroboration of 2,3-dimethyl-2-butene with BMS in 1:1 ratio proceeds cleanly to the monoalkylborane stage. At 0 °C, the conversion of the olefin to thexylborane in THF, EE, CH_2Cl_2, and pentane is almost complete in 2.5–6 h (eq 1). Aliquots of the reaction mixture



were withdrawn at definite intervals of time and estimated for residual hydride by hydrolysis. The hydride utilized for hydroboration was calculated by difference and thus the rate of the reaction established.

The reaction with neat reagent is fast, complete in about 2 h at 0 °C. The rate of the reaction was determined by oxidizing individual reaction mixtures at appropriate intervals of time. The yields of 2,3-dimethyl-2-butanol, analyzed by GC at these intervals, correspond to the percentage of hydroboration at the specified intervals and hence to the rate of reaction.

The reaction of 2,3-dimethyl-2-butene with borane in diglyme[30] or borane—THF[31] is virtually complete in 1–2 h at 0 °C. From the results of the BMS study, it is evident that the reaction of olefin with neat BMS is comparable in rate with that realized with 1 M BH_3·THF or BH_3·DG. The results of hydroboration with BMS in various solvents (e.g., THF, EE, CH_2Cl_2, and pentane) indicated that the reaction is slightly faster in THF. In the case of EE, CH_2Cl_2, and pentane, the hydroboration is about 90% complete within 3 h, with further reaction being slow. As revealed in Figure 1, only minor variations in the rates of hydroboration in the different solvents are observed.

In the case of the reaction under neat conditions, methyl sulfide can be easily pumped off and the resulting neat thexylborane (liquid at room temperature) can be used as such, or converted to its amine complexes by addition of the appropriate amine or to the dimethyl thexylboronate by methanolysis.

Application of Thexylborane in the Ketone Synthesis. The presence of methyl sulfide in solution with the reagent thexylborane does not interfere in its application for further hydroboration and subsequent reaction. This was demonstrated in the ketone synthesis via the cyanidation reaction[32] (eq 2). Thexylborane in THF, thus produced from BMS, reacted smoothly with 1 mol of cyclopentene at −25 °C to form thexylcyclopentylborane in 1 h (comparable with the reaction of thexylborane from BH_3·THF[33]). This dialkylborane was readily converted with 1-pentene to thexylcyclopentyl-*n*-pentylborane (1 h, 0 °C). Treatment with NaCN produced the trialkylcyanoborate. Acylation with trifluoroacetic anhydride

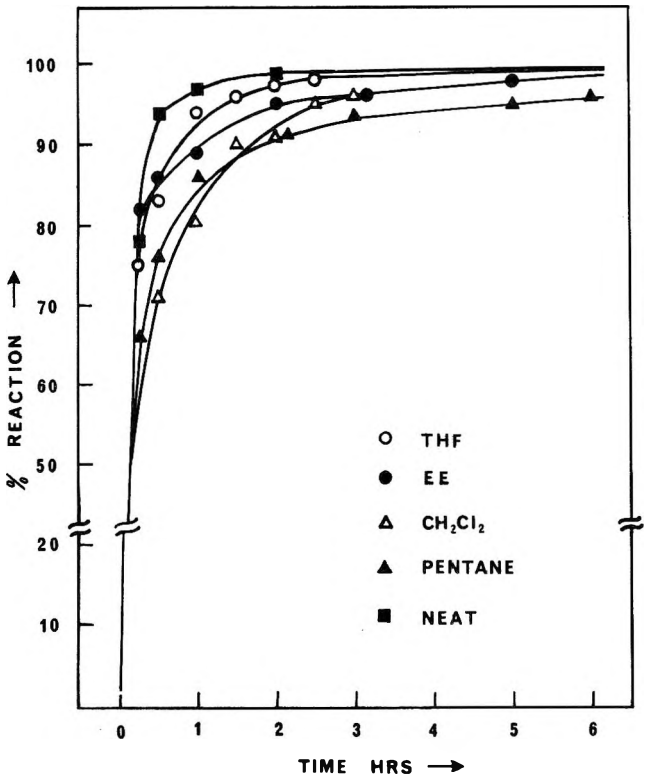
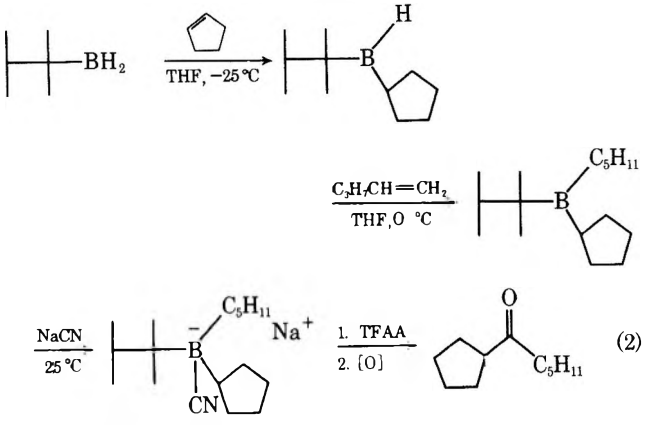
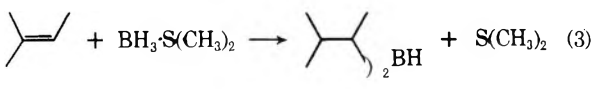


Figure 1. Reaction in a molar ratio of 1:1 of 2,3-dimethyl-2-butene with borane–methyl sulfide in various solvents at 0 °C.

(−78 to 25 °C), followed by oxidation, afforded cyclopentyl *n*-pentyl ketone in 95% yield by GC.



Disiamylborane. The reaction between 2-methyl-2-butene and BMS in 1 M THF,[34] EE, CH_2Cl_2, and pentane at room temperature, in the ratio of 2:1, proceeded smoothly to the synthesis of disiamylborane (Sia_2BH) in 2–2.5 h (eq 3). The

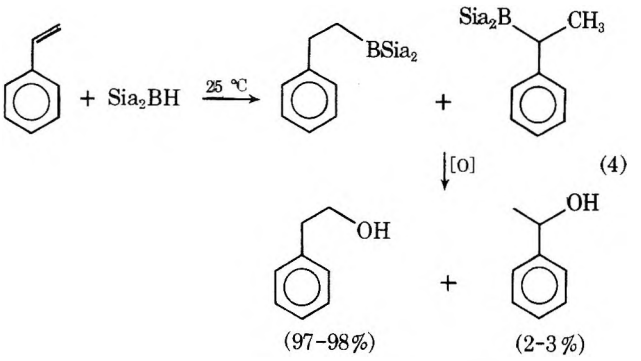


course of the reaction was followed by estimation of residual hydride in solution at different intervals of time. Following completion of the reaction, the mixtures were oxidized and 3-methyl-2-butanol was obtained in quantitative yield (GC).

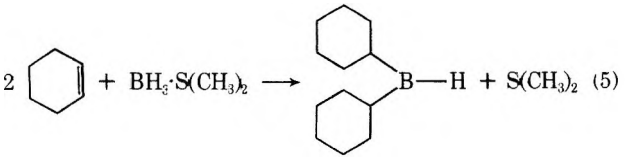
For the reaction utilizing neat reagents, the reaction mixture was kept at −10 °C initially and then stirred at room temperature for 2 h. The rate of hydroboration was established as in the case of the neat thexylborane reaction.

Disiamylborane thus prepared can be used as such for organic synthesis as described below or can be converted to the methyl disiamylborinate in good yield by methanolysis. This is a valuable intermediate for the synthesis of unsymmetrical diynes.[34]

Application of Disiamylborane for the Regiospecific Hydroboration of Styrene. Disiamylborane, prepared as described above, in THF, EE, CH_2Cl_2, and pentane was utilized for the hydroboration of styrene[35] at room temperature. The reaction was complete within 2 h in all of these solvents (eq 4). The reaction mixtures were then oxidized and the composition of the products determined by GC is shown in eq 4.



Dicyclohexylborane. The hydroboration of cyclohexene (2 M) with BMS (1 M in borane equivalent) was carried out at 0 °C in THF, EE,[36] CH_2Cl_2, and pentane. The hydroboration is also effected by mixing the neat reagents at 0 °C (eq 5).



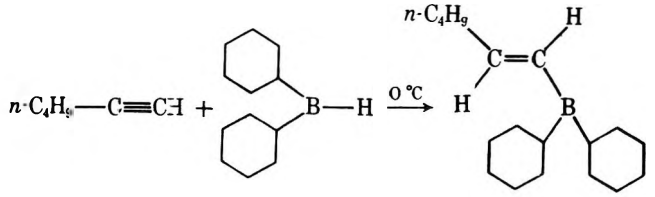
The procedure consists in adding cyclohexene to a well-stirred solution of BMS in the different solvents. At appropriate intervals of time, samples were removed and analyzed for residual olefin by GC for the reactions in EE, CH_2Cl_2, and pentane. The rate of the reaction was thus established. These reactions are essentially complete in 3 h. The rate of hydroboration in THF was followed by methanolyzing individual reaction mixtures at different time intervals. The amount of methyl dicyclohexylborinate was calculated from the NMR spectra using a known amount of benzene as internal standard.

Hydroboration under neat conditions is extremely fast, complete in 15 min at 0 °C. The rate of hydroboration was followed as previously described for neat conditions.

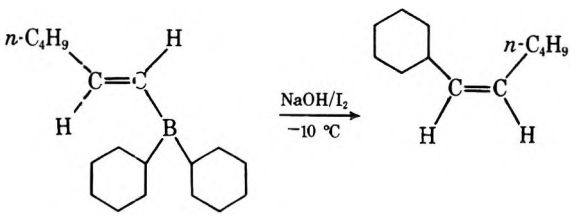
Solutions of dicyclohexylborane undergo disproportionation with time. Consequently, such solutions should be freshly prepared and utilized shortly after their preparation. The presence of dimethyl sulfide appears to stabilize such solutions somewhat, but not sufficiently so as to avoid such disproportionation over several hours.

Application of Dicyclohexylborane in the Zweifel Cis Olefin Synthesis.[37] Dicyclohexylborane in THF, EE, CH_2Cl_2, and pentane was prepared and 1-hexyne added to it at 0 °C. The vinylborane thus formed was treated with NaOH and iodine to yield *cis*-1-cyclohexyl-1-hexene (GC yield: THF, 89%; EE, 84%; CH_2Cl_2, 75%; pentane, 83%) (eq 6). Hence the presence of methyl sulfide does not interfere with this synthesis.

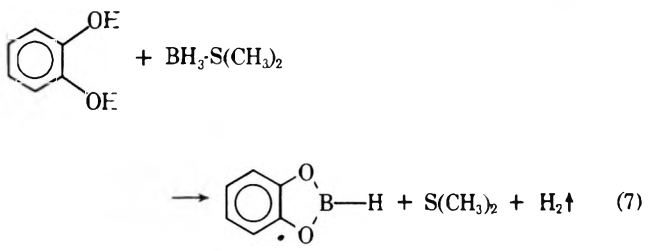
Catecholborane. Until recently, catecholborane was prepared by the reaction of catechol with BH_3·THF at 0 °C.[8] The difficulty in the reaction appears to be the complete removal of THF from the catecholborane during distillation at reduced pressure. The procedure is relatively tedious and time consuming. Hence, the synthesis of catecholborane by the reac-



(6)



tion of catechol with BMS in a volatile solvent, such as EE, was explored (eq 7). The reaction of catechol (1 M) and BMS (1.1



(7)

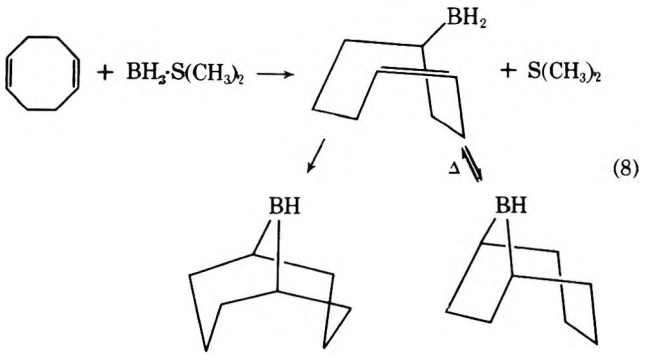
M) in EE at 0 °C is slow and takes about 10 h (as monitored by gas meter) to go to approximate completion.[38] Distillation afforded about 75% catecholborane.

In one experiment, solid catechol (1 M) was added to neat BMS (1.1 M) at 0 °C. Catecholborane was obtained in poor yield (~46%), presumably due to the slow two-phase reaction.

To minimize the reaction time, it was decided to carry the reaction out at room temperature. The reaction of catechol with BMS at room temperature was carried out in both 1 M, as well as 2 M, ether solution and pure catecholborane was obtained by distillation in 72–73% yield. The rate of the reaction in 1 M ether solution was followed by the evolution of hydrogen (as monitored by a gas meter) at different intervals of time. The reaction is essentially complete in 3–4 h.

Catechol proved to be only sparingly soluble in CH_2Cl_2 and pentane. Hence, study of the synthesis in these solvents was not pursued.

9-BBN. Hydroboration of 1,5-cyclooctadiene with BMS, followed by thermal isomerization, yields 9-BBN in high yield (eq 8). Reactions in 2 M THF solution at room temperature and in neat reagents at 0 °C were studied (eq 8). The reaction



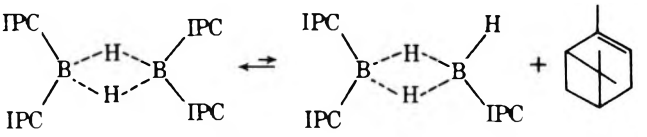
(8)

in THF was carried out by a slow dropwise addition of 1,5-cyclooctadiene to a solution of BMS in THF at room temperature. Hydroboration was complete in 1 h at room temperature, as realized by residual hydride estimation. Oxidation of a small portion of the aliquot with alkaline hydrogen peroxide and GC analysis of the 1,4- and 1,5-cyclooctanediols revealed that the initial hydroboration product is a 30:70 mixture of borabicyclo[4.2.1]- and [3.3.1]nonanes. Thermal isomerization was effected by refluxing in THF. The rate of isomerization was followed by oxidation and GC analysis of a portion of aliquot at definite intervals. In a period of 2 h, isomerization was complete.

In the reaction under neat conditions, BMS was cooled to 0 °C and the diene was added very slowly with vigorous stirring. Several individual 5-mmol scale reactions were carried out. After appropriate time intervals, the contents of an individual reaction mixture were hydrolyzed to determine residual hydride. Hydroboration was complete after 0.5 h at room temperature. The product was approximately a 30:70 mixture of 1,4 and 1,5 isomers, respectively. Isomerization was effected by heating at 160 °C (above the melting point of 9-BBN) for 1 h, when methyl sulfide distilled off quantitatively.

Since 9-BBN can be isolated as a pure, stable crystalline solid, mp 153 °C, it did not appear desirable to examine its preparation in the various solvents. Also, the isomerization of the 1,4 to 1,5 isomer is very slow and incomplete in low-boiling solvents, such as dichloromethane.

Diisopinocampheylborane. The reaction of α-pinene with diborane to form diisopinocampheylborane (IPC_2BH) was previously studied in diglyme and THF at 0 °C.[30,31] The use of the reagent in asymmetric synthesis was studied via hydroboration of *cis*-2-butene, followed by oxidation.[15] The optical purities of 2-butanol realized in diglyme and THF were 87 and 78%, respectively. The lower optical purity in THF compared to that in diglyme was attributed to the greater solubility of IPC_2BH in THF than in diglyme, involving more dissociation in THF to triisopinocampheyldiborane and α-pinene[15] (eq 9).



(9)

In the preceding paper of this series[17] from our laboratory, it was demonstrated that the reaction of excess α-pinene with borane in THF at 0 °C attains equilibrium in 2–3 days with almost quantitative (~99.5%) formation of diisopinocampheylborane. The minor isomer of α-pinene accumulates in the solution, so that the product is almost pure diisopinocampheylborane, enriched in the major isomer. The 2-butanol obtained in the hydroboration of *cis*-2-butene with this pure reagent, followed by oxidation, revealed an optical purity of 98.4%, an almost complete asymmetric induction.

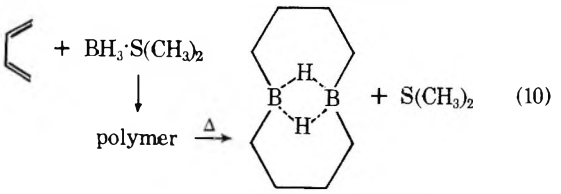
The question arose as to whether the more convenient reagent, BMS, can be utilized for this remarkable asymmetric synthesis. (+)-α-Pinene (optical purity of 95.2%) in 15% excess was slowly added at 0 °C to BMS in sufficient THF to make the final concentration of borane 1.0 M. The reaction mixture was then brought to 25 °C and maintained at that temperature for 14 h, and then kept in the cold room (~−2 °C) for another 10 h. Analysis of the supernatant solution for free α-pinene established that the minor isomer had accumulated in this phase, as in the previous synthesis involving BH_3·THF.[17] Consequently, the product must be the highly pure material, comparable to that prepared from BH_3·THF.[17]

Application of Diisopinocampheylborane to Asymmetric Hydroboration. The utility of this reagent was tested in the hydroboration of *cis*-2-butene. The flask and its contents from a typical preparation, as described above, were cooled to −25 °C and treated with a slight excess of *cis*-2-

butene. The reaction was allowed to proceed for 6 h. The product was then oxidized in the usual manner with alkaline hydrogen peroxide. Distillation provided (−)-2-butanol in a yield of 73%. Following purification by GC, the material exhibited a rotation of $[\alpha]^{25}_{D}$ −13.12°, an optical purity >97.2%.

The preparation of diisopinocampheylborane could also be achieved with BMS in the other solvents, EE, CH_2Cl_2, and pentane. However, there appears to be no advantage over THF to the use of these solvents for the synthesis of diisopinocampheylborane and its application for asymmetric hydroboration.

1,6-Diboracyclodecane. The primary product of the hydroboration of 1,3-butadiene with BMS is mainly a polymeric material, similar to that obtained with BH_3·THF.[22] Three procedures were employed for the hydroboration: (a) addition of BMS to a solution of diene in THF at 0 °C; (b) passing the diene into a solution of BMS in THF;[39] and (c) passing the diene into neat BMS at 0 °C (eq 10). In all of these methods,



(10)

after mixing the reactants at 0 °C, the reaction mixture was stirred for 1 h at room temperature to ensure the completion of hydroboration. Depolymerization was effected by heating to 150 °C under reduced pressure, when the product distilled. The distillate contained a small quantity of active hydride impurity which could be easily removed by washing with cold, dilute alkaline hydrogen peroxide.

Conclusions

The present study has indicated the reaction conditions for the convenient synthesis of borane reagents, e.g., thexylborane, disiamylborane, dicyclohexylborane, catecholborane, 9-BBN, diisopinocampheylborane, and 1,6-diboracyclodecane, via hydroboration with BMS in a wide variety of solvents (e.g., THF, EE, CH_2Cl_2, and pentane). It also indicates the absence of complications in the utilization in organic syntheses of reagents so prepared.

Experimental Section

Since the boron hydrides are extremely sensitive to air and moisture, all reactions were carried out in the atmosphere of dry nitrogen. Special techniques employed in handling the air-sensitive materials and the usual experimental setup for hydroboration reaction or the subsequent utilization of organoboranes are described elsewhere.[40]

Materials. The olefins were distilled from lithium aluminum hydride and stored under nitrogen. High-purity catechol (Eastman Kodak) was sublimed and dried under vacuum. (+)-α-Pinene (Dragoco Co.) was used after distillation from $LiAlH_4$, which showed an optical rotation of $[\alpha]^{26.5}_{D}$ +48.7°, an optical purity of 95.2%.[41] However, after purification through GC using SE-30 column, it revealed $[\alpha]^{25.5}_{D}$ +49.48°, an optical purity of 97.4%. Purifications of EE, THF, CH_2Cl_2, and pentane were carried out according to standard methods.[40] BMS (Aldrich) was analyzed for hydride concentration and used directly. It was found to be nearly 10 M in BH_3 (±5% for different samples). For the active hydride estimation, the aliquot was hydrolyzed using a mixture of glycerine, THF, and water (1:1:1 ratio), except in case of 9-BBN, where a 1:1 mixture of CH_3OH and THF was employed. The volume of hydrogen evolved was measured in a gas buret.[40]

The following columns were utilized for the GC analysis: (A) for the analysis of alcohols, a 6 ft × 0.25 in. column packed with 10% Carbowax 20M on Chromosorb W; (B) for the separation of 1,4- and 1,5-cyclooctanediols as silyl ethers, a 18 ft × 0.125 in. column packed with 5% neopentyl glycol adipate on Varaport-30; (C) for the analysis of olefins and ketones, a 6 ft × 0.25 in. column packed with 10% SE-30 on Chromosorb W.

Reaction of 2,3-Dimethyl-2-butene (1.0 M) with BMS (1.0 M) in THF, EE, CH_2Cl_2, and Pentane at 0 °C. The reaction procedure in all of these solvents is similar. The reaction in THF is described as representative. With the usual experimental setup,[40] the hydroboration is carried out on a 10-mmol scale in a 50-mL flask. The reaction mixture containing a solution of 1.0 mL (10 mmol) of neat BMS, 1.14 mL (5 mmol) of n-dodecane (internal standard for GC) in 6.67 mL of THF was cooled to 0 °C in an ice bath. Hydroboration was initiated by dropwise addition of 1.19 mL (10 mmol) of 2,3-dimethyl-2-butene while stirring the contents of the flask at 0 °C. The total volume was 10 mL (1.0 M in both olefin and BMS). Aliquots (1.0 mL) were withdrawn at intervals of 0.5, 1.0, 1.5, 2.0, and 2.5 h and analyzed for residual hydride by hydrolysis. After 2.5 h, when the reaction was essentially complete, the reaction mixture was oxidized by the careful addition of 0.4 mL of water (at 0 °C), 0.6 mL of 3 M NaOH, 3.0 mL of THF, 1.0 mL of ethanol, and finally 1.0 mL of 30% aqueous H_2O_2 (at 25 °C). The reaction mixture was stirred at 55 °C for 2 h. The aqueous layer was saturated with anhydrous K_2CO_3 and the organic layer then dried over anhydrous $MgSO_4$ and molecular sieve (3 Å). GC analysis using column A revealed a 99.4% yield of 2,3-dimethyl-2-butanol.

As revealed in Figure 1, only minor variations in the rates of hydroboration in the different solvents are observed.

Reaction of 2-Methyl-2-butene with BMS in THF, EE, CH_2Cl_2, and Pentane at 25 °C. The reaction procedure in pentane is described as representative. The usual experimental setup was employed and the reaction flask containing 1.0 mL (neat, 10 mmol) of BMS and 2.43 mL (10 mmol) of n-tridecane in 4.4 mL of pentane was cooled to −10 °C. The contents of the flask were stirred and 2.17 mL (20 mmol) of 2-methyl-2-butene was added dropwise to it. The total volume was 10 mL (1.0 M in BMS). The reaction mixture was stirred at −10 °C for an additional 5 min and then the ice–salt bath was replaced by a water bath (25 °C). Aliquots (1 mL) were withdrawn at 0.5, 1.0, 1.5, and 2.0 h as before and analyzed for residual hydride. After 2 h, the reaction mixture was oxidized as before and analysis by GC using column A revealed a 98.5% yield of 3-methyl-2-butanol.

As in the previous case, variation of the solvent resulted in only minor changes in the observed rates of hydroboration.

Reaction of Cyclohexene with BMS in THF, EE, CH_2Cl_2, and Pentane at 0 °C. The following procedure for the rate of the reaction of cyclohexene with BMS in EE at 0 °C is representative. With the usual experimental setup, the hydroboration on 10-mmol scale was carried out as described above using 1.0 mL (10 mmol) of neat BMS and 2.02 mL (20 mmol) of cyclohexene containing 1.62 mL (10 mmol) of n-octane in 5.36 mL of EE. The reaction mixture was 1.0 M with respect to BMS. Aliquots (1 mL) of the clear supernatant solution were withdrawn at 0.5, 1.0, 2.0, and 3.0 h and quenched in an ice–water mixture; 3 M NaOH was added at 0 °C and the organic material extracted into EE. The EE layer was dried and analyzed for cyclohexene by GC using column C. From the amount of the olefin consumed, the rate of the reaction was estimated.

A modified procedure was utilized to follow the reaction in THF. Four different reactions were carried out on 10-mmol scale in four different 50-mL flasks by the dropwise addition of 2.02 mL (20 mmol) of cyclohexene to a stirred solution of 1.0 mL (10 mmol) of neat BMS in 6.98 mL of THF at 0 °C. Methanol (0.8 mL, 20 mmol) was added at 0.5, 1.0, 1.5, and 2.0 h intervals and each reaction mixture was stirred at 25 °C for 0.5 h. Solvent was removed at 15 mm, 0.44 mL (5 mmol) of benzene (internal standard for NMR analysis) was added, and methyl dicyclohexylborinate was analyzed by NMR. From these data, the rate of the hydroboration was established. The reaction was complete in 0.5 h. Here also, only minor variations in the time required for complete reaction were observed for the various solvents.

Reaction of Neat BMS with (a) 2,3-Dimethyl-2-butene at 0 °C; (b) 2-Methyl-2-butene at (−10 to 25 °C); (c) Cyclohexene at 0 °C. A. Four different reactions were carried out in individual reaction flasks cooled at 0 °C. The flasks were charged with 1.0 mL (10 mmol) of neat BMS and 1.14 mL (5 mmol) of n-dodecane. 2,3-Dimethyl-2-butene (1.19 mL, 10 mmol) was added dropwise while stirring the contents of the flask. The reaction mixtures were oxidized at 0.25, 0.5, 1.0, and 2.0 h by the addition of 10 mL of THF, 3 mL of ethanol, 1 mL of water, 2 mL of 6 M NaOH, and 3.5 mL of 30% aqueous H_2O_2. After stirring for 2 h at 50 °C, the reaction mixtures were cooled and the aqueous layer saturated with anhydrous K_2CO_3. The organic layer was dried and analyzed for 2,3-dimethyl-2-butanol by GC using column A. Thus the rate of hydroboration was determined.

B. The reaction procedure is similar to that described above. The addition of 2-methyl-2-butene (20 mmol) to BMS (10 mmol) was done at −10 °C. After keeping at −10 °C for 0.25 h, the reaction mixture was brought to 25 °C and then as before in A.

C. Three different reactions of 5-mmol scale were carried out by slowly adding 1.01 mL (10 mmol) of cyclohexene to a stirred solution of 0.5 mL (5 mmol) of neat BMS in 1.215 mL (5 mmol) of tridecane at 0 °C. The reaction course was followed by oxidation at 0.25, 0.5, and 1.0 h as described before in A. The hydroboration was complete in 0.25 h.

Preparation and Isolation of Thexylborane. The hydroboration of 2,3-dimethyl-2-butene with BMS was carried out under neat condition. With the usual experimental setup, 10 mL (neat, 100 mmol) of BMS was placed in a preweighed 100-mL flask fitted with a connecting tube and cooled to −10 °C in an ice–salt bath. 2,3-Dimethyl-2-butene (12 mL, 100 mmol) was then added dropwise while stirring the contents of the flask. After the addition was complete, the ice–salt bath was replaced by an ice bath (0 °C) and the reaction mixture was stirred for 2 h at this temperature. Volatile products were pumped off at 25 °C under aspirator vacuum (14 mm) and condensed in a trap cooled in dry ice–acetone (−78 °C). Analysis of the volatile products by GC showed only methyl sulfide and no 2,3-dimethyl-2-butene. the residue in the flask is pure thexylborane (9.6 g, 99%).

The purity of thexylborane was further established by methanolysis. To a solution of 4.25 g (43.8 mmol) of thexylborane in 3 mL of THF, there was added with stirring 7 mL (176 mmol) of methanol dropwise at 25 °C. After stirring for 0.5 h at 25 °C, THF, an excess of methanol was pumped off at 25 °C under 14 mm pressure and the residue was distilled to yield 5.59 g of pure dimethyl thexylboronate, bp 56–57 °C (14 mm), a yield of 82%.

Preparation and Isolation of Disiamylborane. The reaction of 2-methyl-2-butene with BMS can be carried out in THF, EE, CH_2Cl_2, or pentane to obtain disiamylborane. The preparation in THF is representative.[34] In a 500-mL flask with the usual hydroboration setup, 50 mL of THF and 10.2 mL (9.8 M, 100 mmol) of BMS) were placed. The flask was immersed in an ice–salt bath and 22.3 mL (14.7 g, 210 mmol) of 2-methyl-2-butene was added dropwise via a syringe. The reaction mixture was stirred at room temperature for 2 h. Disiamylborane thus obtained in quantitative yield can be used in situ. For example, the dropwise addition of 4.1 mL (3.2 g, 100 mmol) of methanol to the above product, followed by stirring for 1 h, provides methyl disiamylborinate, which can be utilized in situ in the unsymmetrical diyne synthesis.[24]

Preparation and Isolation of Dicyclohexylborane. Hydroboration of cyclohexene with BMS in THF, EE, CH_2Cl_2, and pentane gave almost the same results. The reaction in EE is described as representative.[36] In a 250-mL flask with the usual hydroboration setup, 10.0 mL (100 mmol) of BMS and 75 mL of EE were placed. The flask was cooled in an ice bath and 20.2 mL (16.4 g, 200 mmol) of cyclohexene was added dropwise during 15 min with vigorous stirring. Hydroboration was completed in 3 h at 0 °C. On pumping off the solvent, a quantitative yield of crystalline dicyclohexylborane (17.8 g) free from methyl sulfide was obtained, mp 103–104 °C (lit.[36] 103–105 °C) after sublimation.

The purity of this material was further established by methanolysis. The preparation of dicyclohexylborane was carried out as described above. When the reaction was complete (3 h, 0 °C), 15 mL of methanol was added slowly (~2.5 L of H_2 liberated). The reaction flask was brought to room temperature and solvent pumped off. The resulting material was >95% pure methyl dicyclohexylborinate, as determined by NMR. This can be distilled, bp 75–80 °C (0.005 mm), or can be used without distillation.

Application of Thexylborane. Synthesis of Cyclopentyl *n*-Pentyl Ketone. Thexylborane (10 mmol) in THF (1 M) was prepared from BMS as before. Thexylcyclopentyl-*n*-pentylborane (10 mmol) in THF was prepared following a similar procedure described in the literature.[33] Preparation of thexylcyclopentyl-*n*-pentylcyanoborohydride, its acylation with trifluoroacetic anhydride, and oxidation to cyclopentyl *n*-pentyl ketone were carried out following literature procedure.[32] The yield of cyclopentyl *n*-pentyl ketone, as analyzed by GC using column C, was 95%. The presence of the methyl sulfide created no difficulties, either in the hydroboration or the cyanidation stages.

Application of Disiamylborane. Hydroboration of Styrene in THF, EE, CH_2Cl_2, and Pentane. The experimental procedure for the reaction in pentane is representative. Disiamylborane (10 mmol) in pentane (1 M) was prepared from BMS as before. Hydroboration of styrene with the reagent was carried out following the literature procedure.[5] Analysis by GC showed 90% of alcohol (98% 2-phenylethanol and 2% 1-phenyl-1-ethanol).

Application of Dicyclohexylborane. Zweifel's *cis*-1-Cyclohexyl-1-hexene Synthesis.[37] The reaction in EE is representative. Dicyclohexylborane (10 mmol) in EE was prepared from BMS as before. Hydroboration of 1-hexyne with this reagent to the vinylborane followed by its reaction with iodine was performed following Zweifel's procedure.[37] GC analysis revealed 83% of *cis*-1-cyclohexyl-1-hexene.

Reaction of Catechol with BMS in EE. Preparation of Catecholborane. A. At 25 °C. With the usual experimental setup, the reaction was carried out in a 250-mL three-necked round-bottom flask fitted with a dropping funnel. The flask was immersed in a water bath (25 °C) and 20 mL (200 mmol) of neat BMS and 20 mL of dry EE were placed in the reaction flask. The solution of 22 g (200 mmol) of catechol in 55 mL of EE was introduced in the dropping funnel using a double-ended needle. The catechol solution was added dropwise to the stirred solution of borane over a period of 3 h. The reaction mixture was further stirred for 1 h when hydrogen evolution ceased (as monitored by gas meter). EE and methyl sulfide were removed under reduced pressure (50 mm) at 25 °C and the residue was distilled using a 60-cm Vigreux column to yield 17.22 g of pure catecholborane (72.3% yield), bp 80–81 °C (85–88 mm).

B. At 0 °C. The reaction procedure for 0 °C is similar to that described above in A. The reaction took 10 h for completion. Distillation yielded 75% of pure catecholborane.

9-BBN. A. Rate of Hydroboration in THF. With the usual experimental setup,[40] hydroboration was carried out in a 50-mL flask immersed in a water bath. To a well-stirred solution of 2.0 mL (20 mmol) of BMS in 5.54 mL of THF (to make 2 M in reactants) was added dropwise 2.46 mL (20 mmol) of 1,5-cyclooctadiene during 10 min. After the complete addition, a 1.0-mL aliquot was hydrolyzed at definite intervals of time and the volume of hydrogen liberated was measured. This gives the residual hydride concentration in the reaction mixture. The hydroboration of cyclooctadiene was thus found to be complete in 1 h.

B. Rate of Isomerization in Refluxing THF. Hydroboration of 1,5-cyclooctadiene was carried out as described in A. After completion of the reaction, 1.0 mL of the aliquot was oxidized. The remaining solution was refluxed and at definite intervals a 1.0-mL aliquot was withdrawn for oxidation. Analysis of the oxidation product for cycloocane-1,4- and -1,5-diols gives the extent of isomerization. In 2 h, the isomerization was complete.

C. Oxidation of Aliquots. In a 50-mL flask equipped with reflux condenser, a 1.0-mL aliquot (2 mmol) was introduced with a syringe. Then 10 mL of THF, followed by 2 mL of water, were added. The flask was cooled in an ice bath and 1 mL (3 mmol) of 3 N sodium hydroxide was added, followed by a dropwise addition of 1.0 mL (8 mmol) of 30% hydrogen peroxide (100% excess). After the initial vigorous reaction subsided, the flask was maintained at 50 °C for 2 h. The aqueous layer was saturated with anhydrous potassium carbonate and the organic layer was used for GC analysis.

D. GC Analysis of Diols. Two drops of the THF solution from oxidation was taken in a vial, and 0.1 mL of dry pyridine and 0.1 mL (excess) of *N,O*-bis(trimethylsilyl)acetamide (BSA) were added. The mixture was thoroughly shaken and heated for 5 min. The product was injected into column B. The isomeric disilyl ethers separate nicely. Integration shows the isomer distribution (assuming the same response ratios for both isomers) of the two diols.

E. Isolation of 9-BBN from Reaction in THF. In a 250-mL flask equipped with a reflux condenser, and usual setup, 20 mL (200 mmol) of BMS and 55.4 mL of THF were introduced. The flask was immersed in a water bath, and while stirring vigorously, 24.6 mL (200 mmol) of 1,5-cyclooctadiene was added dropwise (exothermic), and stirring was continued for 1 h followed by 2 h of refluxing. The flask was cooled in an ice–salt mixture, when the 9-BBN crystallized. The supernatant liquid was decanted through a double-ended needle, and the crystals were washed with 50 mL of ice-cold pentane and dried under vacuum, yielding 21 g (86%) of product, mp 148 °C. Recrystallization from THF gave a material, mp 152–153 °C. Most of the 9-BBN can be recovered from the washings.

F. Rate of Hydroboration under Neat Conditions. Five different reactions were carried out, each on a 5-mmol scale in 25-mL flasks. Reactants were mixed at 0 °C. After fixed intervals, one flask at a time was connected to a gas meter and the contents were hydrolyzed by adding 15 mL of a 1:1 mixture of methanol and THF. Thus, the progress of hydroboration was followed by residual hydride estimation. Hydroboration was complete after 0.5 h at 0 °C followed by 0.5 h at room temperature.

G. Rate of Isomerization under Neat Conditions. The hydroboration was carried out as described in F. When the reaction was complete, each flask was heated in an oil bath at 160 °C for fixed intervals of time. After cooling, the contents were oxidized as described in C. GC analysis of the disilyl ethers revealed the isomer ratio in each case. Isomerization was thus found to be complete in 1 h.

H. Isolation of 9-BBN from Reaction of Neat Reagents. The

apparatus was assembled as described in E, except that neat BMS was taken in the flask, cooled in an ice bath, and the diene was carefully added dropwise (exothermic). After 0.5 h at 0 °C, the contents were allowed to warm to room temperature and stirred for an additional 0.5 h. Distillation equipment was attached to the flask and isomerization was carried out by heating in an oil bath for 1 h at 160 °C, when methyl sulfide distilled almost quantitatively (11.7 g, 94%). The resulting solid (24.4 g, 100%) was crystallized from boiling THF, yield 20 g (82%), mp 146–147 °C. Recrystallization from THF afforded pure crystals, mp 153 °C.

Reaction of α-Pinene with BMS at 25 °C. Preparation of Diisopinocampheylborane (IPC_2BH). The experimental procedure for the preparation of IPC_2BH in THF, EE, CH_2Cl_2, and pentane is similar. The reaction in THF is described as representative. With the usual experimental setup, the reaction was carried out in a 300-mL, three-necked, round-bottom flask fitted with a dry ice–acetone condenser. The flask was cooled to 0 °C in an ice bath and was then charged with 39.7 ml (100 mmol) of 2.52 M BMS in THF and 23.5 mL of THF. (+)-α-Pinene (31.4 g, 230 mmol) ($[\alpha]^{23}_D$ +48.7°, an optical purity of 95.2%) was added dropwise over a period of 20 min. The ice bath was replaced by a water bath (25 °C) and the reaction mixture was stirred for another 2 h and then allowed to stand at this temperature for 14 h (the white precipitate of IPC_2BH was observed after 0.5 h). The reaction mixture was then kept in the cold room (~−2 °C) for an additional 10 h.

Application of Diisopinocampheylborane (IPC_2BH). Hydroboration of *cis*-2-Butene at −25 °C. The reaction flask and its contents, from above, were then cooled to −25 °C (dry ice–CCl_4 bath) and 6.5 g (115 mmol) of *cis*-2-butene was added to the reaction mixture by means of a double-ended needle. The reaction mixture was stirred for 6 h at −25 °C and then warmed up to room temperature, followed by addition of 3 mL of water, 33 mL of 3 M NaOH, and 36 mL of 30% aqueous H_2O_2 (added dropwise) maintaining the temperature of the solution below 40 °C. It was further stirred for 2 h at 40 °C. The reaction mixture was then cooled, 33 mL of 3 M NaOH was added, and the aqueous layer was saturated with anhydrous K_2CO_3. The organic layer was separated and the aqueous layer was extracted with four 50-mL portions of ether. The combined ether extracts were washed twice with 20 mL of saturated NaCl solution and finally dried over anhydrous Na_2SO_4 overnight. It was further dried over anhydrous $MgSO_4$ for 4 h and then distilled using a 30-cm Widmer column. There was obtained 5.402 g of (−)-2-butanol [1.452 g at 84–97 °C (752 mm) and 3.950 g at 97 °C (752 mm)], a yield of 73%. The 97 °C fraction was further purified through preparative GC using 20% SE-30 and 10% SE-60 columns, $n^{20.5}_D$ 1.3975, $[\alpha]^{25}_D$ −13.12°, an optical purity of 97.2%.[42]

The α-pinene unreacted was recovered by distillation and purified through a 20% SE-30 column, $n^{20.5}_D$ 1.4660, $[\alpha]^{26.5}_D$ +39.6°, an optical purity of 76.2%.

1,6-Diboracyclodecane. A. Addition of BMS to Diene in THF. In a 250-mL flask fitted with the usual setup, 100 mL of THF was placed and the flask was cooled in an ice bath. A 25-mL graduated test tube was cooled in a dry ice–acetone bath (see Figure 9.22 in ref 2), and 14.8 mL (200 mmol, *d* 0.73 at −78 °C, bp −44 °C) of 1,3-butadiene was condensed. Then it was gradually allowed to distill into the reaction flask to prepare a solution of 1,3-butadiene in THF. To the diene solution in THF at 0 °C was slowly added 20 mL (200 mmol) of BMS during 15 min. After complete addition, the progress of the reaction was followed by the residual hydride estimation for 1 mL of aliquot each time. Reaction was complete after stirring for 1 h at 0 °C followed by 1 h at room temperature.

The solvent was distilled off at atmospheric pressure, and depolymerization was carried out by distillation under reduced pressure (18 mm). No liquid distilled until the oil bath temperature reached 140 °C. Almost all material distilled at 92–94 °C (18 mm) (bath temperature, 150 °C): yield 10.8 g; n^{20}_D 1.4795; IR 2520, 1610, 1560 cm^{-1} absorptions due to >B–H, It contains an active hydride species as impurity, which can be removed by purification as described in the literature.[22] The yield of pure distilled 1,6-diboracyclodecane was 8.5 g (62%): bp 88–89 °C (16 mm), n^{20}_D 1.4888, IR 1610 cm^{-1} in the region expected for >B–H absorption.

Addition of Diene to BMS in THF. The experimental setup is the same as in A, but in the reaction flask, 20 mL (200 mmol) of BMS and 80 mL of THF were placed. 1,3-Butadiene, condensed into the graduated test tube, was then allowed to distill slowly into the flask. The rest of the procedure was the same. After the workup, 1,6-diboracyclodecane was distilled: bp 88–89 °C (16 mm), yield 8.8 g (65%); n^{20}_D 1.4895; IR 1610 cm^{-1} is the only >B–H absorption.

C. Addition of Diene to Neat BMS. The same procedure was followed as in B, but neat BMS was taken in the reaction flask. Since the reaction was very vigorous, an ice–salt mixture was used to cool the flask. After the usual workup, 1,6-diboracyclodecane was distilled: yield 8.7 g (64%); bp 88–89 ° C (16 mm); n^{20}_D 1.4886; IR only 1610 cm^{-1} in the >B–H absorption region.

Registry No.—2,3-Dimethyl-2-butene, 563-79-1; BMS, 13292-87-0; 2-methyl-2-butene, 513-35-9; cyclohexene, 110-83-8; thexylborane, 61505-80-4; methanol, 67-56-1; dimethyl thexylboronate, 56118-62-8; disiamylborane, 61484-00-2; dicyclohexylborane, 61484-01-3; methyl dicyclohexylborinate, 32705-46-7; catechol, 120-80-9; catecholborane, 274-07-7; 9-BBN, 21205-91-4; 1,5-cyclooctadiene, 111-78-4; diisopinocampheylborane, 61997-72-1; (+)-α-pinene, 7785-70-8; *cis*-2-butene, 590-18-1; (−)-2-butanol, 14898-79-4; 1,6-diboracyclodecane, 34629-70-4; 1,3-butadiene, 106-99-0.

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Preparation and Thermolysis Reactions of Hydroxytetraarylantimony Compounds

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Received July 15, 1976

Eight new hydroxytetraarylantimony compounds, **1**, have been prepared and subjected to thermolysis reactions in *p*-xylene solution. From product ratio data, it has been possible to construct a tentative scale of departure aptitudes of aryl radicals from stiboranyl radicals of the type $XC_6H_4(C_6H_5)_3Sb-O\cdot$, **3**, in the propagation steps of induced thermolysis chain reactions. The hydrolysis of pentaphenylantimony in dioxane solution to produce hydroxytetraphenylantimony plus benzene has also been effected, and a preliminary kinetics study of this new reaction has been carried out.

Discussion

Hydroxytetraphenylantimony (**1**, X = H) has been reported[1,2] to undergo decomposition at 50–70 °C, in *p*-xylene solution, under a nitrogen atmosphere, in the dark, to give benzene and triphenylstibine oxide (**2**). A kinetics investigation[3] of this reaction has given results which are consistent with the operation of a radical mechanism in which direct homolytic cleavage of an Sb–C bond is accompanied by an induced radical chain mechanism, a situation analogous to that reported[4,5] for the thermal decomposition of diaroyl peroxides. We have now completed a study of the thermolysis reactions of several compounds of the type $XC_6H_4(C_6H_5)_3SbOH$ (**1**), and the results are summarized in Table I.

Because it was found that many of the triarylstibine oxides (**2** and **4**) underwent decomposition at temperatures above 50 °C, and because the combined yields of C_6H_6 and C_6H_5X were less than quantitative at reaction temperatures of 30–50 °C, even after prolonged reaction periods, it was deemed necessary to determine the material balances in reactions of these types. The results are summarized in Table II. Since all of the material balances given in Table II are close to 100%, the product ratios provided in Table I can be accepted as reasonably accurate measurements of the departure aptitudes of the various aryl groups in the thermolysis reactions. Inasmuch as there are three phenyl groups to one substituted phenyl group in each of the compounds **1**, the significant ratio to be considered is 3 C_6H_5X/C_6H_6. This ratio, corresponding to each of the substituents, X, in **1**, is as follows: *p*-NO_2, 5.6; *m*-NO_2, 9.4; *p*-Cl, 2.5; *m*-Cl, 4.6; *p*-CH_3, 1.3; *m*-CH_3, 0.78; *p*-OCH_3, 2.6; *m*-OCH_3, 2.5.

It is instructive to compare these results with those of known, formally related ionic reactions. Horner, Hoffman, Wippel, and Hassel[6] have determined product ratios in the decomposition reactions of $XC_6H_4(C_6H_5)_3P^+$, OH^-, the product-determining (and rate-limiting)[7] step of which is the dissociation of $XC_6H_4(C_6H_5)_3P-O^-$ into a mixture of $(C_6H_5)_3P{=}O + XC_6H_4^-$ and $XC_6H_4(C_6H_5)_2P{=}O + C_6H_5^-$ Each of the aryl anions is immediately converted to the corresponding hydrocarbon by the gain of a proton from the solvent, and perhaps, in some instances, the solvent molecule which donates the proton is even a part of the transition state of the dissociation reaction of the oxyphosphoranyl anion, $XC_6H_4(C_6H_5)_3P-O^-$.[8-10] In any event, in this strictly ionic process, it can be inferred from the data of Horner and his co-workers[6] that the decomposition reactions of $XC_6H_4(C_6H_5)_3P^+$, OH^- give the following minimum yields of the predominant aromatic compound (C_6H_5X or C_6H_6): nitrobenzene, 70% (from the *p*-NO_2 salt, i.e., X = *p*-NO_2); nitrobenzene, 100% (X = *m*-NO_2); chlorobenzene, 93% (X = *p*-Cl); benzene, 90% (X = *p*-Me); benzene, 90% (X = *m*-Me); benzene, 87% (X = *p*-MeO); benzene, 90% (X = *m*-MeO). In like manner, the data of McEwen, Briles, and Giddings[11] for the ionic dissociation of $XC_6H_4(C_6H_5)_3Sb(OR)_2^-$ to give mixtures of $(C_6H_5)_3Sb(OR)_2 + XC_6H_4Na$ and $XC_6H_4(C_6H_5)_2Sb(OR)_2 + C_6H_5Na$ provide the following departure aptitudes of various aryl anions (which immediately form aromatic hydrocarbons by gain of a proton from the solvent) as calculated from the ratio 3 C_6H_5X/C_6H_6: *p*-$NO_2C_6H_4^-$, >129; *m*-$NO_2C_6H_4^-$, >138; *p*-$CH_3C_6H_4^-$, <0.2; *p*-$CH_3OC_6H_4^-$, <0.75.

All of the data presented above provide further confirmation[3] that the compounds of type **1** undergo thermolysis by radical rather than ionic processes. Although there is only a small degree of discrimination in any of the reactions, it appears that the approximate order of ease of formation of the aryl radicals by the thermolysis of **1** is *m*-nitrophenyl > *p*-nitrophenyl > *m*-chlorophenyl > *p*-chlorophenyl ≃ *p*-methoxyphenyl ≃ *m*-methoxyphenyl > *p*-tolyl > phenyl > *m*-tolyl. The very small difference in the rates of formation of phenyl and *p*-tolyl radicals has been observed repeatedly in the appropriate radical decomposition reactions of triarylsulfonium alkoxides[12-15] and diaryliodonium salts.[16-18] Caserio, Glusker, and Roberts[19] have also reported that, in the hydrolysis of unsymmetrical diaryliodonium salts by a radical mechanism, the direction of cleavage is insensitive to the nature of the substituents. For example, the cleavage of phenyl-*p*-methoxyphenyliodonium salts gives phenol (plus *p*-iodoanisole) in 57–59% yield and *p*-methoxyphenol (plus iodobenzene) in 41–43% yield. Furthermore, the radical hydrolytic cleavage of (*m*-nitrophenyl)-(*p*-methoxyphenyl) iodonium salts gives *p*-methoxyphenol in 47% yield and *m*-nitrophenol in 34% yield.

It is our belief, based on results reported previously,[3] that the major portion of the products of the thermolysis of **1** arise by competing radical chain reactions, the propagation sequences of which are as follows:

$$\underset{\mathbf{3}}{XC_6H_4(C_6H_5)_3Sb{-}O\cdot} \rightarrow \underset{\mathbf{4}}{XC_6H_4(C_6H_5)_2Sb{=}O} + C_6H_5\cdot$$

$$\underset{\mathbf{1}}{XC_6H_4(C_6H_5)_3Sb{-}O{-}H} + C_6H_5\cdot \rightarrow \mathbf{3} + C_6H_6 \quad (1)$$

$$\mathbf{3} \rightarrow \underset{\mathbf{2}}{(C_6H_5)_3Sb{=}O} + XC_6H_4\cdot$$

$$\mathbf{1} + XC_6H_4\cdot \rightarrow \mathbf{3} + C_6H_5X \quad (2)$$

According to this interpretation, the product ratios 3 C_6H_5X/C_6H_6 given previously are actually a measure of the departure aptitudes of aryl radicals from the intermediate **3** and might have some degree of predictive value in related reactions. Also, as mentioned previously, limited evidence in support of this concept is available in the data on the de-

Table I. Product Ratios in Thermolysis Reactions of $XC_6H_4(C_6H_5)_3SbOH$ (1) in *p*-Xylene

Registry no.	X	Molality of 1	Temp, °C	Time, h	% C_6H_6	% C_6H_5X
61203-18-7	*p*-NO_2	0.0447	35	268	28	52
61203-19-8	*m*-NO_2	0.0447	35	268	14	44
61203-20-1	*p*-Cl	0.0637	35	204	18	15
61203-21-2	*m*-Cl	0.0637	35	204	15	23
61203-22-3	*p*-Me	0.0750	38	238	31	13
61203-23-4	*m*-Me	0.0458	38	238	54	14
61203-24-5	*p*-MeO	0.0258	35	348	28	24
61203-25-6	*m*-MeO	0.0258	35	348	24	20

Table II. Material Balances in Thermolysis Reactions of $XC_6H_4(C_6H_5)_3SbOH$ (1) in *p*-Xylene

X	Concn of 1, mol/10 ml of *p*-xylene	Temp, °C	Time, h	Combined yield of $C_6H_6 + C_6H_5X$, %	Recovered 1, %[a]
p-NO_2	0.00223	35	648	60	43
m-NO_2	0.00223	35	648	50	50
p-Cl	0.00484	25	318	21	72
m-Cl	0.00484	25	318	36	57
p-Me	0.00488	35	318	61	39
m-Me	0.00488	35	318	45	60
p-MeO	0.00253	38	476	40	62
m-MeO	0.00253	38	576	54	40

[a] These numbers are estimated to be accurate within ±7 units.

composition of triarylsulfonium alkoxides[12-15] and diaryliodonium alkoxides.[16,17]

Methods of preparation of tetraarylstibonium salts have been discussed in a previous article.[11] Most of the salts used in the present work were prepared by the reactions of triphenylstibine with aryldiazonium fluoroborates in nitrobenzene solution. The stibonium salts, in turn, were readily converted to the hydroxytetraarylantimony compounds, **1**, by the action of ammonium hydroxide solution.

Although of little practical value at the present time, a theoretically interesting method for the preparation of hydroxytetraarylantimony compounds is by the heretofore unreported hydrolysis of pentaarylantimony compounds. However, the latter are relatively insoluble in water, and they undergo hydrolysis only at a slow rate in an aqueous suspension. In fact, pentaarylantimony compounds are frequently isolated by treatment of a lithium hexaarylantimonate with an excess of water,[20,21] the relatively insoluble Ar_5Sb then being collected by filtration.

Since pentaarylantimony compounds undergo solvolysis fairly rapidly in hydroxylic solvents in which they are soluble,[10,21] it seemed reasonable to attempt the preparation of hydroxytetraphenylantimony by treatment of pentaphenylantimony with 1 equiv of water in a homogeneous solution in an appropriate organic solvent. The use of spectral grade dioxane which had been refluxed over sodium for 24 h and then distilled under an argon atmosphere proved to be suitable for this purpose. In a control experiment, heating of a 0.200 M solution of pentaphenylantimony in the highly purified dioxane for 13 h at 98 °C gave only a trace amount of benzene, as detected by VPC analysis, and pentaphenylantimony was recovered unchanged by evaporation of the solvent. Then, in another experiment carried out under the same conditions, except that exactly 1 equiv of water had been added to the solution, benzene was obtained in 102 ± 3% yield (by VPC analysis). Furthermore, evaporation of the solvent gave a residue of pure hydroxytetraphenylantimony, as determined by its melting point and NMR and IR spectra.[22]

It was also possible to carry out a preliminary kinetics experiment of the reaction of pentaphenylantimony with 1 equiv of water in pure dioxane at 69.7 °C. The reaction was followed for the first 9 h of reaction, which corresponded to 45% of completion. The specific rate constant for the indicated second-order reaction was 1.3×10^{-4} l. mol^{-1} s^{-1}. We believe that the use of pentaphenylantimony for the analysis of water in otherwise inert organic solvents has good potential, and the preliminary rate data are given for the convenience of anyone who might wish to explore this analytical method. It should also work well for the analysis of small amounts of alcohols, carboxylic acids, and other hydroxylic compounds in inert solvents.[10,21]

Experimental Section

General. Melting points and boiling points are uncorrected. NMR spectra were taken on a Varian A-60 instrument. All compounds were dissolved in deuteriochloroform, and Me_4Si was used as an internal standard. GLC analyses were carried out on either a Varian 1200-1 or an F & M 609 flame ionization chromatograph. Elemental analyses were carried out by Schwarzkopf Microanalytical Laboratory, Woodside, N.Y., by Alfred Bernhardt Mikroanalytisches Laboratorium, Max Planck Institute, 433 Mulheim (Ruhr), West Germany, and by the late Charles Meade, University of Massachusetts, Amherst, Mass.

Preparation of Aryltriphenylstibonium Fluoroborates. The salts $XC_6H_4Sb^-(C_6H_5)_3, BF_4^-$, in which X = *p*-$NO_2$, *m*-$NO_2$, *p*-Me, and *p*-MeO, were prepared as described previously.[11] With use of nitrobenzene as the solvent, the same method was used to prepare the fluoroborate salts in which X = *m*-Me, *m*-Cl, *p*-Cl, and *m*-MeO. The physical constants of these new salts and preparative data are given in Table III.

Preparation of Hydroxytetraarylantimony Compounds, 1. The dropwise addition of a 10% ammonium hydroxide solution to a stirred solution of 0.005 mol of an aryltriphenylstibonium fluoroborate in about 50–65 ml of acetone and 45–100 ml of water maintained at room temperature gave an immediate precipitate of **1**. The addition of ammondium hydroxide was continued until the mixture became basic to Universal paper. The mixture was then stirred at 0 °C for 5–10 min and filtered, and the precipitate of **1** was washed with cold water, and sometimes subsequently with a small amount of anhydrous acetone. The product was dried in a vacuum desiccator, usually without prior recrystallization. Physical constants of **1** and additional preparative details are provided in Table IV. The melting point hydroxytetra-

Table III. Preparation and Properties of $XC_6H_4Sb^+(C_6H_5)_3, BF_4^-$ [a]

Registry no.	X	Mp, °C	Reaction solvent	Reaction temp, °C	Reaction time, h	Recrystn solvent	% yield
61203-27-8	*m*-Me	164–166	Nitrobenzene	90	3	Acetone–ether	35
61203-29-0	*m*-Cl	153–156	Nitrobenzene	60	30	Acetone–ether	30
61203-31-4	*p*-Cl	161–163	Nitrobenzene	80–120	12	Isopropyl alcohol	33
61203-33-6	*m*-MeO	121–125	Nitrobenzene	85	12	Isopropyl alcohol–ether	31

[a] Satisfactory analytical data (±0.3% for C, H, Sb, and halogen) for all compounds were submitted for review.

Table IV. Preparation and Properties of $XC_6H_4Sb(OH)(C_6H_5)_3$, 1 [a]

X	Mp, °C dec	% yield	NMR, δ ($CDCl_3$)
p-NO_2	157–161	82	0.67 s, 7.13–7.97 m
m-NO_2	161–163	79	0.70 s, 7.33–787 m
p-Cl	177–180	57	0.60 s, 7.30–7.90 m
m-Cl	165–170	79	0.70 s, 7.23–7.73 m
p-Me	108–125	48	0.70 s, 2.40 s, 7.10–7.75 m
m-Me	166–168	52	0.77 s, 2.27 s, 7.15–7.85 m
p-MeO	72–75	42	0.77 s, 3.77 s, 7.17–7.83 m
m-MeO	83–106	20	0.60 s, 3.68 s, 7.12–7.80 m

[a] Satisfactory analytical data for all compounds (except as noted) were submitted for review. Exception: X = *p*-Cl. Calcd: C, 59.84; Sb, 25.28. Found: C, 61.08; Sb, 25.80.

phenylantimony was found to be 214–218 °C dec (reported[24,25] mp 210–213 °C dec); NMR δ ($CDCl_3$) 0.80 s (OH), 7.25–7.80 m (aromatic protons). An x-ray crystallographic study of hydroxytetraphenylantimony has been reported.[26]

The procedure described above was entirely satisfactory for the preparation of 1 in which X = H, *p*-NO_2, *m*-NO_2, *p*-Cl, and *m*-Cl, respectively. However, when electron-donating substituents were present (X = *p*-Me, *m*-Me, *p*-MeO, *m*-MeO), a modified procedure had to be employed, one in which a very dilute aqueous solution of the tetraarylstibonium sulfate was treated with ammonium hydroxide. For example, an aqueous solution of 1 (X = *p*-Me, *m*-Me, *p*-MeO, *m*-MeO) sulfate was prepared by heating a mixture of 0.00094 mol of the desired tetraarylstibonium fluoroborate, 150 ml of water (previously distilled from potassium permanganate solution), and 3.0 g of potassium sulfate until most of the stibonium salt had dissolved. The mixture was then cooled and filtered, the precipitate consisting mainly of potassium fluoroborate. Dropwise addition of 10% ammonium hydroxide to the filtrate caused 1 to precipitate, and the addition of NH_4OH was continued until the solution was distinctly basic to Universal paper. The product was collected by filtration, washed well with water, and dried in a vacuum desiccator.

Thermolysis of 1 in *p*-Xylene Solution. A reaction tube was prepared by sealing one end of a 12-in. section of Corning Pyrex special walled glass tubing (o.d. 10 mm, thickness 2 mm). The tube was charged with 1.00 ml of *p*-xylene (previously purged with nitrogen at reflux to remove dissolved oxygen) and sufficient 1 to achieve the molal concentration given in Table I. The reaction tube was sealed under nitrogen, and the reaction mixture, maintained in the dark, was heated at the temperature and for the time period indicated in Table I. The ampules were opened and analyzed for aromatic hydrocarbons by VPC, either a Varian 1200 or an F & M 609 flame ionization instrument being used. For each compound 1, the column packing, column temperature, injection temperature, and detector temperature were as follows: X = *p*-NO_2, 20% Apiezon M on Chromosorb W, 120 °C, 175 °C, 175 °C; X = *m*-NO_2, same as for *p*-NO_2; X = *p*-Cl, 5% polyethylene glycol on Chromosorb W, 90°C, 210 °C, 260 °C; X = *m*-Cl, same as for *p*-Cl; X = *p*-Me, 5% DC 550 on Chromosorb W, 110 °C, 175 °C, 237 °C; X = *m*-Me, *p*-MeO, or *m*-MeO, same as for *p*-Me. Triplicate experiments were carried out for each compound 1, and the average deviation in the values was about ±5%. The values of the unknowns were obtained by comparisons with calibration curves constructed from results determined with known standard solutions. With the compounds, 1, with X = *p*-Cl, *m*-Cl, *p*-Me, *m*-Me, *p*-MeO, and *m*-MeO, not all of the reactant was completely soluble in the *p*-xylene; thus the thermolysis reactions of these compounds were carried out under partially heterogeneous conditions.

Material Balances. The reactions were carried out in the same manner as described above, but under the conditions specified in Table II. After each ampule had been opened, the contents were filtered. The filtrate was analyzed for hydrocarbon content by VPC, essentially as described above. The remaining filtrate was then concentrated to dryness in vacuo, and the gummy residue was induced to solidify by trituration with a small amount of cold pentane. This solid was combined with the original precipitate. An accurately weighed sample of the solid was dissolved in deuteriochloroform and its NMR spectrum taken. The integrated area corresponding to the hydroxyl proton was compared with a calibration curve obtained by use of standard solutions of the particular hydroxytetraarylantimony in order to calculate the amount of unreacted 1 recovered. The data are provided in Table II.

Hydrolysis of Pentaphenylantimony in Dioxane Solution. Dioxane (Mallinckrodt Scintill AR grade) was refluxed over sodium for 24 h and then distilled under argon. All subsequent manipulations and reactions were carried out under an argon atmosphere.

To 0.205 g (4.00×10^{-4} mol) of pentaphenylantimony contained in a 12-mm Pyrex ampule was added 2.00 ml of the purified dioxane. The ampule was sealed under argon and placed in an oil bath maintained at 98.5 °C for 13 h. At the end of this time, the ampule was opened and a 5-μl aliquot was subjected to VPC analysis. No more than a trace of benzene could be detected.

The operation was repeated, except that 7.00×10^{-3} ml (4.00×10^{-4} mol) of water was introduced into the reaction mixture. Following completion of the procedure described above, benzene was found to be present in 102 ± 3% yield, based on the use of a calibration curve constructed from results obtained with known standard solutions of benzene in dioxane. A 0.125-in. Carbowax 20M column was used in this analysis. Evaporation of the dioxane solution to dryness left a residue of nearly pure hydroxytetraphenylantimony, as indicated by its melting point and by its NMR and IR spectra, all of which were identical with the corresponding items of an authentic sample.[24–26]

Preliminary Kinetics Study of the Hydrolysis of Pentaphenylantimony. To 0.205 g (4.00×10^{-4} mol) of pentaphenylantimony contained in a 10-ml Erlenmeyer flask was added 2.00 ml of purified dioxane. The flask was sealed under argon with a rubber septum and placed in an oil bath maintained at 69.7 ± 0.1 °C. After 15 min, 7.0×10^{-3} ml (4.0×10^{-4} mol) of water was introduced through the septum, and aliquots for VPC analysis were withdrawn every 30 min for a 9-h period (corresponding to 45% completion of the reaction). The data provided an excellent fit to the second-order rate law, and the specific rate constant was calculated to be 1.3×10^{-4} l. mol^{-1} s^{-1}.

Acknowledgment. This work was supported in part by a grant from the National Science Foundation. Also, Professor Knapczyk of Johnson State College acknowledges partial summer support by the Vermont State College Advanced Study Program.

Registry No.—$XC_6H_4Sb^+(C_6H_5)_3BF_4^-$ (X = *p*-NO_2), 61203-35-8; $XC_6H_4Sb^+(C_6H_5)_3BF_4^-$ (X = *m*-NO_2), 61203-37-0; $XC_6H_4Sb^+(C_6H_5)_3BF_4^-$ (X = *p*-Me), 61203-39-2; $XC_6H_4Sb^+(C_6H_5)_3BF_4^-$ (X = *p*-MeO), 61203-41-6; $XC_6H_4Sb^+(C_6H_5)_3BF_4^-$ (X = H), 426-80-2; $XC_6H_4(C_6H_5)_3SbOH$ (X = H), 19638-16-5; 1 (X = *p*-Me) sulfate, 61203-42-7; 1 (X = *m*-Me) sulfate, 61203-43-8; 1 (X = *p*-MeO) sulfate, 61203-44-9; 1 (X = *m*-MeO) sulfate, 61203-45-0.

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Attack of Grignard and Lithium Reagents at Carbonyl Oxygens of *o*-Quinol Acetates[1]

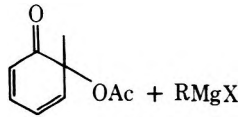
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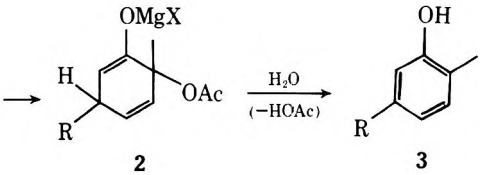
Received July 29, 1976

Grignard and lithium reagents react with o-quinol acetates (6-acetoxycyclohexa-2,4-dien-1-ones) to give alkyl aryl ethers resulting from formal attack at the "wrong ends" of the ketone carbonyls, as well as the normal reduction products and products arising from 1,2 and 1,4 addition to the conjugated carbonyls. Formation of ethers is not catalyzed by the presence of trace metals, which simply increases the yields of reduction products. Benzyl- and *tert*-butylmagnesium halides give exceptionally high relative yields of ethers, with secondary, primary, and methyl Grignards giving progressively lower yields of ethers. The yields of ethers appear to correlate well with the expected ease of oxidation of the Grignard reagents. These results are explained by assuming initial electron transfer from the organometallic reagent to the quinol acetate, giving a ketyl which then loses an acetate ion to give a phenoxy radical. The ethers are then formed by combination of phenoxy and alkyl radicals. This mechanism explains the occasional formation of 4-alkylphenols, which can arise by reaction of the alkyl radical at C-4 of the phenoxy radical, rather than at oxygen.

In an extensive series of papers, Wessely and his co-workers at the University of Vienna reported that reaction of Grignard reagents (including methyl-, ethyl-, and phenylmagnesium halides) with *o*-quinol acetates (6-acetoxycyclohexa-2,4-dien-1-ones) such as 1 gave 3-alkyl- or 3-arylphenols (e.g., 3) as well as a variety of products apparently resulting



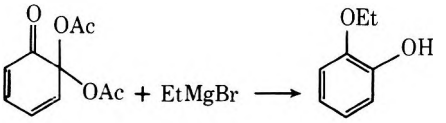
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2 3

from 1,2 addition of the Grignards to the ketone carbonyl.[2-6] This reaction has appreciable synthetic utility as a method for preparing meta-substituted phenols, which may otherwise be accessible only by multistep paths.[1,7] Formation of meta-substituted phenols presumably proceeds by initial conjugate addition of the Grignard reagent to the unsaturated carbonyls to give intermediates such as **2**, which then lose acetic acid, either during the reaction or during workup, to give **3**.

In one paper, Wessely and Kotlan reported that ethylmagnesium bromide reacted with the quinol diacetate **4** to give the ethyl ether, **5**, as the principal product[3]—a unique example of a Grignard reagent attacking the "wrong end" of a carbonyl group. Similar products were not observed in reactions of other quinol acetates,[2,4-6] while reaction of **4** with



4 5

methyl- or phenylmagnesium bromides gave good yields of the meta-substituted phenols which should result from "normal" conjugate addition.[3]

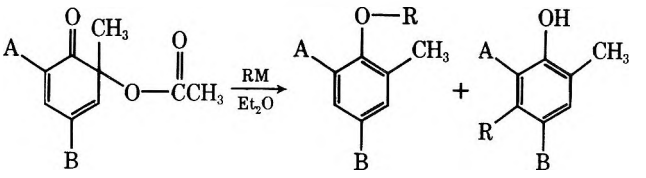
While attempting to prepare meta-substituted phenols by reactions of Grignard and lithium reagents with *o*-quinol acetates, we discovered that attack of the carbanionoid reagents at the oxygen atoms of carbonyls to give ethers is a very common result of these reactions.[1,8] This paper discusses the effect of changes in the structures of the organometallic reagents in determining the extent of attack at carbonyl oxygen atoms, and suggests a mechanism for these unusual reactions.

Results

Solutions of Grignard Reagents (1 M, prepared from >99.99% pure magnesium) were added rapidly to equal volumes of solutions of the quinol acetates in ether. To assure

Table I

a, A = B = CH_3
b, A = CH_3; B = H
c, A = *t*-Bu; B = H



6a–c 7a–c 8a–c

Ketone[d]	Organometallic reagent[e]	7, %	8, %	Redn product (8, R = H), %	Other products (%)	Additives	% 7/% 8
6a	CH_3MgBr	<0.1	39	4	Pentamethylbenzene (42) Unidentified ketones (15)		<0.003
6a	C_2H_5MgBr	4	52	7	2,5-Diethyl-2,4,6-trimethylcyclohex-3-en-1-one (31)		0.08
6a	C_2H_5MgBr	1	11	67	2,5-Diethyl-2,4,6-trimethylcyclohex-3-en-1-one (10)	Cu_2Cl_2 (0.1 g)	0.09
6a	*sec*-BuMgBr	67	16	17			4.2
6a	*sec*-BuMgBr	58[a]	15	28			3.9
6a	*sec*-BuMgBr	16	3	81		Cu_2Cl_2 (0.1 g)	5.3
6a	*sec*-BuMgBr	6	2	92		$CoCl_2$ (0.1 g)	3.0
6a	*sec*-BuMgBr	18	3	79		$FeCl_3$ (0.1 g)	6.0
6a	*t*-BuMgBr	28	<0.1	72			>280
6a	*t*-BuLi	15	<0.1	85			>150
6a	$PhCH_2MgCl$	91	<0.2	9			>450
6a	$PhCH_2MgCl$[a]	83	<0.2	17			>415
6b	*sec*-BuMgBr	46	27	32			
6b	*t*-BuMgBr	38	4	58	4-*tert*-Butyl-2,6-dimethylphenol (0.4)		1.7 9.5
6b	*t*-BuMgBr	38	3	60	4-*tert*-Butyl-2,6-dimethylphenol (0.4)		12.7[b]
6c	*sec*-BuMgBr	16	<1[c]	73	4-*sec*-Butyl-2-*tert*-butyl-6-methylphenol (11)		>16
6c	*t*-BuMgBr	<0.1	<0.1	86	2,4-Di-*tert*-butyl-6-methylphenol (14)		
6c	*sec*-BuMgBr	14	<1[c]	79	4-*sec*-Butyl-2-*tert*-butyl-6-methylphenol (8)		>14[b]
6c	$PhCH_2MgCl$	64	<1[c]	22	3-Benzyl-6-*tert*-butyl-2-methylphenol (2.0) 4-Benzyl-2-*tert*-butyl-6-methylphenol (12.5)		>64
6c	CH_3MgBr	0.1		39	1-*tert*-Butyl-2,3,5-trimethylbenzene (14) Unidentified ketones (39) (15)		

[a] Reagent prepared from "Grignard grade" magnesium. [b] Reaction time 30 s. [c] Estimated from NMR spectra of isomeric phenols. [d] Registry no.: **6a**, 4906-82-5; **6b**, 7218-21-5; **6c**, 51067-62-0. [e] Registry no.: CH_3MgBr, 75-16-1; C_2H_5MgBr, 925-90-6; *sec*-BuMgBr, 922-66-7; *t*-BuMgBr, 2259-30-5; *t*-BuLi, 594-19-4; $PhCH_2MgCl$, 6921-34-2.

complete reaction, ca. 7 mol of Grignard reagent was used for each mole of quinol acetate. The reactions were normally allowed to continue for 30 min, but two runs in which the reactions were worked up only 30 s after addition of the Grignard reagents was started gave identical results with those employing the longer reaction times. The results of the various reactions are summarized in Table I.

Reaction of quinol acetate **6a** with methylmagnesium bromide gave the conjugate addition product, 2,3,4,6-tetramethylphenol, and pentamethylbenzene as the principal addition products. A ketone with a camphorlike odor, which was presumably identical with the product which Wessely's group obtained from reaction of **6a** with methylmagnesium iodide,[2] was also obtained. The spectra of this product were quite complex, with several NMR peaks at other than integral ratios (see Experimental Section). We believe this product to be a mixture, despite failure to separate it on several GLC columns.

The major product, pentamethylbenzene, was presumably formed by 1,2 addition of the Grignard reagent to the ketone carbonyl, followed by a pinacol rearrangement, a second 1,2 addition, and a Wagner–Meerwein rearrangement, which may have occurred during the workup procedure (eq 1). The ke-

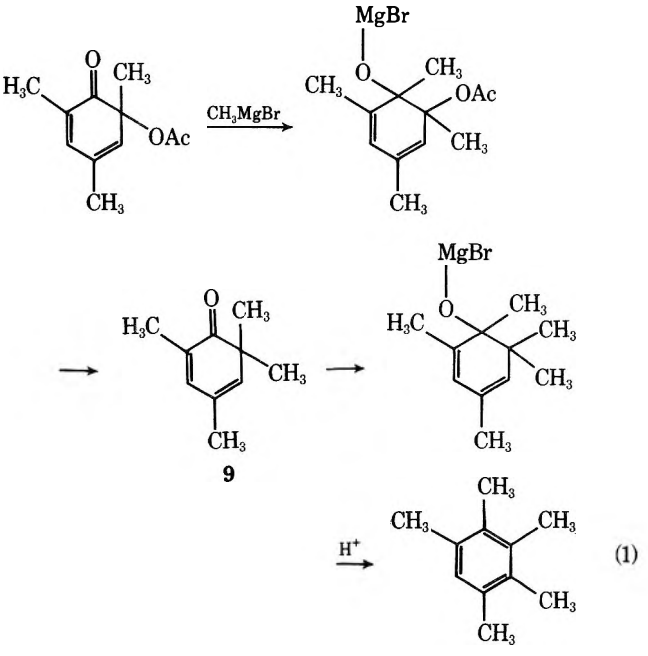
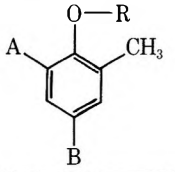


Table II. NMR Spectra of Ethers

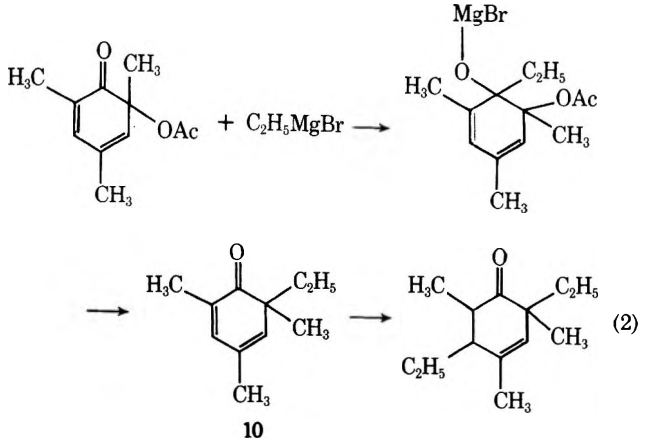


Registry no.		A	B	R	Chemical shifts, δ, ppm: $ArCH_3$	Other	ArH	R
61248-61-1	a	CH_3	CH_3	*t*-Bu	2.27 (s, 9 H)		6.83 (s, 2 H)	1.37 (s, 9 H)
19578-76-8	a	CH_3	CH_3	$PhCH_2$	2.21 (s, 9 H)		6.83 (s, 2 H) 6.97–7.55 (m, 5 H)	4.75 (s, 2 H)
61248-62-2	a	CH_3	CH_3	*sec*-Bu	2.23 (s, 9 H)		6.79 (s, 2 H)	0.99 (t, J = 6 Hz, 3 H) 1.20 (d, J = 6 Hz, 3 H) 3.8–4.1 (m, 1 H)
61248-63-3		CH_3	CH_3	C_2H_5	2.20 (s, 9 H)		6.79 (s, 2 H)	0.82 (t, J = 7 Hz, 3 H) 3.82 (q, J = 7 Hz, 2 H)
4028-66-4		CH_3	CH_3	CH_3	2.21 (s, 9 H)		6.80 (s, 2 H)	3.52
61248-64-4	a	CH_3	H	*sec*-Bu	2.19 (d, J = 0.5 Hz, 6 H)		6.7–6.9 (m, 3 H)	1.00 (t, J = 6 Hz, 3 H) 1.20 (d, J = 6 Hz, 3 H) 3.8–4.1 (m, 1 H)
54350-32-2	a	CH_3	H	*t*-Bu	2.29 (s, 6 H)		6.7–6.9 (m, 3 H)	1.38 (s, 9 H)
61248-65-5	a	*t*-Bu	H	*sec*-Bu	2.28 (d, J = 1 Hz, 3 H)	1.39 (s, 9 H)	6.8–7.3 (m, 3 H)	1.01 (t, J = 6 Hz) } 6 H 1.14 (d, J = 5 Hz) } total 4.3–4.8 (m, 1 H)
61248-66-6	a	*t*-Bu	H	$PhCH_2$	2.25 (s, 3 H)	1.35 (s, 9 H)	6.8–7.3 (m, 8 H)	4.83 (s, 2 H)
60772-80-7		*t*-Bu	H	CH_3	2.33 (s, 3 H)	1.35 (s, 9 H)	6.25–7.28 (m, 3 H)	3.21 (s, 3 H)

[a] Compound not previously reported. Satisfactory analytical data were obtained for C, H.

tonic products are also most likely formed by initial 1,2 addition to **6a** (possibly followed by a conjugate addition to ketone **9**), so that reaction of **6a** with methylmagnesium bromide appears to proceed principally by initial 1,2 addition. No evidence for any attack at carbonyl oxygen could be observed.

Reaction of **6a** with ethylmagnesium bromide gave, in addition to the conjugate addition product 3-ethyl-2,4,6-trimethylphenol, a 31% yield of a ketone, whose NMR spectrum was in excellent agreement with the structure 2,5-diethyl-2,4,6-trimethylcyclohex-3-en-1-one, which Wessely and his group assigned to the neutral product they isolated from this reaction.[4] Formation of this product can be rationalized by a mechanism (eq 2) identical with that previously suggested



(2)

10

for formation of pentamethylbenzene by reaction of **6a** with methylmagnesium bromide, except that the ethyl Grignard gives only 1,4 rather than 1,2 addition to the cyclohexadienone **10**. The absence of 1,2 addition can readily be accounted for by steric interference with addition of ethylmagnesium bromide to the hindered carbonyl group of **10**.

The most interesting difference between reactions of **6a** with ethyl- and with methylmagnesium bromide is that reaction with ethylmagnesium bromide gave a 4% yield of ether **7a** (R = C_2H_5), which could be isolated and identified by comparison with the product obtained from a Williamson synthesis.

On changing from primary Grignard reagents to *sec*-butylmagnesium bromide the ether became the principal product, and the "normal" conjugate addition product was obtained in only 16% yield. No evidence for any 1,2 addition was observed, presumably owing to steric effects.

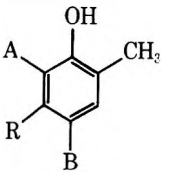
With *tert*-butylmagnesium bromide or *tert*-butyllithium, no evidence could be obtained for any conjugate addition products from reaction with **6a**. Reduction of the quinol acetate to mesitol was the major process in both reactions, but *tert*-butyl 2,4,6-trimethylphenyl ether was obtained in moderate yields. Not surprisingly, attempts to synthesize the ether by a Williamson procedure or by addition of the phenol to isobutylene failed. However, the structure of the ether was clearly established from its spectrum and from the fact that refluxing in acetic acid–sulfuric acid gave a quantitative yield of mesitol.

Reaction of benzylmagnesium chloride with **6a** gave a 91% yield of benzyl 2,4,6-trimethylphenyl ether. No 3-benzyl-2,4,6-trimethylphenol could be detected in the reaction mixture by GLC.

Reaction of quinol acetate **6b** with *sec*-butylmagnesium bromide again gave a mixture of the ether and the conjugate addition product, 3-*sec*-butyl-2,6-dimethylphenol. The somewhat higher yield of conjugate addition from this reaction compared to reaction of *sec*-butylmagnesium bromide with **6a** can readily be accounted for by the lesser steric interference with conjugate addition to **6b**. Reaction of **6b** with *tert*-butylmagnesium bromide, unlike reaction of **6a**, did give some of the conjugate addition product, 3-*tert*-butyl-2,6-dimethylphenol, in addition to the ether and the reduction product, 2,6-dimethylphenol. In this reaction, however, an additional reaction product, 4-*tert*-butyl-2,6-dimethylphenol, was obtained in trace quantities.

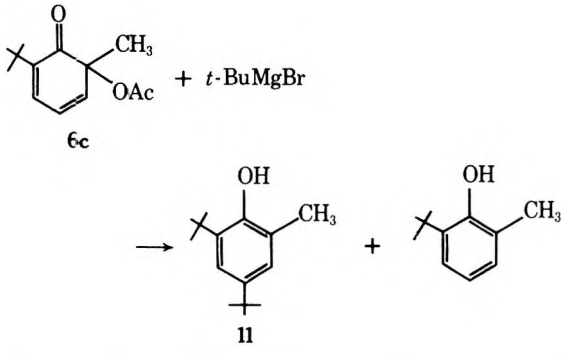
When attack at oxygen and conjugate addition were both inhibited by the presence of a *tert*-butyl group at C-2 in quinol acetate **6c**, reaction with *tert*-butylmagnesium bromide gave reduction and attack at C-4 to give phenol **11** as the only detectable processes. Reaction of **6c** with *sec*-butylmagnesium

Table III. NMR Spectra of Phenols



Registry no.		A	B	R	Chemical shift, δ, ppm: $ArCH_3$	ArH	OH	R[B]
3238-38-8	b	CH_3	CH_3	CH_3	2.11 (s)	6.76 (s, 1 H)	4.45	2.11 (s)
3180-05-0	c	CH_3	CH_3	C_2H_5	2.15 (s, 9 H)	6.73 (s, 1 H)	4.52	1.03 (t, J = 8 Hz, 3 H) 2.55 (q, J = 8 Hz, 2 H)
61248-67-7	a	CH_3	CH_3	*sec*-Bu	2.20 (d, J = 1 Hz, 3 H)	6.77 (s, 1 H)	4.49	0.89 (t, J = 7 Hz, 3 H) 1.32 (d, J = 7 Hz, 3 H) 1.8 (m, 2 H)
61248-68-8	a	CH_3	H	*sec*-Bu	2.26 (s, 6 H)	6.77 (d, J = 7.5 Hz, 1 H) 7.01 (d, J = 7.5 Hz, 1 H)	4.63	0.90 (t, J = 8 Hz, 3 H) 1.26 (d, J = 7 Hz, 3 H) 1.6 (m 2 H) 2.9 (m, 1 H)
61248-69-9	a	CH_3	H	*t*-Bu	2.22 (s, 3 H) 2.42 (s, 3 H)	6.94 (s, 2 H)	4.61	1.42 (s, 9 H)
51067-63-1	a	*t*-Bu	*sec*-Bu	H	2.22 (s, 3 H)	6.79 (d, J = 7 Hz) 6.93 (d, J = 7 Hz)	4.56	[0.82 (t, J = 7 Hz, 3 H) 1.20 (d, J = 7 Hz, 3 H)]
616-55-7		*t*-Bu	*t*-Bu	H	2.22 (s, 3 H)	7.01 (s, 2 H)	4.53	[1.28 (s, 9 H)]

[a] Compound not previously reported. Satisfactory analytical data were obtained for C, H. [b] Mp 78–80 °C [reported [Hey, *J. Chem. Soc.*, 1581 (1931)], mp 79–81°]. [c] Mp 96–98 °C (reported[4] mp 96–97 °C).

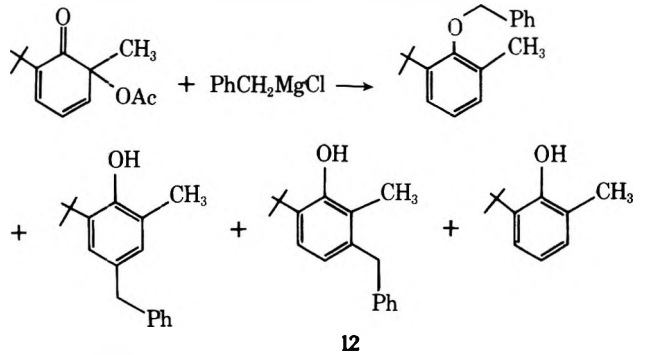


6c

11

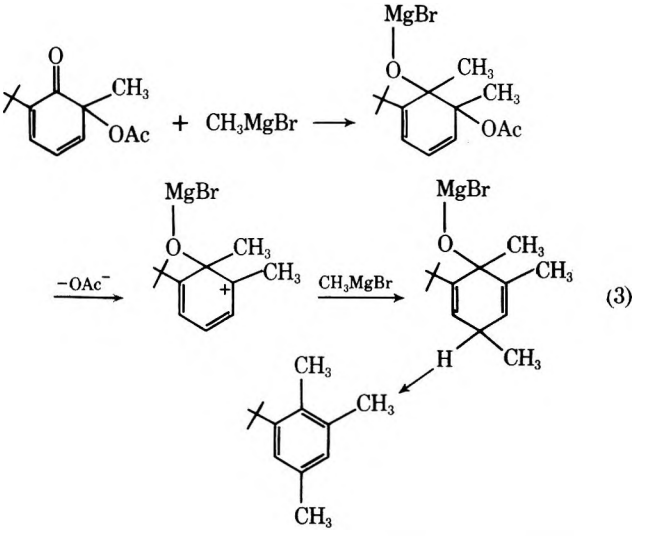
bromide gave reduction as the major process, together with a greatly reduced yield of ether. No conjugate addition was observed. However, a significant yield of 4-*sec*-butyl-2,6-dimethylphenol was obtained.

Not surprisingly, benzylmagnesium chloride, a primary Grignard, was less affected by the presence of a *tert*-butyl group at C-2. The principal product was again the ether, now accompanied by the product of attack at C-4 and by phenol **12**, resulting from conjugate addition at C-5. (Whether addition at C-5 is unique for reaction with **6c** cannot now be determined, since identical products would be obtained from reaction at C-3 or at C-5 in quinol acetates **6a** and **6b**.)



12

Reaction of **6c** with methylmagnesium bromide gave principally the reduction product, together with several ketones whose structures could not be determined and an aromatic hydrocarbon whose NMR spectrum showed the presence of a *tert*-butyl group, three methyl singlets, one of which was significantly downfield from the other two and was therefore presumably ortho to the *tert*-butyl group, and two aromatic protons showing meta coupling, one of which appeared to be ortho to the *tert*-butyl group. It was therefore assigned the structure 1-*tert*-butyl-2,3,5-trimethylbenzene. It was presumably formed by a mechanism similar to that shown in eq 3.



(3)

No evidence for either conjugate addition or ether formation could be detected in this reaction.

The addition of salts of copper, cobalt, and iron to the reactions was investigated, to see whether the presence of these metals favored conjugate addition or ether formation. In all cases, however, these additives simply gave marked increases in yields of reduction products. Similarly, the use of commercial "Grignard grade" magnesium resulted in an increase in reduction, but did not significantly affect the ratios of other products.

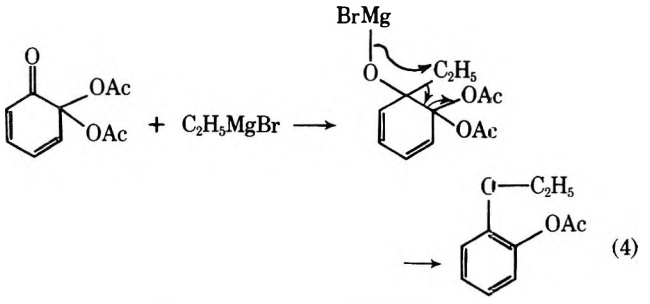
Discussion

The yields of ethers, relative to those of conjugate addition products, obtained from reactions of Grignard reagents with

o-quinol acetates decrease sharply as the structures of the Grignard reagents are changed from benzyl or tertiary to secondary, primary, and finally methyl Grignards. With the exception of the benzyl Grignard, this sequence parallels the decrease in size of the carbanionoid reagents. Since attack at the exocyclic carbonyl oxygen should be less subject to steric hindrance by substituents at C-2 and C-6 than attack at either C-1 or C-3 of the ring, it might be argued that the effects of changes in the nature of the aliphatic Grignard reagents are principally steric in nature. Indeed, the data in Table I do suggest that the ratio of ether formation to conjugate addition is affected by the size of the substituents on the cyclohexadienone ring, although the effects do not seem to be very large.

However, steric effects cannot account for the remarkably high yields of ethers obtained from benzylmagnesium chloride, a primary Grignard reagent. Furthermore, no ether formation is observed in the reaction of methylmagnesium bromide with quinol acetate **6c**. Instead, all the products observed appear to arise from initial 1,2 addition to the carbonyl group, despite the fact that normal addition to the carbonyl in this molecule must be extremely hindered even for a methyl Grignard reagent.

It thus seems that some factor other than steric effects must be invoked to account for the high yields of ethers from tertiary and, particularly, from benzylic Grignard reagents. Does the suggestion of Wessely and Kotlan[3] that the ethyl ether from reaction of **4** with ethylmagnesium bromide is formed by initial 1,2 addition, followed by rearrangement of the ethyl group from carbon to oxygen (a sort of reverse Wittig rearrangement, as in eq 4), help account for these facts? This



(4)

mechanism requires that the ratio of 1,2 to 1,4 addition of Grignard reagents to unsaturated ketones should increase markedly as the structure of the Grignard changes from primary to secondary and then to tertiary. The available evidence suggests that the opposite is true—that the ratio of 1,2 to 1,4 addition *decreases* as the degree of substitution at the carbanionoid center increases.[9] This is supported by the data in Table I, since ethylmagnesium bromide gives a significantly higher yield of the conjugate addition product than does methylmagnesium bromide. Furthermore, this mechanism would require that *tert*-butylmagnesium bromide should add readily to the very hindered carbonyl group of **6b**, in preference to the relatively unhindered β carbon of the double bond, and that the *tert*-butyl Grignard add to the carbonyl of **6b**, and the *sec*-butyl Grignard add to the carbonyl of **6c**, within a total reaction time of at most 30 s. (The actual reaction period seems to be significantly lower than that, since the yellow color of the quinol acetates has disappeared by the time addition of the Grignard is complete—some 5–6 s.) Finally, this mechanism offers no explanation for attack of the Grignard reagents at C-4 of the quinol acetate. While this reaction may proceed by a mechanism which is different from that for ether formation, it would be satisfying to be able to account for both anomalous reactions by a single mechanism, rather than require a fundamentally different, ad hoc, explanation for each.

We suggest that ether formation proceeds by initial electron transfer from the Grignard or lithium reagents to the quinol acetates—a reaction which has ample precedent in other reactions of Grignard reagents with ketones.[10] The fact that the stability of alkyl radicals increases in the order primary < secondary < tertiary is well known, as is the greater reactivity of tertiary and secondary Grignard and lithium reagents, compared to the primary reagents.[11] (Insofar as organometallic reagents can be considered to resemble carbanions, this order of reactivity follows directly from the greater stability of the less substituted carbanions.[12]) The ease of electron donation by Grignard and lithium reagents should therefore be in the order tertiary > secondary > primary > methyl.

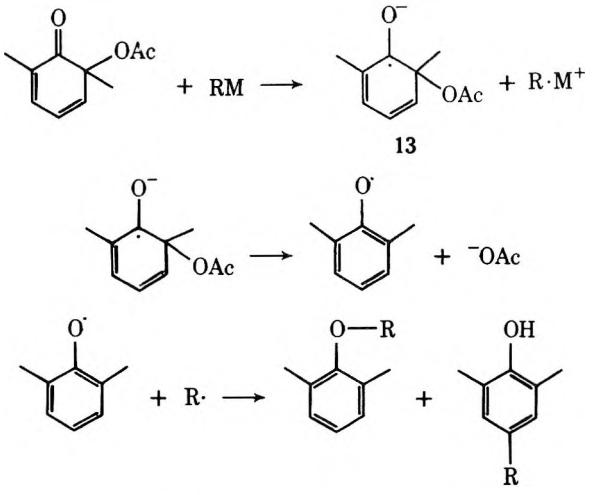
It seems probable that benzyl Grignard reagents are similarly more easily oxidized to free radicals than are other primary Grignards. The benzyl radical has been reported to have a lower electron affinity than the methyl radical (18.4 kcal/mol for the benzyl radical, compared to 24.8 kcal/mol for the methyl radical).[13,14] This is presumably due to the fact that placing a second electron into the p orbital of a benzyl radical should be less exothermic than placing it into the orbital of an alkyl radical, which would rehybridize to form the more stable hybrid anion.

Unfortunately, there seems to be no available evidence which would allow comparison of the electron affinities of benzyl radicals with those of alkyl radicals other than the methyl radical. However, it does not seem unreasonable to assume that the benzyl anion is among the more easily oxidized of hydrocarbon anions, in view of the relatively large (ca. 35%) reported difference in electron affinities between benzyl and methyl radicals.

On this assumption, the expected order of ease of electron transfer by Grignard and lithium reagents parallels the relative yields of ethers obtained from them in reactions with o-quinol acetates. The benzyl and tertiary Grignards, being the best electron donors, give the highest yields of ethers, while the methyl Grignard gives the lowest yield.

The hypothesis that ether formation proceeds by electron transfer explains why phenylmagnesium bromide and phenyllithium give no ethers, even from reaction with **4**,[3] since the phenyl radical has an exceptionally high electron affinity.[13]

We can thus write a simple mechanism for formation of ethers from reaction of o-quinol acetates with Grignard reagents. Initial electron transfer to give the ketyl **13** and an alkyl radical is followed by loss of an acetate anion to give a

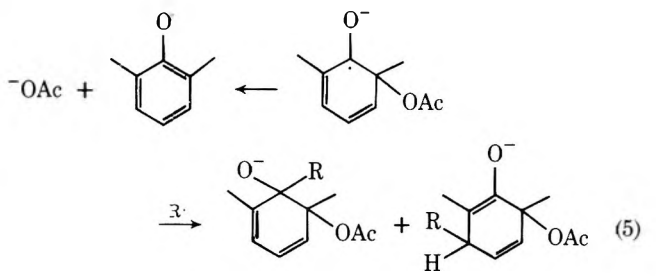


phenoxy radical, which then combines with the alkyl radical to give the ether.

This mechanism has the virtue of providing an obvious mechanism for formation of p-alkylphenols from the reactions of quinol acetates with Grignard reagents.

The hypothesis that there is a close relationship between the mechanisms for formation of ethers and of *p*-alkylphenols is supported by the fact that reaction of methylmagnesium bromide with **6c** gives no trace of either the ether or of 2,4-dimethyl-6-*tert*-butylphenol, even though addition to the carbonyl must be highly hindered.

We have not attempted to suggest mechanisms for normal or conjugate additions to the carbonyl groups of o-quinol acetates. Perhaps the simplest hypothesis is that both 1,2 and 1,4 additions proceed by processes independent of electron transfer. However, it is conceivable that electron transfer is the initial step in all the reactions, but that combination of the more reactive primary radicals with the ketyl is very much faster than loss of an acetate anion (eq 5). Attempts to distinguish between these possibilities are now in progress.



(5)

Experimental Section

General. NMR spectra were taken on Perkin-Elmer R12A or Varian A-60 spectrometers in deuteriochloroform solutions, using Me_4Si as an internal standard. ir spectra were taken on a Perkin-Elmer 237B spectrometer. Mass spectra were taken on a Hitachi Perkin-Elmer RMU-6L instrument. Melting points were taken on a Mel-Temp apparatus, and are uncorrected. Microanalyses were carried out by the University of Massachusetts Microanalytical Laboratory, Amherst, Mass. GLC analyses were carried out on a Varian Model 202c gas chromatograph, using a 6 ft × 0.25 in. column packed with 5% SE-30 on Chromosorb W. Preparative runs were carried out on a 6 ft × 0.375 in. column with the same packing.

o-Quinol Acetates. 6-Acetoxy-2,4,6-trimethylcyclohexa-2,4-dien-1-one (6a), mp 87.5–89 °C (reported[16] mp 84 °C), and **6-acetoxy-2,4-dimethylcyclohexa-2,4-dien-1-one (6b),** mp 36–38 °C (reported[17] mp 36 °C), were prepared as described in the literature.

6-Acetoxy-2-*tert*-butyl-6-methylcyclohexa-2,4-dien-1-one (6c). A suspension of lead tetraacetate (45 g, ca. 90% pure, 0.09 mol) in 50 ml of chloroform was cooled in ice. A solution of 2-*tert*-butyl-6-methylphenol (16.4 g, 0.10 mol) in 20 ml of chloroform was added slowly while the mixture was vigorously stirred, at a rate such that the temperature of the reaction did not give rise above 25 °C. After completion of the addition, the reaction mixture was allowed to stand at room temperature for 1 h and the yellow precipitate filtered off. Water was added to the filtrate, and the precipitated lead dioxide filtered off. The layers were separated, the organic layer dried over magnesium sulfate, and the solvent evaporated to give 16.9 g (0.76 mol, 85%) of a reddish oil which crystallized on standing in the refrigerator. Recrystallization from ether (−20 °C) gave yellow needles, mp 77–79 °C. Their IR spectrum showed a carbonyl peak at 1670 cm^{-1}. The NMR spectrum had peaks at δ 1.23 (s, 9 H), 1.37 (s, 3 H), 2.09 (s, 3 H), 6.19 (s) and 6.27 (d, J = 1 Hz) (totaling 2 H for the two signals), and 6.81 (dd, J = 4, 3 Hz, 1 H). Anal. Calcd for $C_{13}H_{18}O_3$: C, 72.2; H, 5.6. Found: C, 72.2; H, 5.7.

Preparation of Grignard Reagents. Grignard reagent solutions (ca. 1 M) were prepared by slowly dropping a solution of 0.050 mol of the alkyl halide in 25 ml of anhydrous ether into a flask containing 25 ml of ether and 1.2 g (0.050 mol) of magnesium. The mixture was stirred continuously and kept under nitrogen until reaction was apparently complete, and then refluxed for an additional 15 min. The mixture was then filtered under nitrogen pressure through a sintered glass filter, and stored under nitrogen for no longer than 3 days.

When not otherwise specified, the Grignard reagent was prepared using magnesium chips of >99.99% purity (grade m4N) obtained from the Ventron Corp. Reactions indicated in Table I as carried out with "Grignard grade magnesium" employed magnesium turnings obtained from the General Chemical Division of the Allied Chemical Co.

***tert*-Butyllithium.** Solutions of *tert*-butyllithium in *n*-pentane (2 M) were obtained from the Ventron Corp.

Reactions of Grignard Reagents with o-Quinol Acetates. In the general procedure, a ca. 0.50-g (2.1–2.7 mmol) sample of o-quinol acetate was dissolved in 15 ml of anhydrous ether under a nitrogen atmosphere. The Grignard solution (15 ml, ca. 15 mmol) was added rapidly from an equalizing addition funnel. The reaction mixture was stirred for 0.5 h (except where otherwise indicated) and a dilute solution of ammonium chloride in water was added. The ether layer was separated, and the aqueous layer was extracted with ether. The combined ether layers were washed with water and dried over magnesium sulfate, and the solvent was evaporated under vacuum. The product was weighed and analyzed by GLC, and then dissolved in hexane and extracted twice with Claisen alkali. The base-insoluble fraction was washed with water and dried over magnesium sulfate, and the solvent was evaporated. The base-soluble fraction was acidified with dilute hydrochloric acid and extracted twice with methylene chloride, the methylene chloride solution was washed with water and dried over magnesium sulfate, and the solvent was evaporated. Both base-soluble and base-insoluble products were weighed and analyzed by GLC. Corrections for differences in thermal conductivity of the products were made by analyzing standard mixtures of the products.

In synthetic runs, all products were isolated by preparative GLC. Reaction of *tert*-butyllithium with quinol acetate **6a** was carried out in precisely the same manner as reactions with Grignard reagents, except that a 10-ml aliquot of the lithium reagent was employed.

Reaction of Quinol Acetate 6a with Methylmagnesium Bromide. The base-insoluble fraction contained pentamethylbenzene, identified by comparison with a sample obtained from the Aldrich Chemical Co., and a ketone with IR peaks at 1670 and 1720 cm^{-1}. Its NMR spectrum had peaks at δ 1.08 (s, 2.3 H), 2.20 (s, 3 H), 2.6 (m, 8 H), 2.85 (dd, J = 6, 1 Hz, 4 H), 3.35 (m, 0.8 H), 4.45 (m, 1 H), 5.25 (bs, 0.7 H), 5.85 (bs, 1 H), 6.35 (bs, 1 H). Its mass spectrum showed peaks at m/e 166 (M^+) and 153.

Reaction of 6a with Ethylmagnesium Bromide. The base-insoluble fraction contained a ketone assigned the structure 2,5-diethyl-2,4,6-trimethylcyclohex-3-en-1-one.[3] Its NMR spectrum had peaks at δ 1.25 and 1.28 (triplets, J ca. 7 Hz, totaling 6 H), a singlet and a doublet (J = 7 Hz) at 1.04, totaling 6 H, 1.80 (s, 3 H), 2.15–2.45 (m, 1 H, proton at C-5), 2.65–3.15 (m, 1 H, proton at C-6), 5.31 (bs, 1 H). Its IR spectrum had a carbonyl peak at 1720 cm^{-1}.

Reaction of 6c with Benzylmagnesium Chloride. The alkali-soluble fraction contained 3-benzyl-5-*tert*-butyl-2-methylphenol and 4-benzyl-2-*tert*-butyl-6-methylphenol, which were identified by comparison of their IR and NMR spectra and GLC retention times with those of samples previously prepared.[18]

Reaction of 6c with Methylmagnesium Bromide. The alkali-insoluble fraction contained three components, with retention times (at 120 °C) of 4.0, 5.0, and 6.4 min. The component with the highest retention time was assigned the structure 1-*tert*-butyl-2,3,5-trimethylbenzene. Its NMR spectrum had peaks at δ 1.40 (s, 9 H), 2.23 (s, 3 H), 2.27 (s, 3 H), 2.35 (s, 3 H), 6.91 (d, J = 2 Hz, 1 H), and 7.08 (d, J = 2 Hz, 1 H). Its mass spectrum had peaks at m/e 176 (M^+) and 161. Anal. Calcd for $C_{13}H_{20}$: C, 88.6; H, 11.4. Found: C, 88.3; H, 11.5.

The component with intermediate retention time had a peak in its IR spectrum at 1675 cm^{-1}. Its NMR spectrum had peaks at δ 1.04 (s, 6 H), 1.24 (s, 9 H), 1.33 (s, 3 H), 2.22 (m, 1 H), and 5.60 (m, 2 H). Its mass spectrum had a peak at m/e 192 (M^+). Anal. Found: C, 92.4; H, 10.2.

The peak with lowest retention time could not be completely separated from the adjacent peak. Its IR spectrum had a peak at 1730 cm^{-1}, in addition to a smaller peak at 1675 cm^{-1}.

Synthesis of Alkyl Aryl Ethers. Potassium *tert*-butoxide (6.55 g, 0.05 mol) was dissolved in 30 ml of dimethyl sulfoxide. The appropriate phenol (0.05 mol) was added to the solution, which was shaken until a homogeneous solution was obtained. The alkyl halide (0.05 mol) was added, and the solution allowed to stand at room temperature for 15 min. Water was then added, and the mixture extracted with pentane. The organic layer was extracted with Claisen alkali, washed with water, and dried over magnesium sulfate. The solvent was evaporated to give the ether, which was essentially pure. Analytical samples were purified by preparative GLC.

Acknowledgment. I thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for a grant in partial support of this work.

Registry No.—2-*tert*-Butyl-6-methylphenol, 36078-59-8; 2,2,4,5,6-pentamethylcyclohex-3-en-1-one, 61248-70-2; 2,5-diethyl-

2,4,6-trimethylcyclohex-3-en-1-one, 61248-71-3; 1-*tert*-butyl-2,3,5-trimethylbenzene, 61248-72-4.

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Substituent Effects on Reactions of Benzylmagnesium Chlorides with *o*-Quinol Acetates[1]

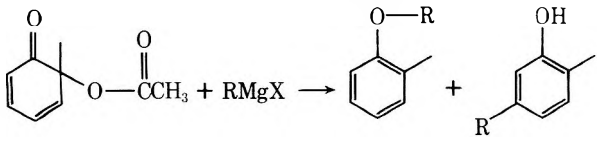
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Received July 29, 1976

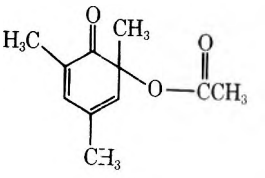
Reaction of 6-acetoxy-2,4,6-trimethylcyclohexa-2,4-dien-1-one with a series of meta- and para-substituted benzylmagnesium chlorides gave decreasing yields of benzyl aryl ethers and increasing yields of *m*-benzylphenols as the electron-withdrawing powers of the substituents increased. Reaction of 6-acetoxy-2,4-dimethylcyclohexa-2,4-dien-1-one with the same Grignard reagents yielded *p*-benzylphenols in addition to aryl benzyl ethers and *m*-benzylpherols. While the ratio of ethers to *m*-benzylphenols increased sharply when more electron-donating substituents were present on the Grignard reagents, the ratio of ethers to *p*-benzylphenols remained almost constant. These results support a mechanism for formation of ethers and of *p*-benzylphenols involving initial electron transfer from the Grignard to the ketone to form phenoxy radicals, and combination of phenoxy and benzyl radicals to form the products.

Grignard and lithium reagents normally react with α,β-unsaturated ketones by addition to the carbon atoms of the carbonyl groups or by conjugate addition to the double bonds. In the preceding paper, however, it was shown that Grignard and lithium reagents react with o-quinol acetates (6-acetoxycyclohexa-2,4-dien-1-ones) to give aromatic ethers resulting from attack at the carbonyl oxygen atoms, as well as the "normal" 1,4 and (for primary Grignard reagents) 1,2

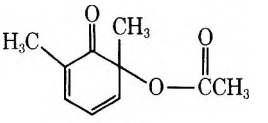


addition to the unsaturated carbonyl systems.[2] While primary Grignard reagents gave only traces of ethers, tertiary and benzylic Grignards yielded ethers as the primary or only addition products. Secondary Grignards gave significant yields of the products of attack at both oxygen and carbon. The relative yields of ethers to those of the "normal" addition products appeared to roughly parallel the expected order of electron-donating abilities of the organometallic reagents. However, the relative importance of the sizes of the carbanionoid reagents and of their electron-donating abilities were difficult to evaluate, since changes in these factors parallel each other for simple alkyl Grignard reagents.[1]

In order to determine whether Grignard attack at oxygen atoms of o-quinol acetates is indeed a function of the electron-donating abilities of the Grignards, rather than their steric requirements, we have studied the products obtained from reaction of 6-acetoxy-2,4,6-trimethylcyclohexa-2,4-dien-1-one (1) and 6-acetoxy-2,6-dimethylcyclohexa-2,4-dien-1-one (2) with benzylic Grignard reagents bearing substituents in the meta and para positions.



1



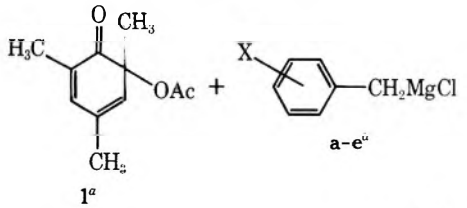
2

Results

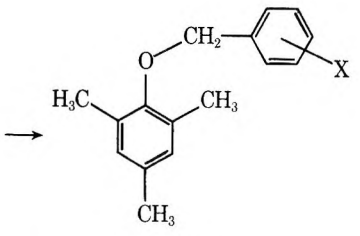
A solution of 1 (ca. 2 mmol) in 10 ml of ether was added rapidly to 10 mmol of the Grignard reagent in 10 ml of ether, and the products were analyzed by GLC. Each reaction was carried out two times, using a freshly prepared Grignard solution for each run. The results of these reactions are summarized in Table I.

Benzyl 2,4,6-trimethylphenyl ethers (3), which were readily identified by their NMR spectra and by comparison with synthetic samples, were obtained as major products from each reaction. However, neither reaction with benzylmagnesium chloride nor with 4-methylbenzylmagnesium chloride gave a detectable yield of a *m*-benzylphenol. The results obtained with benzylmagnesium chloride agree with those reported in the preceding paper,[2] which differ from those reported here only in that the Grignard reagent was added to the quinol acetate, rather than vice versa.

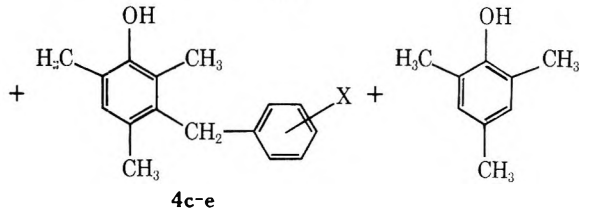
Table I. Relative Yields of Products from Reaction of 1 with Benzylmagnesium Chlorides



1[a]



3a-e



4c-e

a. X = H d, X = m-Cl
b, X = p-CH$_3$ e, X = m,p-di-Cl
c. X = p-Cl

X	3	4	Mesitol	% 3/% 4
p-CH$_3$	100	<0.5	16 ± 4	>200
H	100	<0.5	8 ± 3	>200
p-Cl	100	17 ± 6	4 ± 1	5.8
m-Cl	100	42 ± 2	9 ± 2	2.4
m,p-di-Cl	100	101 ± 4	7 ± 4	0.99

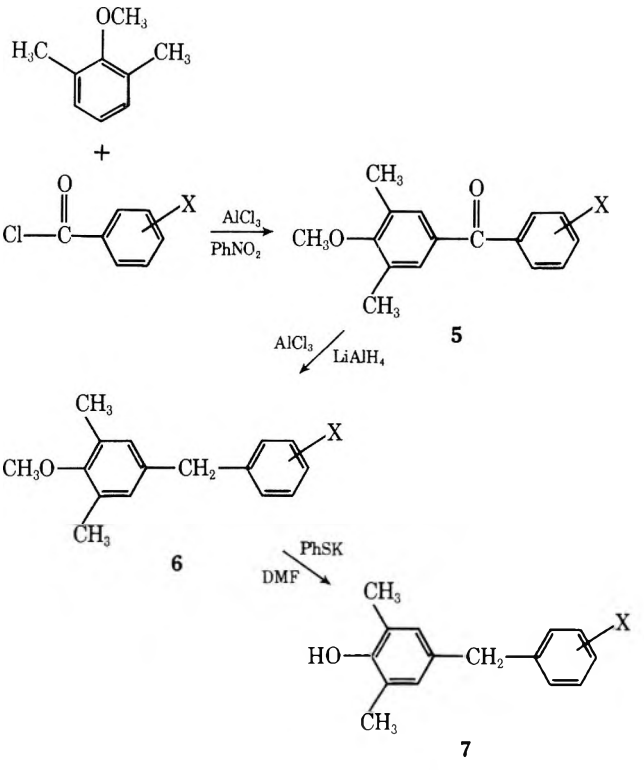
[a] Registry no.: 1, 4906-82-5; a, 6921-34-2; b, 29875-07-8; c, 874-72-6; d, 29874-01-9; e, 61259-69-6.

In contrast, reactions employing Grignard reagents with electron-withdrawing substituents did give phenols (**4c–e**) resulting from conjugate addition to the unsaturated ketone. The yields of conjugate addition products increased with increasing electron-withdrawing power of the substituents, until reaction with 3,4-dichlorobenzylmagnesium chloride gave equal yields of products of attack at oxygen and at C-3 of the ketone.

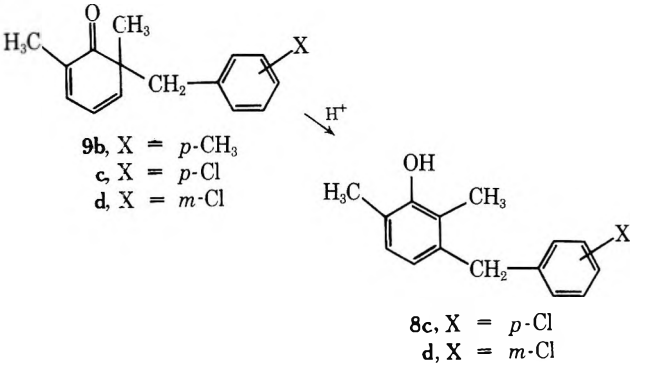
Reaction of substituted benzylmagnesium halides with quinol acetate **2**[3] again gave the expected benzyl 2,6-dimethylphenyl ethers and the reduction product, 2,6-dimethylphenol. Instead of a single *m*-benzylphenol, however, each reaction appeared to give a mixture of phenolic addition products. It proved impossible to isolate the individual components of these mixtures, although the products from reaction with 4-methylbenzylmagnesium chloride and 4-chlorobenzylmagnesium chloride showed two distinguishable, though overlapping, peaks on analytical GLC. The NMR spectra of each of these mixtures was characterized by the presence of two singlets of unequal intensities in the region (δ 3.7–4.0) characteristic of diarylmethylene resonances.

In view of our previous observation that 2,6-dialkyl quinol acetates can give rise to *p*-alkylphenols on reaction with organometallic reagents,[2] it seemed likely that the phenolic products consisted of mixtures of the *m*- and *p*-benzylphenols from each reaction. The *m*- and *p*-benzylphenols were therefore independently synthesized for comparison with the mixtures obtained from the Grignard reactions.

Attempts to prepare the *p*-benzyl isomers by direct Friedel–Crafts benzylation of 2,6-dimethylphenol or of 2,6-dimethylphenyl ether failed, since a mixture of isomers was obtained in each case.[4] Instead, Friedel–Crafts reactions between substituted benzoyl chlorides and 2,6-dimethylphenyl methyl ether gave the 4-methoxybenzophenones (**5**), which were reduced to diphenylmethanes by LiAlH$_4$ and AlCl$_3$. Cleavage of the ethers with potassium thiophenolate in *N,N*-dimethylformamide gave the desired *p*-benzylphenols (**7**).



Synthesis of the *m*-benzylphenols was initially attempted by acid-catalyzed rearrangements of the corresponding o-cyclohexadienones (**9**). This worked reasonably well for synthesis of the *m*-chloro and *p*-chloro isomers **8c** and **8d**, although each product was contaminated with small amounts of the *p*-benzyl isomers resulting from [1,3] benzyl migrations.[5]

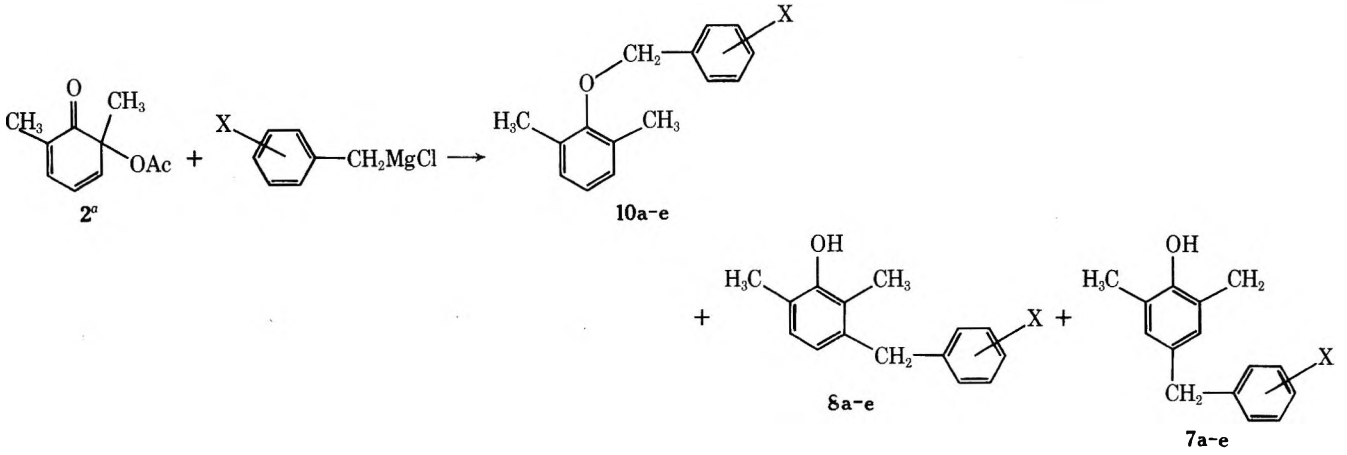


9b, X = p-CH$_3$
c, X = p-Cl
d, X = m-Cl

8c, X = p-Cl
d, X = m-Cl

Attempts to prepare the dichlorobenzylcyclohexadienone **9e** as a precursor to the corresponding phenol were fruitless, since the cyclohexadienone appeared to dimerize as quickly as it formed. Attempts to prepare phenol **8b** by rearrangement of **9b** also failed, since, as has previously been reported,[5a] rearrangement of **9b** gave a mixture containing a large amount of the para isomer **7b**. Instead, **8b** was prepared by the synthesis shown below. 3-Benzyl-2,6-dimethylphenol (**8a**) has

Table II. Relative Yields of Products from Reaction of 2 with Benzylmagnesium Chlorides

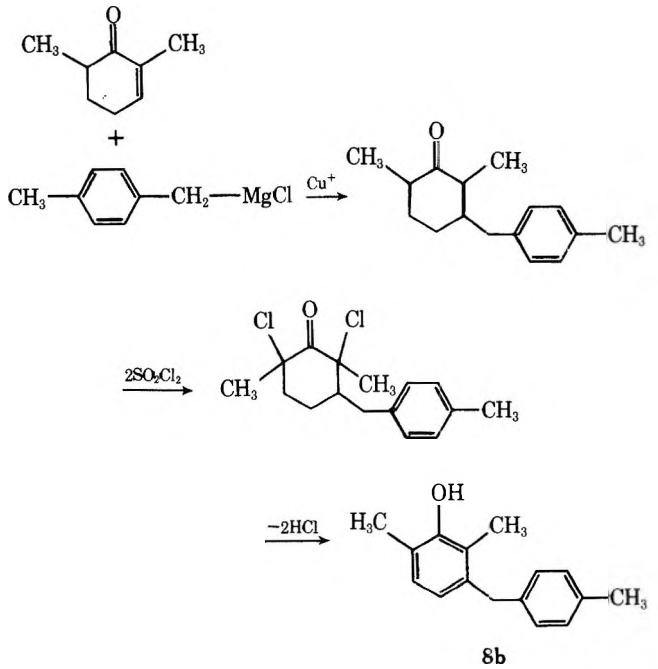


2[a] 10a-e 8a-e 7a-e

a, X = H
b, X = *p*-CH_3
c, X = *p*-Cl
d, X = *m*-Cl
e, X = *m,p*-di-Cl

X	10	8	7	2,6-Dimethylphenol	% 10/% 8	% 10/% 7
p-CH_3	100	3.5 ± 0.7	3.1 ± 0.6	11 ± 4	29	32
H	100	4.0 ± 1.0	4.0 ± 0.8	6 ± 1	20	25
p-Cl	100	30.4 ± 3.0	3.0 ± 0.4	8 ± 5	3.3	33
m-Cl	100	50.5 ± 1.5	2.4 ± 0.7	12 ± 5	2.0	42
m,p-di-Cl	100	84.9 ± 11	5.0 ± 0.9	7 ± 2	1.2	20

[a] Registry no.: 2, 7218-21-5.



8b

been prepared in a similar manner by Mr. M. McLaughlin.[4]

Mixtures of the meta and para isomers of each of the substituted phenols 7 and 8 (with the exception of the 3,4-dichloro derivatives) had NMR and IR spectra and GLC retention times which were identical with those of the mixtures obtained from the reactions of Grignard reagents with **2**. For each pair of isomers, the peaks for the diarylmethylene groups of the meta isomers appeared ca. 0.15 ppm downfield from those for the para isomers. This enabled us to directly analyze the composition of the phenolic mixtures from the Grignard reactions by comparison of the areas of these peaks.

The relative yields of products obtained from reaction of **2** with substituted benzylmagnesium chlorides are shown in Table II.

Discussion

The yields of benzyl aryl ethers from reactions of *o*-quinol acetates with benzylmagnesium chlorides increase as the electron-donating abilities of the substituents on the Grignard reagents increase. When C-4 of the quinol acetate is unsubstituted, the yields of *p*-benzylphenols similarly increase with electron-donating powers of the substituents.

For reactions with quinol acetate **2**, a Hammett plot of the ratio of yields of ethers to those of *m*-benzylphenols vs. the σ values for the Grignard substituents fits a relatively straight line, with a ρ value of −2.0 (s.d. = 0.052) (Figure 2). However, the line which best fits these points shows a moderate curvature, with the more electron-donating substituents giving higher yields of ethers than would be expected on the basis of the straight line plot through the other points.

For reaction with quinol acetate **1**, a similar Hammett plot gives a curve which becomes asymptotic to the vertical axis, since no *m*-benzylphenols are obtained when the substituents are H or *p*-CH_3 (Figure 1). For Grignards with electron-donating substituents, the ratio of ethers to *m*-benzylphenols is higher for reaction with **1** than for reaction with **2**. For the Grignard reagent with the most electron-withdrawing substituent, however, the relative yield of ether is lower for reaction with **1** than with **2**.

These results are consistent with the free-radical mechanism for formation of ethers proposed in the preceding paper,[2] in which the initial step is electron transfer between the Grignard reagent and the quinol acetate (eq 1). The greater curvature of the Hammett plot for reaction with **1** can be attributed to the conflicting steric and electronic effects of the methyl group at C-4 in **1**. For Grignard reagents with electron-donating substituents, which can readily donate electrons even to **1**, the principal effect of the methyl at C-4 of the quinol acetate is to sterically inhibit formation of *m*-benzylphenols by attack at C-3. For Grignards which bear strong electron-withdrawing substituents, the electronic effect of the methyl group, which inhibits electron donation to **1**, is more important, and yields of *m*-benzylphenols are high from reaction

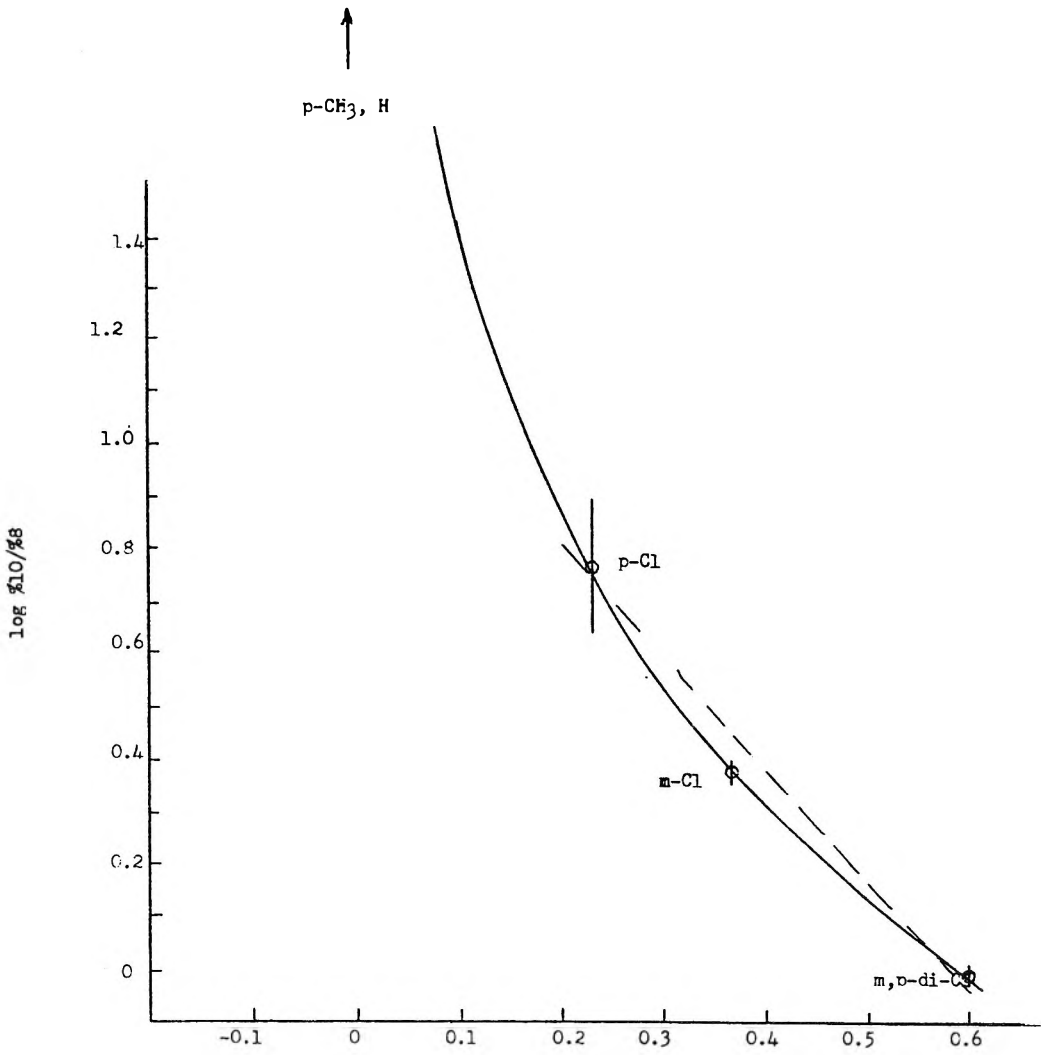
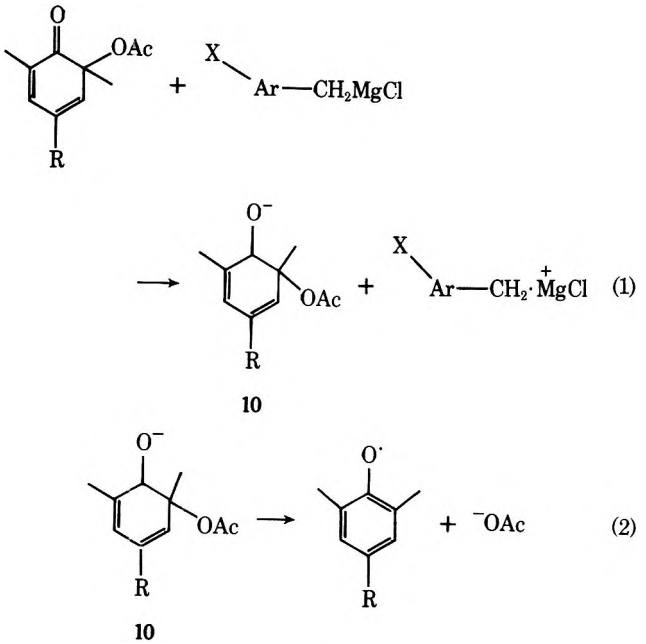


Figure 1. Plot of ratios of yields of benzyl aryl ethers to yields of *m*-benzylphenols from reaction of 1 vs. substituent σ constants. Dashed line is best straight line for Grignards with chlorine substituents.



with **1** in spite of steric interference with their formation. (An additional effect of the *p*-CH_3 group may be to increase the rate of decomposition of ketyl **10** (eq 2), and thus prevent either reverse electron transfer to the benzyl radical or formation of *m*-benzylphenols by reaction between the ketyl and a benzyl radical. Since this effect would increase yields of ethers from all Grignards, however, it cannot be the only electronic effect of the methyl at C-4.)

Of particular interest is the relative constancy of the ratio of yields of ethers to those of *p*-benzylphenols from reaction with **2**. Whereas the ratio of ethers to *m*-benzylphenols varies by a factor of approximately 25 when the substituents on the Grignard ring are changed from *p*-CH_3 to *m,p*-di-Cl, the ratio of ethers to *p*-benzylphenols varies by less than a factor of 2—barely above experimental error—and shows no consistent relationship to the electronic properties of the substituents. (The experimental error in estimating yields of *p*-benzylphenols is relatively high, owing to the fact that they are obtained in low percentages in all reactions.) The fact that formation of *p*-benzylphenols and of ethers show a similar dependence on effects of substituents supports the assumption that the mechanisms for these reactions proceed through the same initial steps, rather than by completely different mechanisms. The hypothesis that ethers and *p*-benzylphenols are both formed by combination of phenoxy and benzyl radicals (eq 3), which was proposed in the preceding paper, is consistent with all our observations.

In contrast to the other products, the yields of the reduction products, mesitol and 2,6-dimethylphenol, from these reactions show no obvious trends with changes in substituents. The yields are quite variable, even for different preparations of the same Grignard reagents. At present, the mechanisms for these reactions remain obscure.

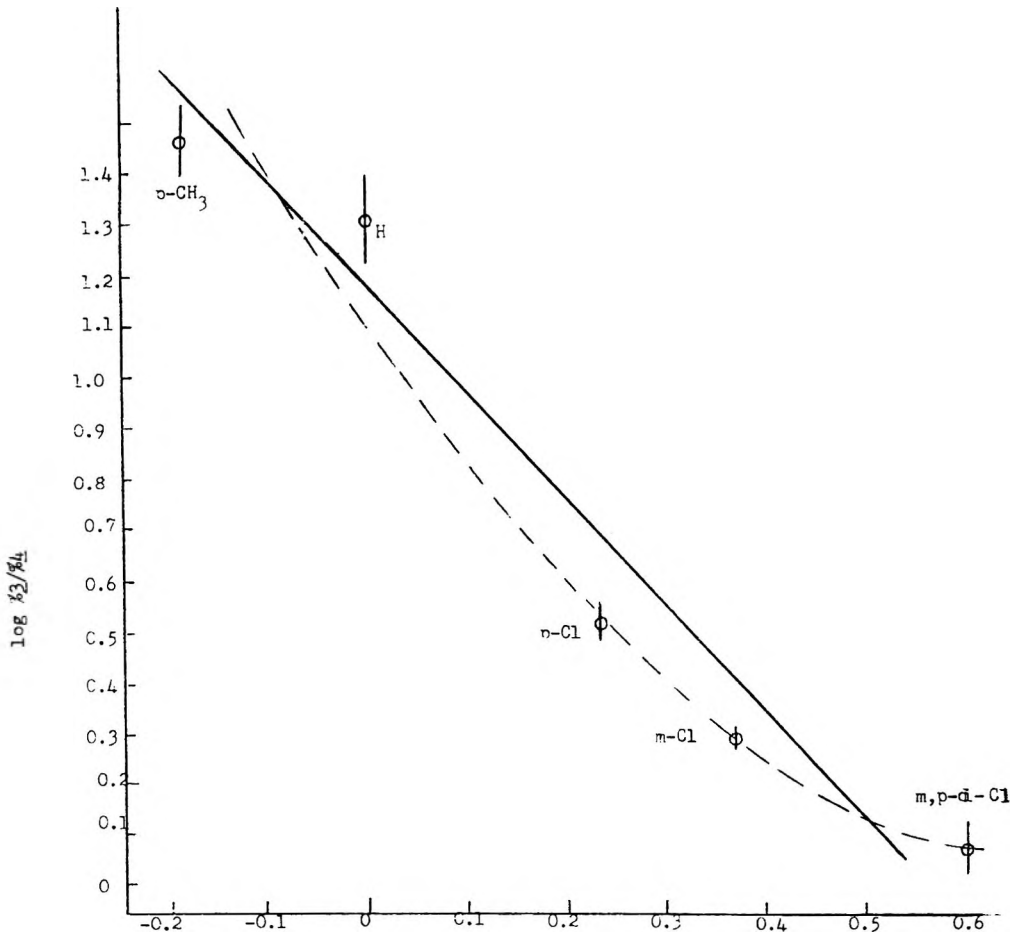
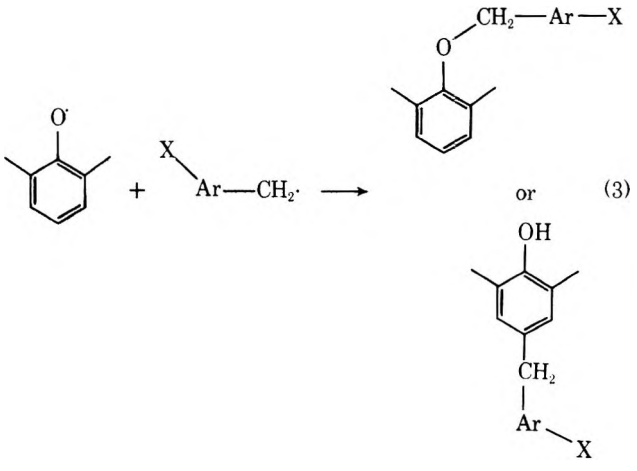


Figure 2. Plot of ratios of yields of benzyl aryl ethers to yields of *m*-benzylphenols from reaction of **2** vs. substituent σ constants. Dashed curve is approximate best fit to all points.



(3)

Experimental Section

General. NMR spectra were taken on Varian A-60 or Perkin-Elmer R12A spectrometers in deuteriochloroform solution, using Me_4Si as an internal standard. IR spectra were taken on Beckman IR-10 or Perkin-Elmer 273B spectrometers.

GLC analyses were carried out on Varian Aerograph Model 202c or Model 2400 instruments, using one of the following columns: column A, 6 ft × 0.25 in., 5% SE-30 on Chromosorb W; column B, 12 ft × 0.125 in., 3% XE-60 on Chromosorb W. Preparative separations were carried out using column C, 5 ft × 0.375 in., 5% SE-30 on Chromosorb W.

Melting points were taken on a Mel-Temp apparatus and are uncorrected.

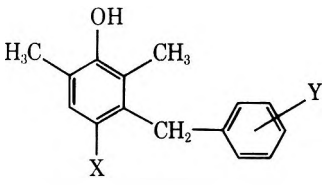
Grignard Reagents. Grignard reagent solutions (ca. 1 M) were prepared by adding a small amount of a benzyl chloride to 1.2 g (0.050 mol) of magnesium in 35 ml of anhydrous ether. When the reaction had started, the remainder of 0.050 mol of the benzyl chloride in 15 ml of ether was added to the reaction mixture as rapidly as possible. The mixture was stirred continuously under a nitrogen atmosphere until reaction was apparently complete, and then refluxed for an additional 15 min. The reaction mixture was then filtered under nitrogen pressure through a sintered glass filter and used immediately.

The Grignard reagents were prepared from magnesium chips of >99.99% purity (grade m4N) obtained from the Ventron Corp. Anhydrous ether was obtained from the Fisher Scientific Co. and used without further purification.

Reaction of Benzylmagnesium Chlorides with 6-Acetoxy-2,4,6-trimethylcyclohexa-2,4-dien-1-one (1). A solution of quinol acetate **1** (0.40 g, 2.08 mmol) in 10 ml of anhydrous ether was added rapidly to 10 ml of 1 M Grignard reagent in ether. The mixture was stirred under a nitrogen atmosphere for 10 minutes, and then refluxed for an additional 10 minutes. A solution of ammonium chloride in water was added, the organic layer was separated, washed with water, and dried over magnesium sulfate, and the solvent was evaporated to give a yellow oil. The product was analyzed by GLC on column A. In preparative runs, the product was dissolved in benzene and extracted with Claisen alkali. The alkaline layer was acidified with dilute hydrochloric acid and extracted with methylene chloride. The organic layer was washed with water and dried over magnesium sulfate, and the solvent was evaporated to give a mixture of 2,4,6-trimethylphenol and (for benzyl groups with chlorine substituents) 3-benzyl-2,4,6-trimethylphenols. The products were isolated by preparative GLC on column C. The NMR spectra of the products are summarized in Table III.

The alkali-insoluble layer from Claisen alkali extraction of the Grignard reaction product was washed with water and dried over magnesium sulfate, and the solvent was evaporated. The various benzyl 2,4,6-trimethylphenyl ethers were isolated by preparative GLC on column C, and were identified by comparison of their spectra and GLC retention times with those of samples independently prepared

Table III. NMR Spectra of *m*-Benzylphenols[a]



Registry no.	X	Y	Chemical shifts, δ, ppm: $ArCH_3$(s)	$ArCH_2Ar$(s)	ArH	−OH (bs)
61259-70-9	CH_3	*p*-Cl	2.07, 2.11, 2.21	3.98	6.86 (s, 1 H) 6.97 (d, *J* = 9 Hz, 2 H) 7.18 (d, *J* = 9 Hz, 2 H)	4.50
61259-71-0	CH_3	*m*-Cl	2.10, 2.13, 2.23	4.00	6.87 (s, 1 H) 6.95–7.30 (m, 9 H)	4.52
61259-72-1	CH_3	*m,p*-di-Cl	2.12, 2.14, 2.26	4.01	6.90 (s, 1 H) 6.90 (dd, *J* = 8, 1 Hz, 1 H) 7.14 (d, *J* = 1 Hz, 1 H) 7.33 (d, *J* = 8 Hz, 1 H)	4.50
55563-88-7	H	*p*-CH_3	2.07, 2.14, 2.25	3.92	6.66 (d, *J* = 8 Hz, 1 H) 7.08 (s, 4–5 H)	4.50
61259-73-2	H	*p*-Cl	2.07, 2.21	3.93	6.66 (d, *J* = 8 Hz, 1 H) 6.85–7.40 (m, 5 H)	4.64
61259-74-3	H	*m*-Cl	2.08, 2.21	3.92	6.67 (d, *J* = 8 Hz, 1 H) 6.75–7.30 (m, 5 H)	4.65
61288-73-1	H	*m,p*-di-Cl	2.07, 2.21	3.92	6.66 (d, *J* = 8 Hz, 1 H) 7.22 (s, 1 H) 6.78–7.40 (m, 3 H)	4.61

[a] Satisfactory C, H analyses were reported for all compounds.

by Williamson syntheses, as described below.

Reaction of Benzylmagnesium Chlorides with 6-Acetoxy-2,6-dimethylcyclohexa-2,4-dien-1-one (2). A solution of quinol acetate **2** (0.40 g, 2.23 mmol) in 10 ml of anhydrous ether was added rapidly to 10 ml of 1 M Grignard reagent in ether. The mixture was stirred under nitrogen for 10 min and then refluxed for an additional 10 min. A solution of ammonium chloride in water was added, the organic layer was separated, washed with water, and dried over magnesium sulfate, and the solvent was evaporated to give a yellow oil. The product was analyzed by GLC on column A. It was then dissolved in benzene and extracted with Claisen alkali. The alkali-insoluble layer was washed with water and dried over magnesium sulfate, and the solvent was evaporated to give a yellow oil consisting principally of benzyl 2,6-dimethylphenyl ethers. The ethers were isolated by preparative GLC on column C, and identified by comparison with synthetic samples. The alkaline layer was acidified with dilute hydrochloric acid and extracted with methylene chloride. The organic layer was washed with water and dried over magnesium sulfate, and the solvent was evaporated to give a viscous oil. The combined mixture of phenols **7** and **8** was isolated by GLC on column C, and the ratio of *m*- to *p*-benzyl isomers was determined by the ratio of the two methylene peaks in the NMR spectra of the mixture. For phenols **7b** and **8b**, and **7c** and **8c**, the analyses were confirmed by GLC analysis on column B.

Synthesis of Benzyl 2,6-Dimethylphenyl and 2,4,6-Trimethylphenyl Ethers. Potassium *tert*-butoxide (1.0 g, 9.0 mmol) was added to a solution of 2,6-dimethylphenol or 2,4,6-trimethylphenol (9.0 mmol) in 20 ml of dimethyl sulfoxide. The mixture was stirred at room temperature for 10 min and 9.0 mmol of the substituted benzyl chloride was then added. After standing at room temperature for 1 h, the solution was poured into water and extracted with methylene chloride. The organic layer was washed four times with water and dried over magnesium sulfate, and the solvent was evaporated to give 8.0–9.0 mmol of almost pure ethers. Analytical samples were prepared by GLC on column C. The NMR spectra of the ethers are listed in Table IV.

3,4′,5-Trimethyl-4-methoxybenzophenone (5). Anhydrous aluminum chloride (8.0 g, 0.060 mol) was added to a solution of 2,6-dimethylanisole (6.8 g, 0.050 mol) and 4-methylbenzoyl chloride (7.0 g, 0.050 mol) in 20 ml of nitrobenzene. The mixture was stirred at room temperature for 14 h. Water was added cautiously, and then sufficient concentrated hydrochloric acid to dissolve the aluminum hydroxide was added. The mixture was extracted with methylene chloride and the organic layer was washed with dilute hydrochloric acid and then with water. The methylene chloride was evaporated, 300 ml of water was added, and the nitrobenzene was removed by steam distillation employing a Dean-Stark trap. The undistilled residue was extracted with methylene chloride and the organic layer was washed with sodium hydroxide solution and dried over magnesium sulfate. The solvent was evaporated to give 9.1 g (0.036 mol, 72%) of essentially pure **5b** as a yellow oil which crystallized on standing, mp 75–77 °C (from hexane).

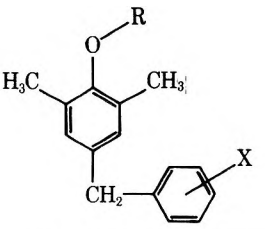
3,5-Dimethyl-4-methoxybenzophenone (**5a**), 3′-chloro-3,5-dimethyl-4-methoxybenzophenone (**5d**), 4′-chloro-3,5-dimethyl-4-methoxybenzophenone (**5c**), and 3′,4′-dichloro-3,5-dimethyl-4-methoxybenzophenone (**5e**) were prepared by the same procedure. Their NMR spectra and melting points are listed in Table V.

3,4′,5-Trimethyl-4-methoxydiphenylmethane (6b). 3,4′,5-Trimethyl-4-methoxybenzophenone (7.50 g, 0.0295 mol) was dissolved in 20 ml of anhydrous ether, and the solution was slowly added to a suspension of lithium aluminum hydride (2.5 g, 0.065 mol) in 20 ml of ether which was stirred by a magnetic stirrer under a nitrogen atmosphere. A mild reaction ensued. After 25 min the reaction was cooled in ice and anhydrous aluminum chloride powder (8.5 g, 0.062 mol) was added cautiously. The reaction mixture was then stirred and refluxed overnight, cooled to room temperature, and water added. Concentrated hydrochloric acid was added, the layers were separated, the organic layer was washed with water and dried over magnesium sulfate, and the solvent was evaporated to give 5.2 g of 3,4′,5-trimethyl-4-methoxydiphenylmethane (0.0212 mol, 72%) as a dark brown oil. Its IR spectrum showed no hydroxy or carbonyl peaks.

3,5-Dimethyl-4-methoxyphenylmethane (**6a**), 4-chloro-3,5-dimethyl-4-methoxydiphenylmethane (**6c**), 3′-chloro-3,5-dimethyl-4-methoxydiphenylmethane (**6d**), and 3′,4′-dichloro-3,5-dimethyl-4-methoxydiphenylmethane (**6e**) were prepared in the same way. Their spectra are listed in Table IV.

Preparation of 4-(4-Methylbenzyl)-3,5-dimethylphenol. 3,4′,5-Trimethyl-4-methoxydiphenylmethane (5.0 g, 0.021 mol) was dissolved in 50 ml of *N,N*-dimethylformamide containing a mixture of 8.0 g (0.071 mol) of potassium *tert*-butoxide and 7.7 g (0.070 mol) of thiophenol. The mixture was refluxed under nitrogen for 2 h, and 100 ml of 12 M hydrochloric acid solution was added. The resulting mixture was refluxed for 15 h, and then poured into 100 ml of water. Methylene chloride (50 ml) was added. The solution was extracted with methylene chloride (50 ml) and the organic layer washed three times with water and extracted with Claisen alkali. The alkaline extract was acidified with dilute hydrochloric acid and extracted with methylene chloride. The organic layer was washed with water and dried over magnesium sulfate, and the solvent was evaporated to leave 2.20 g (0.0098 mol, 46%) of 4-(4-methylbenzyl)-3,5-dimethylphenol

Table IV. NMR Spectra of *p*-Benzylphenols and Ethers[a]



Registry no.	R	X	Chemical shifts δ, ppm: $ArCH_3$ (s)	$ArCH_2$ Ar (s)	ArH	OR (s)	Mp, °C
41772-31-0	H	H	2.18	3.77	6.79 (s, 2 H) 7.06 (m, 5 H)	4.5	68–68.5
55563-86-5	H	*p*-CH_3	2.15 (6 H) 2.28 (3 H)	3.77	6.78 (s, 2 H) 7.06 (s, 4 H)	4.45	90.5–91.0
61259-75-4	H	*p*-Cl	2.18	3.77	6.79 (s, 2 H) 7.11 (d, *J* = 8 Hz, 2 H) 7.24 (d, *J* = 8 Hz, 2 H)	4.6	
61259-76-5	H	*m*-Cl	2.17	3.78	6.80 (s, 2 H) 7.0–7.4 (m, 4 H)	4.7	
61259-77-6	H	*m,p*-di-Cl	2.18	3.78	6.78 (s, 2 H) 7.05 (dd, *J* = 8, 2 Hz, 1 H) 7.27 (d, *J* = 2 Hz, 1 H) 7.33 (d, *J* = 8 Hz, 1 H)	4.6	83–85
61259-78-7	CH_3	H	2.20	3.78	6.78 (s, 2 H) 7.03 (s, 5 H)	3.61	
61259-79-8	CH_3	*p*-CH_3	2.18 (6 H) 2.23 (3 H)	3.75	6.79 (s, 2 H) 7.04 (s, 4 H)	3.61	
61259-80-1	CH_3	*p*-Cl	2.20	3.79	6.80 (s, 2 H) 7.10 (d, *J* = 9 Hz, 2 H) 7.23 (d, *J* = 9 Hz, 2 H)	3.63	
61259-81-2	CH_3	*m*-Cl	2.19	3.78	6.78 (s, 2 H) 6.95–7.35 (m, 4 H)	3.63	
61259-82-3	CH_3	*m,p*-di-Cl	2.20	3.78	6.78 (s, 2 H) 6.95–7.35 (m, 4 H)	3.65	

[a] Satisfactory C, H analyses were reported for all compounds.

as a dark brown oil which crystallized on standing in ice, mp 90.5–91.0 °C (from hexane).

Other 4-benzyl-3,5-dimethylphenols were synthesized in the same way. Their melting points and NMR spectra are listed in Table IV.

2,6-Dimethyl-3-(4-methylbenzyl)cyclohexanone. Cuprous iodide (1.0 g, 2.6 mmol) was added to a solution of 4-methylbenzylmagnesium chloride formed from 1.55 g (0.064 mol) of magnesium turnings (commercial Grignard grade) and 9.0 g of 4-methylbenzyl chloride (9.0 g, 0.064 mol) in 250 ml of ether. A solution of 2,6-dimethylcyclohex-2-en-1-one (8.0 g, 0.064 mol) in 50 ml of anhydrous ether was immediately added. The reaction mixture was stirred at room temperature for 15 h. Dilute hydrochloric acid was then added and the layers separated. The ether layer was washed with water and dried over magnesium sulfate, and the solvent was evaporated to give 15.3 g of yellow oil, whose IR spectrum showed strong hydroxy and carbonyl peaks. The product was chromatographed on 600 g of activity II neutral alumina. Elution with 20% methylene chloride in pentane gave 1.70 g (7.4 mmol, 11.5%) of 2,6-dimethyl-3-(4-methylbenzyl)-cyclohexanone as a colorless oil. Its IR spectrum showed a carbonyl peak at 1740 cm^{-1}. Its NMR spectrum showed peaks at δ 1.05 (d, *J* = 6 Hz, 3 H), 1.20 (d, *J* = 6 Hz, 3 H) (methyl groups at C-2 and C-6), 2.32 (s, 3 H), 7.07 (s, 4 H), and 3.00 (dd, *J* = 14, 3 Hz, 1 H, one proton on benzylic methylene group).

2,6-Dimethyl-3-(4-methylbenzyl)phenol. Sulfuryl chloride (1.20 g, 8.9 mmol) was added to a solution of 2,6-dimethyl-3-(4-methylbenzyl)cyclohexanone (1.0 g, 4.38 mmol) in 15 ml of carbon tetrachloride, and the mixture was stirred at room temperature for 16 h. Water was added and the organic layer was washed with sodium bicarbonate solution and dried over magnesium sulfate. The solvent was evaporated to give 1.30 g of yellow fluid whose NMR spectrum showed a methyl singlet (6 H) at δ 1.28 replacing the doublets at δ 1.05/1.20 in the starting ketone. The crude product was dissolved in 15 ml of *N,N*-dimethylformamide. Lithium chloride (150 mg, 3.5 mmol) was added, and nitrogen bubbled through the mixture for 10 min. The mixture was then heated at 135 °C under a nitrogen atmosphere for 1.5 h. It was cooled slightly, and a solution of 5% sulfuric acid was added. The mixture was allowed to stand at room temperature for 18 h, after which methylene chloride was added. The organic layer was washed with water and then with dilute sodium bicarbonate solution and dried over magnesium sulfate, and the solvent was evaporated to give 0.38 g (1.68 mmol, 19%) of 2,6-dimethyl-3-(4-methylbenzyl)phenol as a dark brown oil which crystallized on standing, mp 52–53 °C (from pentane).

6-(4-Chlorobenzyl)-2,6-dimethylcyclohexa-2,4-dien-1-one (9c). *n*-Butyllithium in hexane (48 ml, 0.1 mol) was added to a solution of 2,6-dimethylphenol (12.2 g, 0.1 mol) in 200 ml of benzene. 4-Chlorobenzyl chloride (16.1 g, 0.1 mol) was added and the mixture was refluxed for 24 h. The reaction mixture was cooled, washed with water, and extracted with Claisen alkali. The organic fraction was washed with water and dried over magnesium sulfate, and the solvent was evaporated to give 12.0 g of yellow oil, which was immediately chromatographed on 400 g of neutral alumina (activity III). Elution with 20% methylene chloride in pentane gave 3.0 g of partially purified product, which was rechromatographed on 100 g of alumina. Elution with 10% methylene chloride in pentane gave 0.80 g (3.3 mmol, 3%) of the desired cyclohexadienone as a yellow oil. Its IR spectrum showed an intense carbonyl peak at 1660 cm^{-1}. Its NMR spectrum showed peaks at δ 1.10 (s, 3 H), 1.76 (d, *J* = 1 Hz), 2.65 (d, *J* = 13 Hz, 1 H), 3.00 (d, *J* = 13 Hz, 1 H), 5.8–6.7 (m, 3H), 7.0 (d, *J* = 8 Hz, 2 H), 7.09 (d, *J* = 8 Hz, 2 H).

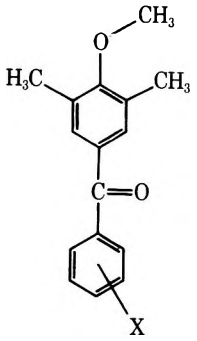
Anal. Calcd for $C_{15}H_{15}ClO$: C, 73.0; H, 6.1. Found: C, 73.0; H, 6.3.

6-(3-Chlorobenzyl-2,6-dimethylcyclohexa-2,4-dien-1-one (9d) was prepared in 5% yield using the same procedure. Its NMR spectrum was essentially identical with that above, except that the aromatic protons appeared as a multiplet.

Anal. Calcd for $C_{15}H_{15}ClO$: C, 73.0; H, 6.1. Found: C, 73.2; H, 6.3.

3-(4-Chlorobenzyl)-2,6-dimethylphenol. One drop of concentrated sulfuric acid was added to a solution of dienone 9c (0.40 g) in 5 ml of glacial acetic acid. The solution was kept at room temperature for 0.5 h, and then water was added. The mixture was extracted with methylene chloride, and the organic layer washed with sodium bicarbonate solution and dried over methylene chloride. The solvent

Table V. NMR Spectra of 4-Methoxybenzophenones[a]



Registry no.	X	$ArCH_3$ (s)	OCH_3	ArH	Mp, °C
14753-87-8	H	2.29	3.75	7.3–7.9 (m, 7 H)	
61259-83-4	*p*-CH_3	2.30 (6 H) 2.41 (3 H)	3.75	7.48 (s, 2 H) 7.30 (d, J = 8 Hz, 2 H) 7.70 (d, J = 8 Hz, 2 H)	75–77 (hexane)
61259-84-5	*p*-Cl	2.30	3.75	7.45 (s, 2 H) 7.46 (d, J = 9 Hz, 2 H) 7.68 (d, J = 9 Hz, 2 H)	93.5–94.5 (hexane)
61259-85-6	*m*-Cl	2.30	3.74	7.46 (s, H) 7.4–7.7 (m, 4 H)	
61259-86-7	*m,p*-di-Cl	2.30	3.76	7.45 (s, 2 H) 7.57 (d, J = 1 Hz, 2 H) 7.86 (d, J = 1 Hz, 1 H)	101.5–102.5 (hexane)

[a] Satisfactory C, H analyses were reported for all compounds.

was evaporated leaving 0.40 g of dark brown oil. GLC analysis on column A showed the presence of a single major component, which was isolated as a pale yellow oil by preparative GLC on column C. Its NMR spectrum showed peaks at δ 2.02 (s, 3 H), 2.18 (s, 3 H), 3.91 (s, 2 H), 4.4 (bs, 1 H) 6.58 (d, J = 8 Hz, 1 H), 6.81 (d, J = 8 Hz, 1 H), 7.01 (d, J = 8 Hz, 2 H), 7.11 (d, J = 8 Hz, 2 H). Small peaks at δ 2.16 and 3.78 showed the presence of some 4-(4-chlorobenzyl)-2,6-dimethylphenol.

3-(3-Chlorobenzyl)-2,6-dimethylphenol. Concentrated sulfuric acid (1 drop) was added to a solution of dienone **9d** (0.30 g) in 5 ml of glacial acetic acid. After 0.5 h, water was added and the mixture was extracted with methylene chloride. The organic layer was washed with sodium bicarbonate solution and dried over magnesium sulfate, and the solvent was evaporated to give 0.26 g of phenol **8d** as a dark brown oil. An analytical sample of the product was isolated as an oil by preparative GLC on column C. Its NMR spectrum showed peaks at δ 2.04 (s, 3 H) 2.19 (s, 3 H), 3.93 (s, 2 H), 4.54 (bs, 1 H), 6.59 (d, J = 8 Hz, 1 H), 6.81 (d, J = 8 Hz, 1 H), 7.1 (m, 4 H).

Acknowledgment. We thank the Research Corporation for a Cottrell Grant in partial support of this work.

Registry No.—9c, 61259-87-8; **9d,** 61259-88-9; 2,6-dimethylanisole, 1004-66-6; 4-methylbenzoyl chloride, 874-60-2; 2,6-dimethylcyclohex-2-en-1-one, 4079-59-5; 2,6-dimethyl-3-(4-methylbenzyl)cyclohexanone, 61259-89-0; 4-chlorobenzyl chloride, 104-83-6; 2,6-dimethylphenol, 576-26-1; 3-chlorobenzyl chloride, 620-20-2.

References and Notes

(1) Reactions of Cyclohexadienones. 38. For part 37, see ref 2.
(2) B. Miller, *J. Org. Chem.*, preceding paper in this issue.
(3) Part of this work was published as a preliminary communication: B. Miller, *J. Chem. Soc., Chem. Commun.*, 750 (1974).
(4) M. McLaughlin, to be published.
(5) Acid-catalyzed [1,3]benzyl migrations in cyclohexadienones have been reported: (a) B. Miller, *J. Am. Chem. Soc.*, **96,** 7155 (1974); (b) B. Miller and M. R. Saidi, *ibid.*, **98,** 2227 (1976).

Solvent Effects in the Benzylation of Aniline

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Received October 5, 1976

Second-order rate constants for the reaction of benzyl chloride with aniline were measured in various solvents: methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2,2-methylpropanol, benzyl alcohol, ethylene glycol, water, *N*-methylformamide, dimethyl sulfoxide, and some mixtures of alcohols with acetonitrile. The kinetic results depend on the dielectric constant and on the electrophilic parameter E_T of the reaction medium. The protic solvent acts also a reaction catalyst, by favoring the displacement of the chloride ion by hydrogen bonding. The reaction is third order overall depending on the concentrations of the substrate, of the nucleophile, and of the protic solvent (electrophile), in agreement with the "push–pull" termolecular mechanism.

Solvent effects on the rate of a bimolecular nucleophilic substitution cannot easily be predicted on the basis of the electrostatic properties of the solvent, considered as a continuum dielectric. The solvent, in fact, can exert many kinds of specific interactions on the reagent and on the transition state.[1] However, if these effects are well understood, the study of the solvent effects is a useful diagnostic tool to elucidate the reaction mechanism.

Table I. Rate Constants and Activation Parameters for the Reactions of Benzyl Chloride with Aniline in Various Solvents

Registry no.	Solvent	ϵ[a]	n[a]	E_T[a]	$10^5 k_2$, L mol^{-1} s^{-1} 30 °C	40 °C	50 °C	60 °C	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, cal mol^{-1} K^{-1}
67-56-1	1 Methanol	32.6	1.329	55.5	5.15	11.4	23.9		14.3	−31.2
64-17-5	2 Ethanol[b]	24.3	1.361	51.9		6.55	14.2	26.7	14.0	−33.0
71-23-8	3 1-Propanol	20.1	1.385	50.7			13.4			
67-63-0	4 2-Propanol	18.3	1.377	48.6		6.36	10.8	19.3	11.2	−42.2
71-36-3	5 1-Butanol	17.1	1.399	50.2			13.0			
75-65-0	6 2-Methyl-2-propanol	12.2	1.384	43.9			6.07			
100-51-6	7 Benzyl alcohol	13.1	1.540	50.8			16.4			
107-21-1	8 Ethylene glycol	37.7	1.432	56.3			141			
7732-18-5	9 Water	78.5	1.333	63.1			870			
123-39-7	10 *N*-Methylformamide	182.4	1.431	54.1			130			
67-68-5	11 Dimethyl sulfoxide	48.9	1.478	45.0			17.8			
75-05-8	12 Acetonitrile[c]	37.5	1.344	46.0	1.37	2.72	4.04	5.59	8.7	−52.0

[a] References 9, 10. [b] Reference 5b. [c] Reference 5a.

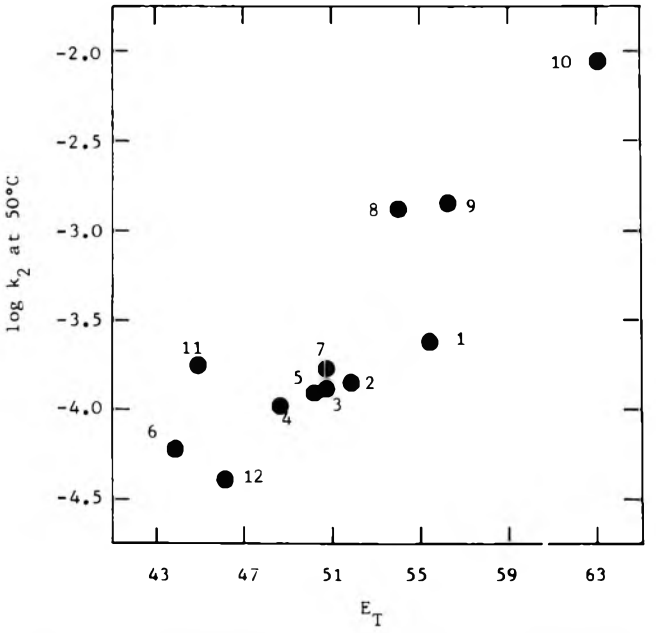


Figure 1. Correlation between log k_2 and Dimroth–Reichardt parameter, E_T, for the reaction of benzyl chloride with aniline at 50 °C in the solvents 1–12, as in Table I.

A classic example of solvent effect is the reaction of alkyl halides with tertiary amines (Menschutkin reaction),[2] where the importance of electrostatic and nonelectrostatic (polarizability, hydrogen bonding, etc.) effects on the reagents and the transition state solvation has been recently pointed out.[3]

The reaction of alkyl halides with primary and secondary amines has been extensively studied kinetically,[4,5] while the available data on the solvent effect, for the reaction of aliphatic amines with alkyl iodides,[6] cannot be generalized.

The difference between the reactions with primary or secondary amines and that of tertiary amines, apart from the nucleophiles' intrinsic reactivity, might seem negligible as both reactions go from neutral reagents to a transition state of similar structure:

$$RCH_2X + R_3'N \rightarrow RCH_2N^+R_3'\,X^- \quad (1)$$

$$RCH_2X + R'NH_2 \rightarrow RCH_2N^+H_2R'\,X^- \rightarrow RCH_2NHR' + HX \quad (2)$$

However, differences between these reactions were observed in the solvent effects and in the reaction mechanism.

In reaction 1, in fact, the rate in dipolar aprotic solvents is higher than in the protic ones,[3] while the opposite trend is observed for reaction 2.[4,5]

Moreover, the reaction of benzyl chloride with aniline in aprotic solvents (acetonitrile and benzene) follows third-order kinetics, first order with respect to the substrate and second order with respect to the nucleophile.[5a,7] In protic solvents, instead, the reaction is second order, first order with respect to each reactant.[4,5b] Then, the reaction seems to proceed through a different mechanism, depending on the protic or the aprotic solvent.

We are interested in the study of the solvent effects on the rate of nucleophilic reactions, by the empirical multiple correlations approach;[8] we now report kinetic data on the reaction of benzyl chloride with aniline in various solvents and solvent mixtures, to determine the empirical solvent parameters responsible for the observed reactivity and to obtain information on the reaction mechanism.

Results and Discussion

The reaction of benzyl chloride with aniline in seven aliphatic alcohols, water, ethylene glycol, *N*-methylformamide, and dimethyl sulfoxide yields *N*-benzylaniline quantitatively. The solvolysis reactions are always negligible with respect to the nucleophilic substitution. The rate was followed by titration of anilinium chloride formed in the reaction.

The reactions, carried out in a large excess of aniline, follow a pseudo-first-order kinetics to at least 65% completion. k_{obsd} values are linearly correlated with the aniline concentration, indicating that the reaction is second order overall, first order with respect to each reagent, according to the simple rate law

$$k_{obsd} = k_2[C_6H_5NH_2] \quad (3)$$

Second-order rate constants were calculated from the slope of the plot of k_{obsd} vs. aniline concentration, obtained from four to six kinetic runs. Table I reports k_2 values in various solvents, together with the corresponding polarity parameters (ϵ, n, E_T).

Dielectric constants, refraction indexes, and some of their functions do not correlate log k_2 values in the solvents 1–11. A poor correlation is found with E_T parameters (Figure 1).

The best statistical two parameters correlation is given by eq 4:

$$\log k_2 = 0.0865E_T + 10.87\,\frac{\epsilon - 1}{2\epsilon + 1} - 13.125 \quad (4)$$

The observed reactivity depends both on $\epsilon - 1/2\epsilon + 1$

Table II. Second-Order Rate Constants (10^4 k_2, L mol^{-1} s^{-1}) at 50 °C for the Reaction of Benzyl Chloride with Aniline in Some ROH–CH_3CN Mixtures

ROH,	CH_3OH					C_2H_5OH					2-C_3H_7OH				
vol %	X^a	Mol L^{-1}	$E_T{}^b$	k_2	$\Delta \log k_2$	X^a	Mol L^{-1}	$E_T{}^b$	k_2	$\Delta \log k_2$	X^a	Mol L^{-1}	$E_T{}^b$	k_2	$\Delta \log k_2$
100	1.0	24.7	55.5	2.39	0.00	1.0	17.2	51.9	1.42	−0.05	1.0	13.1	48.6	1.08	0.00
90	0.92	22.2	54.7	1.96	−0.05	0.89	15.5	51.3	1.19	−0.09	0.86	11.8	48.2	0.894	−0.06
80	0.84	19.8	54.0	1.54	−0.12	0.78	13.8	50.6	0.950	−0.15	0.73	10.4	47.9	0.803	−0.09
70	0.75	17.3	53.1	1.15	−0.20	0.68	12.0	50.0	0.729	−0.24	0.62	9.1	47.6	0.678	−0.15

[a] Molar fraction of ROH in the ROH–CH_3CN mixture. [b] The E_T values for the solvent mixtures were calculated by the equation. $E_{T(mixt)} = E_{T(S_1)}X_{(S_1)} + E_{T(S_2)}X_{(S_2)}$; where $E_{T(S_1)}$ and $E_{T(S_2)}$ are the E_T values for the pure solvents (S_1 and S_2) and $X_{(S_1)}$ and $X_{(S_2)}$ are the respective molar fractions in the mixture.

(Kirkwood's function) and E_T (Dimroth–Reichardt parameter); in fact the higher rates were measured in water, ethylene glycol, and *N*-methylformamide, solvents which exhibit high ϵ and E_T values; in dimethyl sulfoxide the balance between the high ϵ and the low E_T gives a rate constant similar to that of 1-butanol (low ϵ, high E_T).

For the reactions in aliphatic alcohols (solvents 1–7) a satisfactory correlation with E_T is found (eq 5), the effect of the dielectric constant being negligible:

$$\log k_2 = 0.0512E_T - 6.458 \quad (5)$$

E_T measures the ability of the solvent to solvate specifically negative charges;[9,10] the positive coefficient indicates an electrophilic stabilization of the transition state with respect to the initial state, where no negative charge is present. The protic solvent, then, favors the chloride ion displacement probably through a determining solvation via hydrogen bonding.

The reactivity sequence in the various solvents (protic > dipolar aprotic) is opposite with respect to that observed for the Menschuntkin reaction with tertiary amines.[3] In the latter case, owing to the formation of a stable addition product (eq 1), the solvation of the reagents should be important. In the reaction with primary amines, where the addition step is followed by elimination of the chloride ion (eq 2), hydrogen bonding between the protic solvent and the leaving group (Cl^-) probably overcomes the reagents solvation.

The reaction in dimethyl sulfoxide is not third order as in the other aprotic solvents.[5a,7] To interpret this behavior a general consideration can be given. The catalytic activity of dimethyl sulfoxide in nucleophilic substitutions, owing to the polarity and to direct chemical effects, is in fact well known;[11] moreover, being a base of medium strength[12] and an hydrogen bonding acceptor,[13] it can well solvate structures with extended charges as the transition states.[14,15]

In order to verify if the solvent acts only as a solvation medium or also as a catalyst, kinetics in alcohol mixtures with acetonitrile were carried out. The results are reported in Table II.

If the hypothesis is correct, changes in k_2 at various solvent compositions should depend not only on the medium polarity, but also on the alcohol concentration.

k_2 values can be "cleaned" for the medium effect, by subtracting log k_2 values calculated by eq 5 from the observed k_2. The differences, $\Delta \log k_2$ (Table II), are linearly correlated with log [ROH] (Figure 2). The slope is very close to 1, indicating a first-order dependence on the alcohol concentration. The rate law is then

$$k_{obsd} = k_3[C_6H_5NH_2][ROH] \quad (6)$$

These results indicate that the protic solvent favors the stabilization of the transition state through the same catalytic

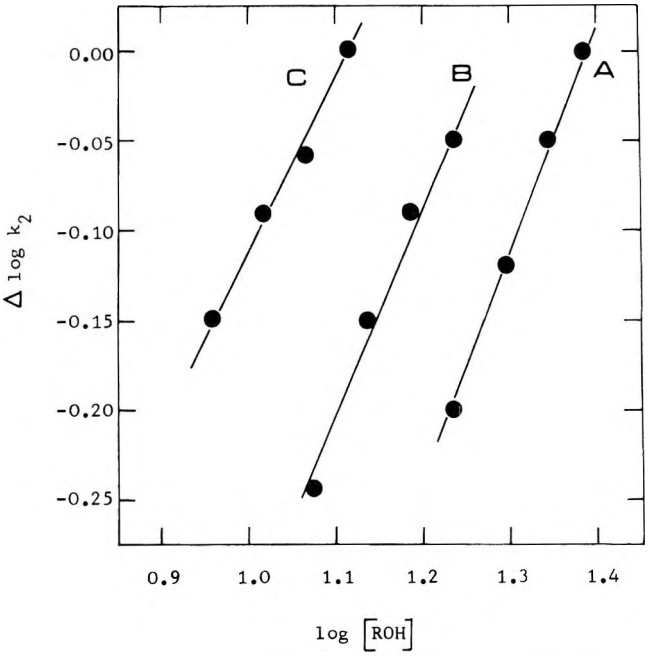


Figure 2. Reaction orders with respect to ROH for the reactions of benzyl chloride with aniline in (A) CH_3OH–CH_3CN; (B) C_2H_5OH–CH_3CN; (C) 2-C_3H_7OH–CH_3CN.

effect which in aprotic solvents was exerted by the second aniline molecule.[5a]

The data are in agreement with the termolecular "push–pull" mechanism proposed by Swain for nucleophilic substitutions[16] and provide a unitary explanation for the reaction mechanism in protic and aprotic solvents, notwithstanding the apparent difference in the reaction order (eq 7).

$$C_6H_5NH_2\cdots CH_2(C_6H_5)\cdots Cl\cdots HOR \quad (7)$$

nucleophile substrate electrophile

In the mixture ROH–CH_3CN, in the concentration range 100–70% ROH, used to calculate the order with respect to ROH, the reaction order with respect to aniline is 1. The order with respect to aniline was measured in the concentration range 0–100% CH_3OH–CH_3CN. Table III lists the order with respect to aniline, the rate constants, and the activation parameters. This order, calculated by the initial rates method,[17] is 1 up to 40% CH_3OH; on increasing the CH_3CN percentage, the apparent order increases, and is 2 in 100% CH_3CN. The catalysis of nucleophile (in the concentration range 0.25–1.0 mol L^{-1}) becomes effective below 5 mol L^{-1} of methanol.

This trend is represented in eq 8, where methanol- and aniline-catalyzed reactions are shown:

Table III. Orders with Respect to Aniline (n), Rate Constants at 30 °C, and Activation Parameters for the Reactions of Benzyl Chloride with Aniline [a] in CH_3OH–CH_3CN Mixtures

CH_3OH			$10^5 k_2$,	$\Delta H^{\ddagger}$,	$\Delta S^{\ddagger}$,
Vol %	Mol L^{-1}	n	L mol^{-1} s^{-1}	kcal mol^{-1}	cal mol^{-1} K^{-1}
100	24.7	1.0	5.15	14.3	−31.2
90	22.2	1.0	4.68	13.4	−34.4
80	19.8	1.0	4.25	12.0	−39.2
70	17.3	1.0	3.73	10.4	−44.7
60	14.8	1.0	2.93		
40	9.89	1.0	1.86		
20	4.94	1.2			
10	2.47	1.4			
5	1.24	1.6			
0	0.00	2.0	1.37 [b]	8.7	−52.0

[a] Reagent concentrations: benzyl chloride, 0.02 mol L^{-1}; aniline, 0.25–1.0 mol L^{-1}. [b] k_3 value in acetonitrile (L^2 mol^{-2} s^{-1}): ref 5a.

$$C_6H_5CH_2Cl + C_6H_5NH_2 \underset{k'_3[C_6H_5NH_2]}{\overset{k_3[CH_3OH]}{\rightleftharpoons}} \text{products} \qquad (8)$$

Experimental support for the proposed catalytic mechanism is provided by the kinetic experiments in pure acetonitrile for the reaction of benzyl chloride with *o*-phenylendiamine (OPDA). In this nucleophile, in fact, both amino groups can react with the substrate exerting an intramolecular catalysis, and the predicted reaction order with respect to the nucleophile is 1. The geometry of the transition state (Figure 3) does not exclude this internal catalysis.

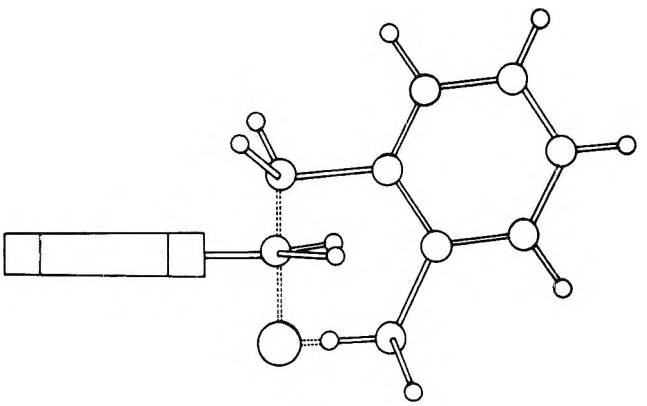


Figure 3. Geometry of the transition state for the reaction of benzyl chloride with *o*-phenylenediamine.

Experimental results confirmed the above hypothesis: the order with respect to OPDA, calculated by the initial rates method, is very close to 1.[18]

Experimental Section

Starting Materials. Benzyl chloride and aniline, commercially available samples, were distilled before use. The solvents (Carlo Erba RP) were used without further purification.

Kinetic Procedure. Rate measurements were done conductometrically by continuous titration of the acid produced with 0.1 M sodium hydroxide, following the procedure already described.[19] The reagent concentrations were 0.002 mol L^{-1} for the benzyl chloride and 0.1–1.0 mol L^{-1} for the aniline. Pseudo-first-order rate constants (k_{obsd}, s^{-1}) were obtained from the slope of conventional plots of log ($a - x$) vs. time, calculated by the least squares method. The estimated precisions were ±5% for k_{obsd}, ±0.5 kcal mol^{-1} for $\Delta H^{\ddagger}$, and ±3 cal mol^{-1} K^{-1} for $\Delta S^{\ddagger}$ values.

Reaction Product. Benzyl chloride (0.05 mol) and aniline (0.11 mol) in the same solvents used for the kinetic runs were allowed to react at 50 °C for 2–4 h, depending on the reaction rate. Solvent was evaporated, and then the residue treated with anhydrous ether; the solution was separated from the anilinium chloride, insoluble in ether, and evaporated. The residue was crystallised from light petroleum–*N*-benzylaniline, yield ca. 90%, mp 36–37 °C.[5,20]

Registry No.—Benzyl chloride, 100-44-7; aniline, 62-53-3.

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(18) Calculated on keeping constant the benzyl chloride concentration (0.02 mol L^{-1}) and varying the OPDA one (0.2–1.0 mol L^{-1}) [log V_0, log [OPDA]: −6.54, −0.644; −6.20, −0.312; −5.87, −0.099; −5.76, 0.00]. The slope of the linear plot is 1.2 (r = 0.996; s = 0.08).
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Correlation of Rates of Solvolysis for Tertiary Methyl with Tertiary Benzylic Derivatives

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Received April 28, 1976

A linear free energy relationship, $\log (k/k_0) = \rho\gamma^+$, with group constants, γ^+, was defined. The group constants are characteristic of the ability of a group to stabilize an adjacent cationic center. These groups can be either aromatic or nonaromatic. The γ^+ for methyl was determined to be 0.77. This group constant was found to be generally applicable in correlating rates of solvolysis of tertiary methyl derivatives with the analogous tertiary benzylic derivatives. Indeed, excellent $\rho\gamma^+$ plots were obtained. However, in cases with bulky substituents at the reaction center of arylcarbinyl systems, nonlinear $\rho\gamma^+$ plots were obtained. This was attributed to steric inhibition of resonance.

Among the most striking developments in the history of physical organic chemistry has been in methods for the quantitative correlation of rate and equilibrium constants.[1] Such approaches are based on the correlation of relative reactivities in terms of relative free energy changes. One of the best known and most useful of these is an equation proposed by Hammett which relates equilibrium and rate constants for the reactions of meta- and para-substituted benzene derivatives.[1,2] The Hammett relationship is based on the fact that as the substituent is varied, the logarithms of the rate constants for aromatic side-chain reactions are linearly related to one another. Thus, a rate or equilibrium constant of a compound in a reaction is related to the rate or equilibrium constant for the unsubstituted compound in terms of two parameters, ρ and σ. In the case of rate constants the relationship is shown in

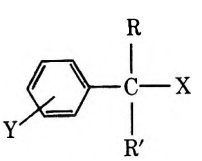
$$\log \frac{k}{k_0} = \rho\sigma \qquad (1)$$

where k_0 is the rate constant for the unsubstituted compound. Of these two parameters, the substituent constant σ is characteristic only of the substituent on an aryl group, while ρ is a reaction constant and is a function of the reaction being considered. Thus the reaction constant or ρ value is a measure of the sensitivity of a particular reaction to the substituents.

The Hammett equation fails when a full positive charge is developed on the aromatic side chain; an example is the solvolysis of benzyl derivatives. However, Brown and co-workers developed an analogous expression which overcame these shortcomings.[3] Thus in the Hammett–Brown relationship (eq 2), σ^+ represents the resonance and inductive contributions of a substituent on an aryl group in a reaction where a full positive charge is developed during the course of the reaction.

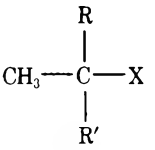
$$\log \frac{k}{k_0} = \rho\sigma^+ \qquad (2)$$

The use of σ^+ constants has been found to be generally applicable to a number of systems.[3c] In particular, Brown, Gassman, Tanida, and other workers have investigated the rates of solvolysis of various tertiary benzylic systems, **1**.



1

Solvolysis of the analogous tertiary methyl derivatives, **2**, has been reported; however, a method for correlating **2** with **1** is lacking.



2

Recently the correlation of rates of acetolysis of secondary tosylates with tertiary benzylic derivatives by a linear free energy relationship was reported.

This relationship uses group constants, γ^+, which are characteristic of the ability of an entire group (i.e., aryl, hydrogen, etc.) to stabilize an adjacent cationic center.[4] The σ^+ values only represent substituents on aryl groups. The γ^+ values for aryl groups will be the same as the σ^+ values for the substituent on that aryl group. This linear free energy relationship for correlating aromatic with nonaromatic derivatives is represented by eq 3.[4]

$$\log \frac{k}{k_0} = \rho\gamma^+ \qquad (3)$$

Since the difference between **1** and **2** is a methyl group vs. an aryl group, a group constant for a methyl group is needed to correlate tertiary methyl derivatives with their analogous tertiary benzylic derivatives.

Results

In attempting to correlate such a diverse assortment of data from the literature one might expect some deviation due to the facts that the rate constants were determined in several laboratories, uncertainties arise from extrapolating the rate constants for unreactive derivatives from high temperatures to 25 °C, and the corrections for differences in solvent may vary from system to system. However, these items can be minimized in the determination of γ^+ for methyl by plotting $-\log (k_{methyl}/k_{phenyl})$ vs. the ρ values (calculated from the aryl derivatives alone) for a series of chlorides and *p*-nitrobenzoates.[5] By definition the slope, of this line, $\gamma^+_{CH_3}$, should be made to go through the origin. The observed and calculated values of $-\log (k_{methyl}/k_{phenyl})$ and ρ values of just the aryl derivatives are listed in Table I. The slope of this data was analyzed by regression analysis and found to be 0.77 ± 0.03 with a confidence level of 99.5 (*F* distribution and *t* distribution).

Solvolysis of Chlorides. The solvolytic rates for 1-aryl-1-cyclopentyl, 1-aryl-1-cyclohexyl, 2-aryl-2-adamantyl, 1-aryl-1-cyclobutyl, and 7-aryl-7-norbornyl chlorides were correlated with 1-methyl-1-cyclopentyl, 1-methyl-1-cyclohexyl, 2-methyl-2-adamantyl, 1-methyl-1-cyclobutyl, and 7-methyl-7-norbornyl chlorides, respectively. The rates of solvolysis of the tertiary benzylic chlorides in 90% acetone were determined by Tanida and Tsushima.[6] The rates of

Table I. Correlation of Rates of Tertiary Methyl with Tertiary Benzylic Derivatives[a]

System	n[b]	ρ without CH_3	−log (k_{CH_3}/k_{phenyl}) Obsd	Calcd	Dif	SD[c]	ρ with CH_3[d]	Corr. coeff.[d]
			Chlorides in 90% Acetone					
Cyclopentyl	5	−4.10[e]	3.1421	3.1626	−0.0205	0.1386	−4.09	1.000
Cyclohexyl	4	−4.65[e]	2.6716	3.5869	−0.9153	0.1573	−4.03	0.987
2-Adamantyl	4	−4.83[e]	2.5607	3.7257	−1.1650	0.1633	−4.24	0.980
Cyclobutyl	5	−4.48[e]	3.4921	3.4557	0.0364	0.1514	−4.49	1.000
7-Norbornyl	4	−5.64[e]	4.5867	4.3505	0.2362	0.1906	−5.75	1.000
2-Propyl	10	−4.54[f]	2.9747	3.5020	−0.5273	0.1535	−4.43	0.998
			Chlorides in Ethanol					
2-Propyl	3	−4.90[g]	2.5800	3.7797	−1.1997	0.1656	−4.51	0.991
Cyclopentyl	3	−4.50[g]	3.5243	3.4712	0.0531	0.1521	−4.47	1.000
2-*exo*-Norbornyl	3	−4.30[g]	3.8327	3.3169	0.5158	0.1453	−4.36	0.998
			p-Nitrobenzoates in 70% Dioxane					
7-Norbornyl	6	−5.25[h]	4.6517	4.0497	0.6020	0.1775	−5.31	0.999
7-*anti*-Norbornenyl	4	−2.30[i]	0.9788	1.5736	−0.5948	0.0690	−2.17	0.985
			p-Nitrobenzoates in 80% Acetone					
Cyclopentyl	4	−3.82[j]	3.0904	2.9466	0.1438	0.1291	−3.88	0.998
Δ^3-Cyclopentenyl	4	−3.92[k]	3.7447	3.0238	0.7209	0.1325	−4.11	0.991
3-Nortricyclyl	4	−3.27[l]	2.3080	2.5224	−0.2144	0.1105	−3.24	0.999
2-*exo*-Norbornyl	4	−3.83[j]	2.8794	2.9543	−0.0749	0.1295	−3.84	1.000
2-*endo*-Norbornyl	4	−3.75[j]	3.6716	2.8926	0.7790	0.1268	−3.90	0.994
2-*exo*-Norbornenyl	3	−4.21[m]	3.4214	3.2475	0.1739	0.1423	−4.13	0.998
2-*endo*-Norbornenyl	3	−4.17[m]	4.0600	3.2166	0.8434	0.1409	−4.49	0.995
5-Methyl-2-*exo*-norbornenyl	2	−3.28[n]	2.2034	2.5301	−0.3267	0.1109	−3.05	0.999
5-Methyl-2-*endo*-norbornenyl	3	−4.19[n]	4.1518	3.2320	0.9198	0.1416	−4.52	0.995

[a] Rate constants at 25 °C. [b] Number of aryl derivatives correlated. [c] Standard deviation of calculated −log (k_{CH_3}/k_{phenyl}). [d] Computer calculated using least-squares program. [e] Reference 6. [f] Reference 3. [g] Reference 12. [h] Reference 4. [i] Reference 11. [j] Reference 16. [k] Reference 18. [l] Reference 21. [m] Reference 23. [n] Reference 25.

solvolysis of 1-methyl-1-cyclopentyl, -cyclohexyl, and -cyclobutyl chlorides were determined in 80% ethanol by Brown and Borkowski[7] and corrected to 90% acetone (5.21×10^{-6}, 4.18×10^{-8}, and 8.83×10^{-9} s^{-1}, respectively) by multiplying the rate constant in 80% ethanol by the factor 1.42×10^{-2}.[8] The rate of 2-methyl-2-adamantyl chloride[9] was similarly obtained (1.26×10^{-6} s^{-1}). The rate constant for 7-methyl-7-norbornyl chloride in 90% acetone (1.03×10^{-12} s^{-1}) was calculated by multiplying the rate of acetolysis for the corresponding tosylate[10] by the factor 3.17×10^{-7}.[11] The data give excellent correlations.

The rates of ethanolysis of 2-aryl-2-propyl, 1-aryl-1-cyclopentyl, and 2-aryl-2-*exo*-norbornyl chlorides[12] were correlated with their anologous methyl derivatives.[13] All three sets of data give excellent correlations with γ^+ constants. The reaction constants follow: 2-propyl, −4.51 (correlation coefficient 0.991); 1-cyclopentyl, −4.47 (1.000); and 2-*exo*-norbornyl, −4.36 (0.998).

p-Nitrobenzoates. The rates of solvolysis of 7-methyl-7-norbornyl[14] and 7-methyl-*anti*-7-norbornenyl *p*-nitrobenzoates[15] correlate with their 7-aryl analogues.[11] For the saturated series, ρ was −5.31 (correlation coefficient 0.999). For the 7-norbornenyl derivatives, a sharp break in the $\rho\gamma^+$ plot occurs at the *p*-anisyl derivative. For the five compounds (i.e., excluding the *p*-dimethylaminophenyl derivative), ρ was −2.17 (correlation coefficient 0.985).

Several tertiary cyclic, bicyclic, and tricyclic *p*-nitrobenzoates have been studied by Brown and co-workers. Thus rates of solvolysis in 80% acetone for the methyl and benzylic derivatives gave good to excellent correlations with γ^+. The ρ values are −3.88 (correlation coefficient 0.998) for cyclopentyl,[16,17] −4.11 (0.991) for Δ^3-cyclopentenyl,[18,19] −3.24 (0.999) for 3-nortricyclyl,[20,21] −3.84 (1.000) for 2-*exo*-norbornyl,[16,22] −3.90 (0.994) for 2-*endo*-norbornyl,[16,22] −4.13 (0.998) for 2-*exo*-norbornenyl,[23,24] −4.49 (0.995) for 2-*endo*-norbornenyl,[23,24] −3.05 (0.999) for 5-methyl-2-*exo*-norbornenyl,[16,25] and −4.52 (0.995) for 5-methyl-2-*endo*-norbornenyl.[16,25]

Thus the use of γ^+ for the methyl group appears generally applicable to a variety of systems.

Steric Hindrance to Resonance. When methyl groups in *tert*-butyl chloride or *p*-nitrobenzoates are replaced by *tert*-butyl and neopentyl groups, the reaction center of the molecule becomes more crowded and the rate of solvolysis increases. This phenomenon was explained in terms of rate-enhancing "B strain".[26] For example, Bartlett and co-workers reported that in the solvolysis of derivatives of highly hindered alcohols tri-*tert*-butylcarbinyl *p*-nitrobenzoate reacts 13 500 times faster than *tert*-butyl *p*-nitrobenzoate. Moreover, di-neopentyl-*tert*-butylcarbinyl *p*-nitrobenzoate reacts 68 000 times faster.[27]

Recently the replacement of a methyl group by a *tert*-butyl group at the tertiary position of tertiary *p*-nitrobenzoates has been reported to result in rate enchancement by factors up to 1 120 000.[20]

Bulky groups at the reaction center of arylcarbinyl systems would similarly increase the B strain; however, since resonance between the developing p orbital of the carbonium ion and the π orbitals of the aryl ring plays an important part in facilitating solvolysis of these systems, a rate-retarding tendency may result by twisting the developing p orbital of the cationic center out of conjugation with the aryl group. Indeed, steric inhibitation of resonance has been demonstrated in several investigations.[28]

Table II. Rate Constants for the Solvolysis of *p*-Nitrobenzoates in 70% Acetone at 25.0 °C[a]

Group	s^{-1}			
	2-Propyl	*tert*-Butylneopentyl-carbinyl	Dineopentyl-carbinyl	Di-*tert*-butyl-carbinyl
p-Anisyl	1.34×10^{-3}	1.71×10^{-4}	8.48×10^{-6}	3.70×10^{-8}
p-Tolyl	9.73×10^{-6}	1.08×10^{-6}	2.00×10^{-7}	8.37×10^{-9}
Phenyl	4.58×10^{-7}	8.32×10^{-8}	6.21×10^{-8}	4.80×10^{-9}
p-Chlorophenyl	9.52×10^{-8}	2.31×10^{-8}	4.56×10^{-9}	1.40×10^{-9}
p-Trifluoromethylphenyl	5.39×10^{-10}	7.25×10^{-10}	3.82×10^{-10}	2.77×10^{-10}
Methyl	4.73×10^{-10} [b]	3.55×10^{-7}	1.15×10^{-7}	7.14×10^{-8}

[a] Calculated from rate constants at other temperatures from ref 28a unless otherwise noted. [b] Calculated by multiplying the rate constant in 80% acetone [H. C. Brown and W. C. Dickason, *J. Am. Chem. Soc.*, **91**, 1226 (1969)] by the factor 1.68 (ref 8).

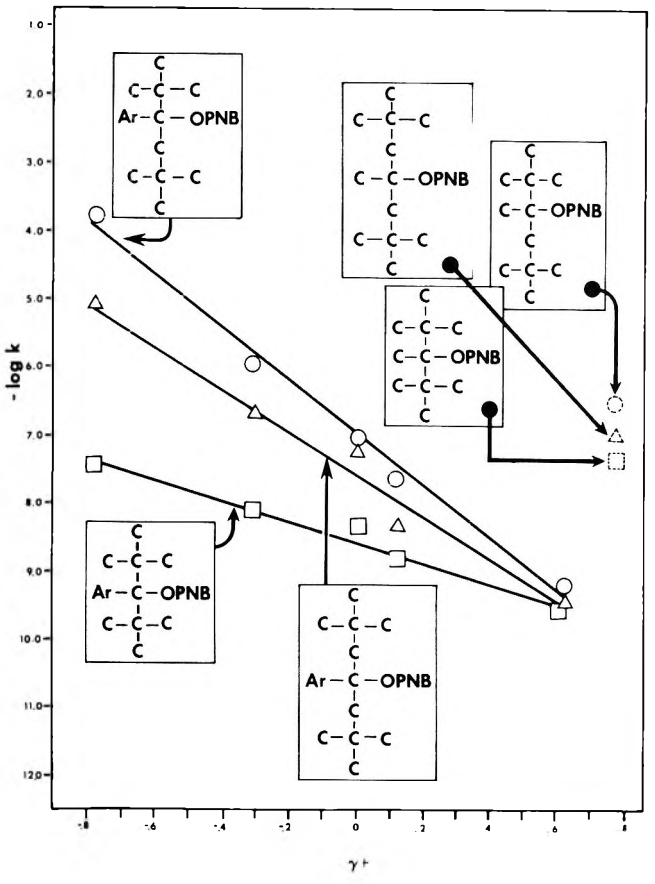


Figure 1. Nonlinearity in γ^+ vs. $-\log k$ plot of sterically hindered derivatives.

Tanida and Matsumura have studied a series of aryldialkylcarbinyl *p*-nitrobenzoates in which the alkyl groups varied from dimethyls to di-*tert*-butyl, dineopentyl, and *tert*-butylneopentyl.[28a] They observed a decrease in ρ values and attributed this to steric hindrance to resonance stabilization by the aryl group.

In order to fully explore the capabilities and limitations of correlating rates of solvolysis of tertiary methyl with tertiary benzylic derivatives, the effect of bulky groups was investigated.

Rate constants for aryl and methyl substituted 2-propyl, *tert*-butylneopentylcarbinyl, dineopentylcarbinyl, and di-*tert*-butylcarbinyl *p*-nitrobenzoates in 70% acetone at 25 °C are listed in Table II. For the aryl derivatives only, the ρ values are −4.60 (correlation coefficient 0.999), −3.87 (0.994), −3.14 (0.985), and −1.53 (0.984), respectively.

In the 2-propyl series, the 2-methyl derivative gives an excellent correlation with the 2-aryl derivatives. However, in the more bulky series nonlinear relationships are obtained. Figure 1 shows the $\rho\gamma^+$ plot for the aryl derivatives and an indication of the deviation of the methyl derivatives.

Clearly when steric hindrance to resonance is important, discretion must be employed in using the $\rho\gamma^+$ relationship in the correlation of nonaryl groups with aryl groups.

Conclusion

A linear free energy relationship has been developed which permits the direct correlation of the rates of solvolysis of tertiary methyl derivatives with their corresponding tertiary benzylic derivatives.

This method was shown to be generally applicable to a large number of systems except in cases where the steric bulk at the cationic center results in steric hindrance to resonance stabilization.

Acknowledgment. The author wishes to thank Professor P. E. Peterson for valuable suggestions on the analysis of the data.

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A Method for the Evaluation of Steric Contributions to ρ^+ Based on Aryl/Methyl Rate Ratios. Application to the Gassman–Brown Tool of Increasing Electron Demand

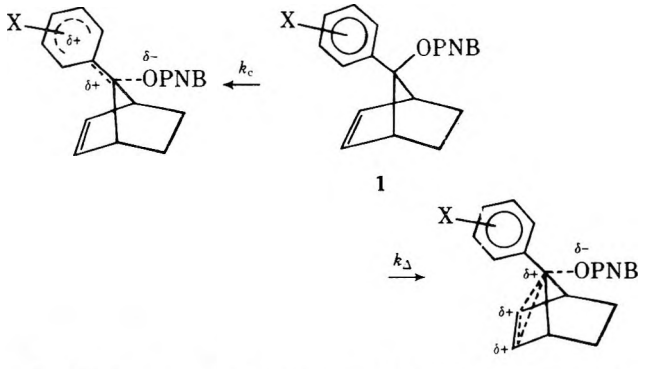
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Received August 17, 1976

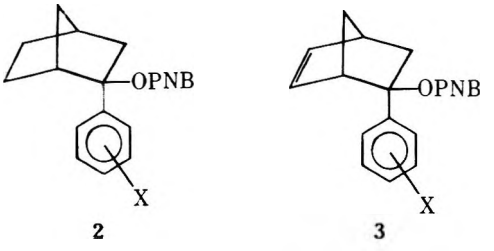
It has been shown that either of two factors may cause a large decrease in the magnitude of ρ^+ values determined for the solvolysis of a series of aryl-substituted tertiary derivatives. The factors are steric effects and neighboring group participation. In this article we define a method which can be empirically used to assess whether or not steric factors are affecting the magnitude of ρ^+. Toward this end a substituent constant, γ^+, for the methyl group directly attached to an incipient cationic center has been obtained by comparing *tert*-cumyl derivatives with *tert*-butyl derivatives. The constant is apparently solvent dependent with a value of 0.63 in 70–90% aqueous acetone and 0.79 in pure alcohols (methanol, ethanol, and 2-propanol). Using the derived γ^+ values, rate constants for methyl-substituted derivatives **6** were calculated. A comparison of calculated and observed rates for a variety of substrates reveals that the rates of **6** calculated from the rates of **7**, X = H, and ρ^+ are within 0.7 log units except when unusual steric effects cause a deviation. Both steric acceleration and steric deceleration of some aryl-substituted tertiary derivatives **7** were detected by the application of this treatment. The method described is applicable to both k_c and k_Δ substrates.

Gassman and Fentiman[1] have observed that decreasing the electron demand at the reaction site in a substrate undergoing anchimerically assisted solvolysis can cause abrupt cessation in assistance by a neighboring group. Thus the *anti*-7-norbornenyl system (**1**) undergoes a change in mechanism from k_Δ to k_c as the aryl group becomes sufficiently electron releasing to overcome the stabilization afforded by electron donation from the C_2–C_3 π bond. This change in mechanism is reflected by the magnitude of ρ^+, which is −5.2 for hydrolysis of **1** in 70% aqueous dioxane when X = *p*-NMe_2



and *p*-OMe and −2.30 when X = H, *p*-CF_3, and *m,m'*-di-CF_3.

Brown and his co-workers[2-17] have made extensive use of the tool of increasing electron demand in characterizing a variety of systems. The method has been successfully used in detecting contributions from π and σ participation[1-15,17,18] and from other conjugating groups.[16] Yet examples where participation was not detected (e.g., the *exo*-2-norbornyl system, **2**)[2,11,18] or was too weak to positively identify (e.g., the *exo*-norbornen-2-yl system, **3**)[13,19] have also been treated.



Sargent[20] has claimed that the tertiary 2-norbornyl system (**2**) may undergo accelerated ionization because of relief of the nonbonded repulsion between the endo 6-H and the endo 2 substituent. Brown, however, has maintained[21] that his own data[22] and that of Goering and Schewene[23] show only a small difference (~0.4 kcal) between the ground-state free energies of the isomeric tertiary 2-norbornyl derivatives. Hence the tool of increasing electron demand is claimed to be valid for these systems since steric factors are similar in the exo and endo derivatives.[24] However, the fact that Brown and others have established that exo and endo tertiary 2-norbornyl derivatives have similar *ground state* energies does not rule out significant energy differences in the solvolytic *transition state*. Since the *preferred* ground state conformation and the *required* transition state conformations of aryl-substituted tertiaries may differ,[25] steric factors affecting the energy of the transition state are obviously the quantities which need assessing.

It is established that either steric factors[26] or neighboring group participation[1,7,10,17] can produce a remakable change in the magnitude of ρ^+. However, it has not been established whether or not these factors act independently or in concert in producing an effect on ρ^+, because previously there has been no method available to separate the effects of these factors. Accordingly, we have sought a method to evaluate the im-

Table I. Determination of γ^+ for the Methyl Group by a Hammett–Brown Treatment of *tert*-Cumyl and *tert*-Butyl Derivatives

Entry no.	Solvent	Leaving group, L	ρ^+, 25 °C, *t*-cumyl series (4)	Log *k*, 25 °C, 4, X = H	Log *k*, 25 °C, *tert*-butyl-L (5)	Calcd γ^+
1	70% aq acetone	OPNB[b]	−3.74[c]	−2.83[c]	−5.17[d]	0.63
2	30% aq acetone	OPNB[b]	−4.72[e]	−7.14[f]	−10.13[g]	0.63
3	90% aq acetone	Cl	−4.54[h]	−3.88[h]	−6.80[i]	0.64
4	Methanol	Cl	−4.82[h]	−2.29[h]	−6.12[j]	0.79
5	Ethanol	Cl	−4.67[h]	−3.40[h]	−7.07[j]	0.79
6	2-Propanol	Cl	−4.43[h]	−4.29[h]	−7.76[k]	0.78

[a] Using eq 1. [b] *p*-Nitrobenzoate. [c] At 100 °C, ref 26. [d] At 100 °C, cf. C. F. Wilcox, Jr., and M. E. Mesirov, *J. Am. Chem. Soc.*, **84**, 2757 (1962). [e] H. C. Brown, E. N. Peters, and M. Ravindranathan, unpublished results, cf. ref 16. [f] Reference 9. [g] H. C. Brown and W. C. Dickason, *J. Am. Chem. Soc.*, **91**, 1226 (1969). [h] Y. Okamoto, T. Inukai, and H. C. Brown, *ibid.*, **80**, 4972 (1958). [i] Extrapolated from *t*-BuBr in 90% aqueous acetone, log *k* = −4.90; cf. L. C. Bateman, M. G. Church, E. D. Hughes, C. K. Ingold, and N. A. Taher, *J. Chem. Soc*, 979 (1940), using average Br/Cl-ratio from 80% acetone, Br/Cl = 56.7, cf. E. D. Hughes, *ibid.*, 255 (1935), and L. C. Bateman, K. A. Cooper, E. D. Hughes, and C. K. Ingold, *ibid.*, 925 (1940), and from absolute ethanol which has a similar *Y* value to 90% aqueous acetone, Br/Cl = 66.2, cf. E. D. Hughes, C. K. Ingold, S. Masterman, and B. J. McNulty, *ibid.*, 899 (1940). [j] A. H. Fainberg and S. Winstein, *J. Am. Chem. Soc.*, **78**, 2770 (1956). [k] Extrapolated from rate of *t*-BuBr using *Y* = −2.73, cf. footnote *j*.

portance of steric factors on the rates of ionization of aryl-substituted tertiary derivatives.

For maximum stabilization of a cationic transition state in a *tert*-cumyl solvolysis, the benzene ring must adopt a conformation in which its plane is perpendicular to the axis of the bond between carbon and the leaving group.[25] Tanida and Matsumura convincingly demonstrated that bulky groups attached to the reaction site of aryl-substituted tertiaries show low ρ^+ values. This was attributed to the preferred transition state geometry of the aryl group being difficult to attain in these cases, thus leading to an effect on the magnitude of ρ^+. On the other hand, no special methyl group orientation for carbocation stabilization in the transition state is expected; the methyl group is assumed to be spherically symmetrical in the transition state since ab initio calculations on the ethyl cation have revealed no significant barrier to C–C bond rotation.[27] This essential difference between the transition state requirements of an aryl and methyl group provides the basis for our method of evaluating steric factors on the rates of ionization of aryl-substituted tertiary derivatives. Thus we report the determination of a substituent constant which is a special kind of σ^+ constant, called the γ^+ constant,[28] for a methyl group directly substituted on a tertiary carbon undergoing ionization. We use this constant and ρ^+ for the tertiary aryl-substituted compounds to calculate the rates of ionization of methyl-substituted tertiary derivatives. If this calculated rate of the methyl-substituted derivative agrees with the observed rate, then we assume that there are no unusual steric factors operating in solvolysis of the aryl derivatives. However, if the calculated and observed rates for the methyl-substituted derivatives differ, then we assume that the ρ^+ value from solvolysis of the aryl derivatives is affected by special steric requirements (recall that methyl has no orientational requirements). These conclusions also apply to the use of Ph/Me ratios, which of course are directly related to the present consideration.

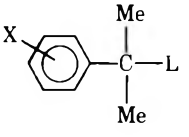
Incidental to this work we have observed that the derived γ^+ constant for the methyl group is solvent dependent. The significance of this observation is briefly discussed.

Results and Discussion

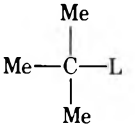
Calculation of γ^+ Values for the Methyl Group. Solvent Effects. We have calculated γ^+ values for the methyl group, Table I, by applying the modified Hammett–Brown equation,[30] eq 1, to a large body of available data on the solvolysis of *tert*-cumyl (4) and *tert*-butyl (5) derivatives.

$$\gamma^+ = \frac{\log k - \log k_0}{\rho^+} \tag{1}$$

Equation 1 may be used to calculate a γ^+ value for the methyl group when log *k* (the rate constant for 5), log k_0 (the rate constant for 4, X = H), and ρ^+ (for the aryl series 4) are known.



4



5

The data in Table I show that the same γ^+ value can be calculated from three different studies in aqueous acetone (entries 1–3). Surprisingly, however, *there appears to be a significant solvent effect on the* γ^+ *value* calculated in aqueous acetone as compared to that calculated in alcoholic solvents.

A number of reasons for the observed solvent effect can be postulated: (1) there may be a change in mechanism for solvolysis in aqueous acetone as compared to alcoholic solvents; (2) the observed effect may be a leaving group effect; (3) the σ^+ values of the aryl substituents (X in 4) may vary with solvent causing ρ^+ to be solvent dependent, so that γ^+ may or may not be solvent dependent; and (4) γ^+ may be solvent dependent. These points are considered below.

A change in mechanism from rate-limiting ionization to rate-limiting elimination has been proposed[31] to account for the deviant behavior of *tert*-butyl chloride in aqueous trifluoroethanol (TFE). Thus it is possible that rate-limiting elimination may be occurring for the *tert*-butyl derivatives in the relatively basic alcohol solvents, although such behavior might be just as probable in the *tert*-cumyl derivatives. Nevertheless, this possibility can be experimentally tested. Schleyer et al.[32] have found that, with the exception of aqueous TFE results, a linear relationship results when log *k* for 1-adamantyl bromide in a particular solvent is plotted vs. the *Y* value of that solvent. Since *Y* values were determined from the solvolysis of *tert*-butyl chloride, any point that falls on the log *k*, 2-adamantyl bromide, vs. *Y* plot is considered

Table II. Correlation of Cyclic Methyl-Substituted Chlorides and *p*-Nitrobenzoates with Aryl-Substituted Analogues

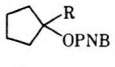
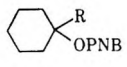
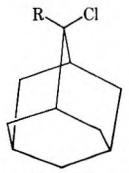
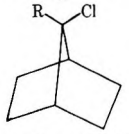
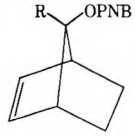
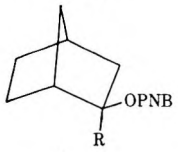
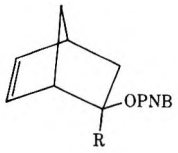
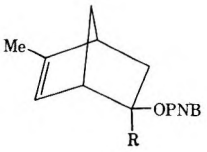
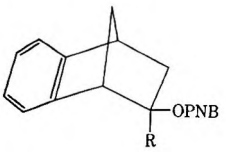
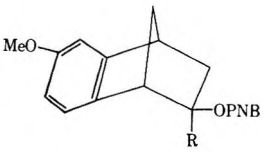
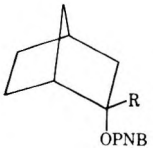
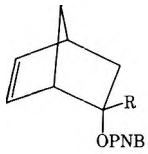
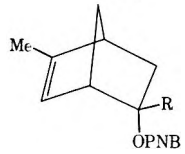
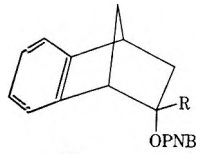
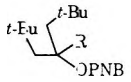
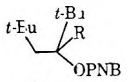
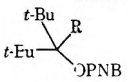
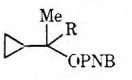
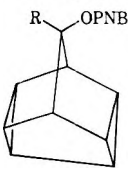
Structure no.	Substrate	ρ^+, R = Ar (Solvent, temp)	k, s^{-1}, R = Ph (log k_0)	k_{calcd}, s^{-1}, R = Me (log k_{calcd})	k_{obsd}, s^{-1}, R = Me (log k_{obsd})	log k_{calcd} − log k_{obsd}
8		−4.48[a] (90% aq acetone, 25°C)	2.74×10^{-5}[a] (−4.56)	4.16×10^{-8} (−7.38)	8.76×10^{-9} (−8.06)	0.68
9		−4.10[a] (90% aq acetone, 25°C)	7.23×10^{-3}[a] (−2.14)	1.91×10^{-5} (−4.72)	5.12×10^{-6}[b] (−5.29)	0.57
10		−4.5[c] (abs ethanol, 25°C)	1.88×10^{-2}[c] (−1.73)	5.25×10^{-5} (−5.28)	3.39×10^{-6}[d] (−5.47)	0.19
11		−3.82[e] (80% aq acetone, 25°C)	2.6×10^{-6}[e] (−5.59)	1.00×10^{-8} (−8.00)	2.11×10^{-9}[f] (−8.68)	0.68
12		−4.65[a] (90% aq acetone, 25°C)	1.96×10^{-5}[a] (−4.71)	2.29×10^{-8} (−7.64)	4.07×10^{-8}[b] (−7.39)	−0.25
13		−4.60[g] (80% aq acetone, 25°C)	1.46×10^{-8}[h] (−7.84)	1.82×10^{-11} (−10.74)	5.48×10^{-11}[i] (−10.26)	−0.48
14		−4.83[a] (90% aq acetone, 25°C)	4.59×10^{-4}[a] (−3.34)	4.17×10^{-7} (−6.38)	9.12×10^{-7}[j] (−6.04)	−0.34
15		−5.64[a] (90% aq acetone, 25°C)	3.98×10^{-8}[a] (−7.40)	1.22×10^{-11} (−10.95)	6.03×10^{-12}[k] (−11.22)	0.27
16		−2.30[l,m] (70% aq dioxane, 25°C)	4.23×10^{-9}[m] (−8.37)	1.51×10^{-10} (−9.82)	4.44×10^{-10}[n] (−9.35)	−0.47
17		−3.83[e] (80% aq acetone, 25°C)	7.56×10^{-6}[o] (−5.12)	2.95×10^{-8} (−7.53)	1.00×10^{-8}[q] (−8.00)	0.47
18		−4.21[r] (80% aq acetone, 25°C)	1.22×10^{-6}[r,s] (−5.91)	2.75×10^{-9} (−8.56)	4.70×10^{-10}[t] (−9.33)	0.77
19		−3.28[u] (80% aq acetone, 25°C)	9.18×10^{-6}[u] (−5.04)	7.76×10^{-8} (−7.11)	5.75×10^{-8}[t] (−7.24)	0.13
20		−4.50[v] (80% aq acetone, 25°C)	2.78×10^{-7}[v] (−6.56)	3.98×10^{-10} (−9.40)	6.31×10^{-11}[w] (−10.20)	0.80
21		−3.72[x] (80% aq acetone, 25°C)	1.36×10^{-6}[x] (−5.87)	6.16×10^{-9} (−8.21)	1.51×10^{-9}[w] (−8.82)	0.61
22		−3.75[e] (80% aq acetone, 25°C)	5.30×10^{-8}[o] (−7.28)	2.29×10^{-10} (−9.64)	1.13×10^{-11}[q] (−10.95)	1.31

Table II (*Continued*)

Structure no.	Substrate	ρ^+, R = Ar (Solvent, temp)	k, s^{-1}, R = Ph (log k_0)	k_{calcd}, s^{-1}, R = Me (log k_{calcd})	k_{obsd}, s^{-1}, R = Me (log k_{obsd})	log k_{calcd} − log k_{obsd}
23		−4.17[r] (80% aq acetone, 25°C)	6.03×10^{-9}[r] (−8.22)	1.41×10^{-11} (−10.85)	5.25×10^{-13}[t] (−12.28)	1.43
24		−4.19[u] (80% aq acetone, 25°C)	7.28×10^{-9}[u] (−8.14)	1.66×10^{-11} (−10.78)	5.13×10^{-13}[t] (−12.29)	1.51
25		−4.52[v] (80% aq acetone, 25°C)	9.71×10^{-11}[v] (−10.01)	1.38×10^{-13} (−12.86)	5.5×10^{-14}[w] (−13.26)	0.40
26		−2.91[y] (70% aq acetone, 100°C)	2.79×10^{-4}[y] (−3.55)	4.17×10^{-6} (−5.38)	1.17×10^{-3}[y] (−2.93)	−2.45
27		−2.64[y] (70% aq acetone, 100°C)	1.20×10^{-3}[y] (−2.92)	2.63×10^{-5} (−4.58)	2.23×10^{-3}[y] (−2.65)	−1.93
28		−1.30[y] (70% aq acetone, 100°C)	1.38×10^{-4}[y] (−3.86)	2.09×10^{-5} (−4.68)	7.13×10^{-4}[y] (−3.15)	−1.53
29		−2.78[z] (80% aq acetone, 25°C)	2.41×10^{-4}[z] (−3.62)	4.27×10^{-6} (−5.37)	3.75×10^{-5}[aa] (−4.43)	−0.94
30		−2.05[bb] (80% aq acetone, 25°C)	1.23×10^{-7}[bb] (−6.91)	6.31×10^{-9} (−8.20)	8.62×10^{-9}[bb] (−8.06)	−0.14

[a] H. Tanida and T. Tsushima, *J. Am. Chem. Soc.*, **92**, 3397 (1970). [b] Calculated from the rate constant in 80% aqueous EtOH; cf. H. C. Brown and M. Borkowski, *ibid.*, 74, 1894 (1952), assuming $m = 1$ and $Y = -1.856$, cf. E. M. Kosower, "An Introduction to Physical Organic Chemistry", Wiley, New York, N. Y., 1968, p 306. [c] H. C. Brown and K. Takeuchi, *J. Am. Chem. Soc.*, 88, 5336 (1966). [d] Calculated from the rate constant in 80% aqueous EtOH, cf. H. C. Brown and M. Borkowski, *ibid.*, 74, 1894 (1952), assuming $m = 1$ and $Y = -2.033$, cf. E. M. Kosower in footnote *b*. [e] Reference 11. [f] H. C. Brown and W. J. Hammer, *J. Am. Chem. Soc.*, 89, 6378 (1967). [g] Reference 16. [h] E. N. Peters, unpublished result; see footnote *g*. [i] E. N. Peters and H. C. Brown, *J. Am. Chem. Soc.*, 96, 263 (1974). [j] Calculated from the value in 80% aqueous ethanol; J. M. Harris, unpublished result quoted by J. M. Harris and S. P. McManus, *ibid.*, 96, 4693 (1974). [k] Calculated from the rate in 80% aqueous acetone; cf. R. K. Lustgarten, J. Lhomme, and S. Winstein, *J. Org. Chem.*, 37, 1075 (1972), assuming $m = 1$ and $Y = -1.856$ for 90% aqueous acetone and −0.673 for 80% aqueous acetone, cf. E. M. Kosower in footnote *b*. [l] For the k_Δ portion of the aryl series only. [m] Reference 1. [n] P. G. Gassman and J. M. Pascone, *J. Am. Chem. Soc.*, 95, 7801 (1973). [o] D. L. Vander Jagt, Ph. D. Thesis, Purdue University, 1967; cf. ref 4. [p] Reference 4. [q] S. Ikegami, D. L. Vander Jagt, and H. C. Brown, *J. Am. Chem. Soc.*, 90, 7124 (1968). [r] Reference 8. [s] E. N. Peters, and H. C. Brown, *J. Am. Chem. Soc.*, 94, 7920 (1972). [t] Reference 12. [u] Reference 10. [v] Reference 6. [w] Calculated from values in 50% aqueous acetone using $m = 0.58$ or $k_{50A}/k_{80A} = 24.2$; J. P. Dirlan and S. Winstein, *J. Am. Chem. Soc.*, 91, 5905 (1969); H. C. Brown and G. L. Trittle, *ibid.*, 88, 1320 (1966). [x] Reference 5. [y] Reference 26. [z] Reference 7. [aa] Reference 9. [bb] Reference 17.

evidence that *tert*-butyl chloride is solvolyzing with rate-limiting ionization.

We have solvolyzed 1-adamantyl bromide in absolute ethanol and find that the logarithm of its rate constant falls on the plot of log k for 1-adamantyl bromide against Y. The aqueous acetone solvolyses have previously been correlated.[32] Hence the solvent effect on the γ^+ constant calculated for the methyl group is not indicated to be a result of a change in mechanism.

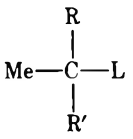
When entries 1 and 2 of Table I are compared with entry 3, one notes that essentially the same value for γ^+ is calculated for solvolysis of the *p*-nitrobenzoates in aqueous acetone as for chlorides in aqueous acetone. Therefore, there seems to be no leaving group effect on the γ^+ constant.[33]

The possibility that σ^+ values for aryl substituents are solvent dependent has been considered before, but there is little evidence indicating that this is a general problem.[34,35] Thus we dismiss this as the cause of the calculated solvent effect on the γ^+ constant.

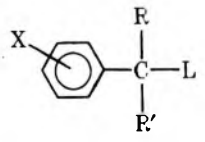
We therefore conclude that γ^+ for the methyl group is solvent dependent. If this conclusion withstands further scrutiny, it implies that alkyl groups in general have a solvent dependent electronic effect when compared to aryl groups. Also, in the application of the Taft equation, σ^* values obtained in one solvent may not be applicable in another solvent.[36]

Use of γ^+ Values in Evaluating Structural Effects. Recognizing the limitations imposed by the above conclusion, we have used our γ^+ values to compare calculated rate constants for solvolysis of methyl-substituted tertiary substrates (6) with the corresponding aryl-substituted tertiary substrates

(7), Table II. The γ^+ value of 0.63 was used for calculations in aqueous acetone and aqueous dioxane and the γ^+ value of 0.79 was used for calculations in absolute ethanol.



6

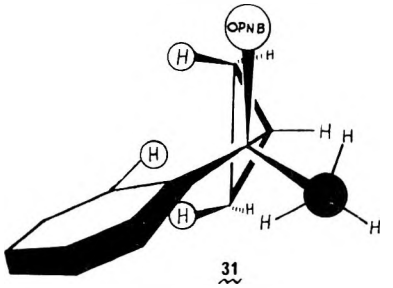


7

Examination of Table II shows that the rate of the methyl-substituted compound is calculated within 0.7 log units for most systems. While it might be tempting to evaluate any difference between the calculated and observed rates, we have assumed that a difference between log k_{calcd} and log k_{obsd} for **6** of less than 0.7 represents the limits of our method, and is thus consistent with there being no significant steric effect on the magnitude of ρ^+. Differences greater than ~0.7 are assumed to reflect an unusual effect.

There are two mechanistic types among the substrates studied which fall within the "normal" category. Compounds **8–15, 17,** and **25** describe substrates which solvolyze by a k_c mechanism, and entries **16, 19, 21,** and **30** are examples of substrates which solvolyze by k_Δ mechanisms.[37] Thus it appears that our method is applicable to both k_c and k_Δ mechanisms as long as the ρ^+ used for calculating log k for the methyl-substituted tertiary derivative is from a linear plot for the range of aryls which includes phenyl and *p*-trifluoromethylphenyl.[38]

It is interesting to note the entries which correlate poorly, that is, those for which log k_{calcd} − log k_{obsd} > ±0.7. We believe that these systems are examples in which unusual steric factors are operating. Entry **29** provides an example. It is well established that the cyclopropyl group requires a bisected conformation for maximum conjugation with the developing positive center.[39] Steric factors which prohibit this conformation reduce stabilization by the cyclopropyl group. Examination of molecular models shows that if the aryl group is put in a configuration where it can best stabilize the incipient cationic center in **29,** the cyclopropyl group in *either* bisected configuration interferes; e.g. structure **31**.[40] Thus, it is

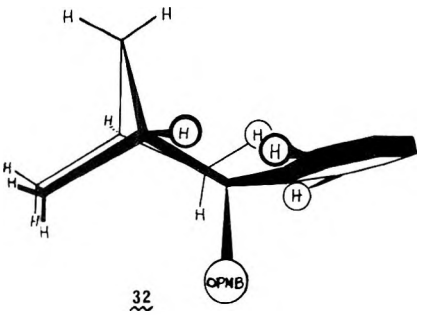


31

likely that the aryl groups do not offer their normal stabilizing effect because of steric inhibition to resonance. The sign of the variance (methyl faster than predicted by calculation from aryl rates) is consistent with this explanation.

Compounds **26, 27,** and **28** are well known[26] examples of substrates where, like compound **29,** steric effects prevent the aryl groups from providing their full stabilizing effect. With these compounds the methyl group is far better at stabilizing the transition state than aryl groups with σ^+ values similar to the γ^+ value of the methyl group.

The final group of compounds that correlate poorly, **22–24,** are of interest because a great deal of attention has been given to them. Brown has claimed that these *endo*-2-norbornyl derivatives all ionize slowly because of steric hindrance to ionization.[21] Since both the aryl- and methyl-substituted compounds should be subject to the same steric hindrance to ionization, the failure of our γ^+ method to accurately predict the rates of the methyl-substituted compounds for **22, 23,** and **24** must have some origin other than that suggested by Brown. A possible explanation can be based on the nonbonded interaction of the exo aryl groups with the C-1 and exo C-3 hydrogens as shown in **32.** The aryl group must adopt the con-



32

formation shown if it is to provide effective stabilization of the developing positive center. As ionization proceeds and the aryl group swings down, the nonbonded interactions shown in **32** are relieved. There is no counterpart for this strain relief in the methyl group. Consequently, the aryl series is fast relative to the methyl-substituted derivative, and a positive value of log k_{calcd} − log k_{obsd} is observed for the methyl-substituted derivative.

A cursory comparison of ρ^+ values for the *exo*- and *endo*-2-norbornyl derivatives (e.g., compare compounds **17** and **22,** and **18** and **23**) indicates nothing unusual about either series.[41] The exo and endo derivatives having similar ρ^+ values has been assumed to mean that the isomeric pairs have similar mechanisms with similar electron demand.[8,11,13] We have just concluded that steric factors affect the magnitude of ρ^+ values for the endo derivatives **22–24.** Examination of the log k_{calcd} − log k_{obsd} values for the corresponding exo derivatives (**17–19**) shows that steric effects are relatively unimportant. Thus the similarity of ρ^+ values for these exo and endo isomers must result from a blending of electronic and steric factors, and the prior assumption that the isomers react with similar electron demand at the developing cationic center must be incorrect.[42]

In summary, low Ph/Me rate ratios and low ρ^+ values have been taken as evidence for neighboring group participation.[43] However, our treatment reveals that these parameters can be dramatically influenced by steric factors. Those instances in which steric complications are involved can be readily identified by use of the method described in this article. Hence we strongly encourage the use of this method of assessing the steric characteristics of a reaction when Ph/Me rate ratios and ρ^+ values are to be utilized as mechanistic probes.

Finally, ρ^+ values may be unusually low for steric reasons, because of neighboring group effects, or because of a combination of these factors. For example, the solvolysis of **27** results in low values of the Ph/Me rate ratio and of ρ^+,[26] yet the high negative value of log k_{calcd} − log k_{obsd} (Table II) shows that the "low" values actually result from steric inhibition to resonance when R = aryl. In **30,** however, no unusual steric factors are indicated, and the low Ph/Me rate ratio and low ρ^+ values are assignable solely to the presence of σ participation[17] which lowers the requirement for stabilization by the group R whether it be methyl or aryl. For **29,** a low ρ^+ value combined with a negative value of log k_{calcd} − log k_{obsd} of 0.94 signals that a combination of steric and electronic factors are causing the observed change in ρ^+ as compared to model compounds.[44]

Experimental Section

Ethanolysis of 1-Adamantyl Bromide. The solvolysis rate of

1-adamantyl bromide in absolute ethanol was measured in routine fashion:[32]

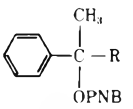
Temp, °C	k, s^{-1}
119.9 ± 0.1	$1.22 \pm 0.02 \times 10^{-3}$
100.3	$1.58 \pm 0.18 \times 10^{-4}$
75.6	5.06×10^{-6}
75.1	3.53×10^{-6}
25.0 (extrapolated)	8.64×10^{-10}

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research (S.P.M.). Discussions with Professors H. C. Brown, D. J. Raber, P. E. Peterson, P. v. R. Schleyer, and T. T. Tidwell are also acknowledged.

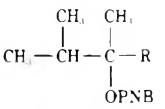
Registry No.—**8** (R = Me), 10523-97-4; **9** (R = Me), 61491-20-1; **10** (R = Me), 6196-85-6; **11** (R = Me), 19013-42-4; **12** (R = Me), 931-78-2; **13** (R = Me), 31058-46-5; **14** (R = Me), 37723-65-2; **15** (R = Me), 33686-58-7; **16** (R = Me), 33686-61-2; **17** (R = Me), 22467-58-9; **18** (R = Me) 55829-78-2; **19** (R = Me), 57955-29-0; **20** (R = Me), 7525-46-4; **21** (R = Me), 26184-43-0; **22** (R = Me), 13351-30-9; **23** (R = Me), 55829-76-0; **24** (R = Me), 55829-77-1; **25** (R = Me), 7572-53-4; **26** (R = Me) 40544-08-9; **27** (R = Me), 40544-09-0; **28** (R = Me), 40544-10-3; **29** (R = Me), 23437-99-2; **30** (R = Me), 61491-21-2; methyl, 2229-07-4.

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(18) For a brief review on the use of this method see B. Capon and S. P. McManus, "Neighboring Group Participation", Vol. 1, Plenum Press, New York, N.Y., 1976, pp 89–94.
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(27) For example, the barrier to rotation in the ethyl cation is close to zero; cf. L. Radom, J. A. Pople, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **94**, 5935 (1972), and references cited therein.
(28) The designation given is to avoid confusion between the σ^+ for the methyl group as an aryl substituent and a constant useful in correlating reaction rates where methyl is directly attached to a reaction center; cf. ref 29. E. N. Peters [*J. Am. Chem. Soc.*, **98**, 5627 (1976)] sets the precedent for the use of γ^+.
(29) K. Oyama and T. T. Tidwell, *J. Am. Chem. Soc.*, **98**, 947 (1976).
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(33) No temperature effect on the value of ρ^+ is evident; cf. entries 2 and 3 vs. entry 1, Table I.
(34) Y. Okamoto, T. Inukai, and H. C. Brown, *J. Am. Chem. Soc.*, **80**, 4972 (1958).
(35) There are exceptions; cf. D. N. Kevill, K. C. Kolwyck, D. M. Shold, and C.-B. Kim, *J. Am. Chem. Soc.*, **95**, 6022 (1973).
(36) The discussion here could include solvent effects on ρ^+ and ρ^* but the reasoning tends to become cyclical and largely conjectural.
(37) Refer to Table II for references for a particular system.
(38) The σ^+ value for p-CF_3 is 0.61. Thus, this group should generally have a polar response similar to the methyl group.
(39) H. G. Richey, Jr., in "Carbonium Ions", Vol. 3, G. A. Olah and P. v. R. Schleyer, Ed., Wiley-Interscience, New York, N.Y., 1972, Chapter 25; K. B. Wiberg, B. A. Hess, Jr., and A. J. Ashe, III, *ibid.*, Chapter 26.
(40) The alternate configuration with a bisected cyclopropyl group has nonbonding interactions between the cyclopropyl C-1 hydrogen and the aryl group. It is difficult to determine from models which conformation is the poorer.
(41) M. A. Battiste and R. A. Fiato, *Tetrahedron Lett.*, 1255 (1975), have treated the constancy of the exo/endo rate ratio of 2-norbornyl derivatives.
(42) It is bothersome to see that entry **25**, an *endo*-norbornyl derivative, behaves "normally". Apparently some other factor has become important to change the steric requirements for ionization. There, of course, may be alternate explanations for these endo derivatives since it is observed that *exo*-2-norbornyl derivatives with a 5,6 double bond or with a 5,6 fused aryl group, i.e., **18**, **20**, and **21**, correlate somewhat poorly.
(43) For example, ref 17.
(44) After submission of this manuscript, experimental data on two interesting systems were found in preprints kindly furnished by Professor H. C. Brown.



i, R = CH_3 or Ar



ii, R = CH_3 or Ar

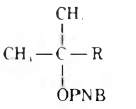
The systems are the 1-substituted 1-phenyl-1-ethyl-*p*-nitrobenzoate (i) and the 2-substituted 3-methyl-2-butyl-*p*-nitrobenzoate (ii). Using the format of Table II, the pertinent data for the aryl/methyl treatment (all rates are for solvolysis in 80% aqueous acetone extrapolated to 25 °C) are

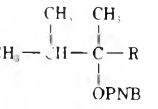
Substrate	ρ^+, R = Ar	Log k_0, R = Ph	Log k_{calcd}, R = Me	Log k_{obsd}, R = Me	Log k_{calcd} − log k_{obsd}
i	−3.23[a]	−6.11[a]	−8.15	−7.14[b]	−1.01
ii	−4.76[c]	−8.02[c]	−11.02	−9.67[d]	−1.35

[a] H. C. Brown, M. Ravindranathan, and E. N. Peters, unpublished results. [b] Reference 9. [c] H. C. Brown, E. N. Peters, and M. Ravindranathan, *J. Am. Chem. Soc.*, **99**, 505 (1977). [d] E. N. Peters and H. C. Brown, *J. Am. Chem. Soc.*, **96**, 263 (1974).

The γ^+ treatment clearly indicates that the aryl-substituted tertiary systems i and ii suffer from a degree of steric hindrance to ionization. Thus, when i bears two aryl groups, both cannot stabilize the transition state to an equal extent because of steric factors; hence the ρ^+ value is lowered for the series i, R = Ar. 1-Aryl-1-phenylethyl cations have been well studied (cf. ref 45) and are known to have the aryl groups in a propeller-like conformation owing to nonbonding interactions between the ortho protons. Our results then imply that the steric factors also operate in the transition state to form these cations.

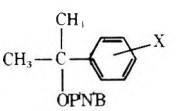
The result with ii was surprising since we did not expect the isopropyl group to interfere with aryl conjugation in ii, R = Ar; yet, as indicated by a log k_{calcd} − log k_{obsd} of −1.35, an effect is apparent. The following rate comparison taken from data in our tables verifies that the steric effect is real.

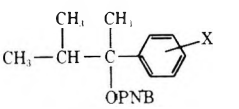




k_{rel}, R = Me	1.0	2.9
k_{rel}, R = Ph	1.0	0.181

Furthermore, Hart and Law (ref 46) concluded that the isopropyl group is more sterically demanding than the cyclopropyl group. Thus, our intuition must yield to the data forcing the conclusion that ii, R = Ar, is experiencing steric inhibition to resonance stabilization of the solvolytic transition state. This conclusion, however, is difficult to accept since the ρ^+ value *is not lowered* by replacing methyl with isopropyl. Further study may be necessary before this dilemma is resolved.





ρ^+	−4.72	−4.76

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Studies of the Catalyzed Reaction between Alcohols and Alkyl Isocyanates. Evidence for a Light-Assisted Reaction[1]

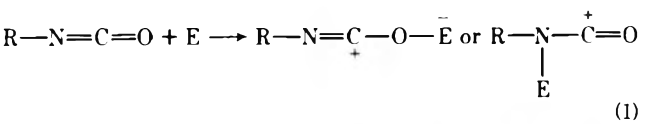
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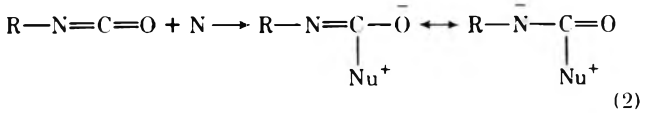
Received October 12, 1976

The thermal reaction between cyclohexyl isocyanate and 1-butanol to produce the expected carbamate occurs spontaneously in degassed CCl_4 at 50 °C with a measured second-order rate constant of 4.67×10^{-5} L mol^{-1} s^{-1}. By maintaining the identical conditions but exposing the reaction to light from a tungsten lamp, we have observed a 125-fold rate increase. The light-assisted reaction is greatly enhanced upon the addition of certain transition metal catalysts, such as ferrocene. By studying the effect of electronic and steric factors and the influence of light and solvent, we propose that the enhanced reactions occur by excited state charge-transfer complexes involving the isocyanate and solvent or ferrocene and solvent. A set of mechanistic reactions and the experiments supporting them are discussed. The steric influence of the alkyl group on the reactivity of alkyl isocyanates is also reported under a variety of conditions.

Catalysis of alcohol–isocyanate reactions is a topic which has received a considerable amount of study. Tarbell et al.[3] observed that these reactions are subject to either electrophilic or nucleophilic catalysis. This may be rationalized in terms of the electrophile (E, a Lewis acid) or nucleophile (Nu, a Lewis base) activating the isocyanate group for attack as shown in eq 1 and 2. The alcohol itself may be assumed to react as in eq 2.

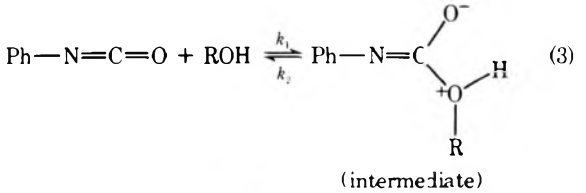


(1)

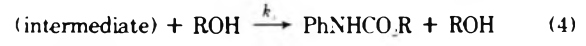


(2)

Baker and Gaunt[4] have extensively studied the thermal reaction and have postulated a mechanism that generally accounts for their observations. The reaction sequence was written as a two-step process where the alcohol was catalytically involved in the second step; see eq 3 and 4. Owing to a



(intermediate)



(4)

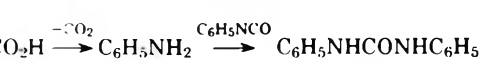
mild catalysis by the product, the reaction kinetics are not completely linear throughout the reaction.[4,5]

Several groups[4-12] have studied the kinetics of the nucleophilically catalyzed reaction. 1,4-Diazobicyclo[2.2.2]octane (Dabco) is found to be one of the best nucleophilic catalysts owing to the availability of its electron pairs. The mechanism for the action of nucleophilic catalysts generally follows that pictured in eq 3 and 4 with the nucleophilic catalysts replacing the alcohol in the formation of the complex.[13-15]

Studies of catalysis by electrophilic or acidic agents have essentially been confined to organometallic compounds owing to the interest in the great rate enhancement seen with many of these materials. Organometallic compounds offer room for additional mechanistic complications since they may offer sites for coordination for both the isocyanate and the alcohol.[13-15] Kinetic surveys on various organometallic compounds,[16] organotin catalysts,[17] and metal carboxylates[18] have appeared, and mechanistic papers on the action of metal chelates,[19] organotin compounds,[19] and ferric acetylacetonate[20] have been published.

Since the practical interest in catalysts is their effect on rate, steric effects must also be considered. Because of the mechanistic complexities, it is difficult to predict how catalysts will affect the rates when steric factors in the reactants are operative. Davis and Farnum[21] observed that among aliphatic alcohols, the relative rates of reaction of primary, secondary, and tertiary alcohols are approximately 1.0, 0.3, and 0.003–0.007, respectively. These results, while in agreement with the general order expected from steric hindrance due to branching, are not entirely accurate for the tertiary system owing to the elimination process that becomes preponderant in tertiary aliphatic alcohols (Scheme I).

Scheme I



Although a few generalizations have been drawn from studies on aromatic isocyanates,[15] not too much is known about the steric influence on rate upon changing the substituent R in RNCO.[22] One would predict a less important effect in the isocyanate substrate than in the alcohol moiety since the reacting site is further removed in the former. Since, in many polymer applications, diisocyanates are added to extend or cure polyesters or other hydroxy-terminated prepolymers, we were interested in observing the effects of branching on rate in alkyl isocyanates with and without typical added catalysts.

In the course of our studies on the catalytic effects of organometallic agents on the alcohol–isocyanate reaction, we observed a remarkable light-assisted process[23] which we now wish to discuss. We also discuss here our studies of the steric consequences of branching in alkyl isocyanates on the rate of catalyzed alcohol–isocyanate reactions.

Results

In the course of characterizing the catalytic effect of ferrocene and its derivatives on alcohol–isocyanate reactions we serendipitously discovered that the near-infrared Cary 14 light source was responsible for a light-assisted reaction. The uncatalyzed thermal reaction[24] between a degassed solution of cyclohexyl isocyanate and *n*-butyl alcohol in carbon tetrachloride occurs at a moderate rate at 50 °C (see Table I, entry 1). However, if the solution is subjected to constant exposure to the near-infrared light source of the Cary 14 spectropho-

Table I Second-Order Rate Constants for the Reaction of Cyclohexyl Isocyanate and *n*-Butyl Alcohol in Carbon Tetrachloride at 50.5 ± 0.5 °C

Entry no.	Conditions	[*n*-BuOH] = [$C_6H_{11}NCO$], M	[Ferrocene], M	k_2, L mol^{-1} s^{-1} [a]
1	Thermal[b]	1.00×10^{-1}	0.00	$(4.67 \pm 0.91) \times 10^{-5}$
2	Photoassisted[c]	5.00×10^{-2}	0.00	$(5.85 \pm 0.40) \times 10^{-3}$
3	Thermal[b]	1.00×10^{-1}	3.39×10^{-3}	$(4.61 \pm 1.34) \times 10^{-3}$
4	Photoassisted[c]	4.29×10^{-2}	1.43×10^{-5}	$(2.19)^d \times 10^{-1}$
5	Photoassisted[c]	4.84×10^{-2}	3.23×10^{-6}	$(5.40)^d \times 10^{-2}$

[a] Determined by observing the disappearance of *n*-BuOH in the near infrared; see Experimental Section. Values are average of several runs unless otherwise indicated. [b] Reactions were run on a 200-mL scale in the dark in a thermostated oil bath; small aliquots were removed at intervals for near-IR analysis in a 1.0-cm cell. [c] Reactions were run in a thermostated 10-cm quartz cell with constant light exposure from the Cary 14 near-IR source; see Experimental Section. [d] Represents only one run under these conditions, but similar rates under similar conditions were observed.

tometer, under otherwise similar conditions, the second-order rate constant for the reaction was found to increase by a factor of 125 (compare entries 1 and 2, Table I). The product is the carbamate under both sets of conditions.

The enhancement of the rate of the thermal reaction between cyclohexyl isocyanate and *n*-butyl alcohol by ferrocene has been determined. At a 3.39% molar concentration, ferrocene increases the second-order rate constant of the thermal reaction by a factor of nearly 100; compare entries 1 and 3, Table I. Under conditions nearly identical with those where the light-assisted reaction discussed above was observed but now with 0.033 mol % added ferrocene, an enhancement in rate constant by a factor of approximately 4700 over the uncatalyzed thermal reaction and by a factor of 47.5 over the already efficient ferrocene-catalyzed thermal reaction is observed; compare entry 4 with entries 1 and 3. The ferrocene-catalyzed light-assisted reaction is somewhat sensitive to the amount of added ferrocene as seen by a comparison of entries 4 and 5 of Table I.

The light-assisted reactions with added ferrocene were found to be very sensitive to the presence of oxygen and to known quenchers, e.g., methyl violet. After short exposure times to light in the presence of air, the solution took on a greenish color from ferrocinium ion formation.[25] Hence, at least in the presence of ferrocene, the role of oxygen could be simply to destroy the ferrocene catalyst. Methyl violet would probably act differently. Nevertheless, to protect against oxygen inhibition, all reactions with and without added ferrocene were degassed and dry nitrogen was introduced to the flasks or reaction cells.

There is possible evidence for a chain process. For example, all light-assisted reactions were characterized by an induction period where the reaction began slowly yielding a curve when a second-order kinetic plot was constructed; see Figure 1. After a period of time, the plot became linear. Azobisisobutyronitrile (AIBN), a common free-radical initiator, did not accelerate the thermal reaction when a CCl_4 solution of the reactants with added AIBN was heated at 80–100 °C.

Since the Cary 14 lamp is a broad wavelength source it was of interest to determine what wavelength of light caused the reaction to occur. We found that the photoreaction also occurred readily in a Rayonet reactor.[26] Additionally, we could measure the rates of the thermal reactions by inserting a 650-nm Corning filter[27] between the Cary 14 source and the sample. Using this filter, a rate constant of 5.37×10^{-5} L mol^{-1} s^{-1} was measured for a reaction comparable to that shown as entry 1 of Table I. Further definition of the effective wavelength was not achieved.

The light-assisted reaction was also sensitive to a change in solvent. On changing to either benzene or hexane, a rate effect occurred. A 30-mL benzene solution 0.05 M in cyclohexyl isocyanate and 0.05 M in *n*-butyl alcohol proceeded only

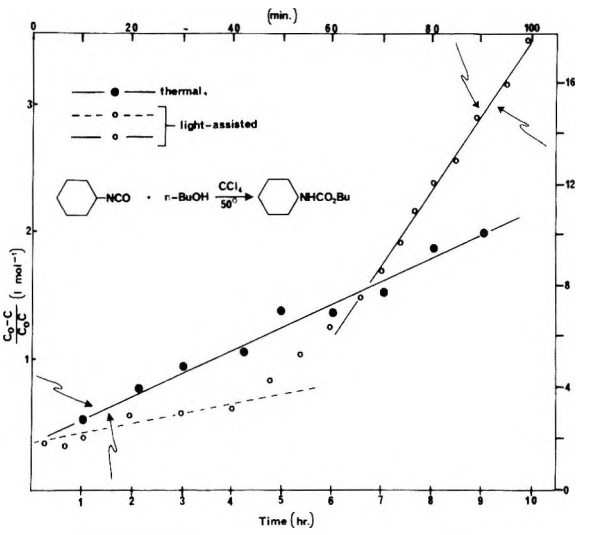


Figure 1. Second-order plots for the thermal and light-assisted reactions of cyclohexyl isocyanate with *n*-butyl alcohol.

to about 5% completion when held either in UV light or in the dark for 4 h. Under the same conditions the reactants in carbon tetrachloride were 95% consumed when exposed to light. A similar result was obtained with hexane as with benzene. When an *o*-dichlorobenzene solution of the reactants was exposed to UV light in a Rayonet reactor, carbamate formation was complete after 12 h. A control run under the same conditions but in the dark gave <5% reaction.

Each light-assisted reaction contained a stable yellowish color after reaction, yet the purified carbamate was colorless in each case. An attempt to isolate or identify the yellow impurity proved to be quite difficult as it was shown to be well less than 1% of the reaction product and no distinctive NMR absorptions in presence of the carbamate were observed. Duplicate kinetic measurements of the light-assisted reaction with an added concentrate of the yellow component proceeded at a rate similar to that measured without the added impurity. The induction period was also still present and of a similar magnitude. Hence buildup of the yellow impurity as a reactive intermediate or catalyst was not considered to be the source of the induction period.[28,29]

The effect of varying the steric environment of the isocyanate on the rate constant of the isocyanate–alcohol reaction under various kinds of catalysis was measured; see Table II. Also, with cyclohexyl isocyanate as the isocyanate reactant, the sensitivity of the light-assisted ferrocene-catalyzed reaction to a change in steric bulk in the alcohol was determined; see Table III. Finally, rate studies were run to measure the effects of varying electronic and steric factors in the ferrocene catalyst; see Table IV.

Table II. Second-Order Rate Constants and Relative Rates for the Catalyzed Reaction of Alkyl Isocyanates with *n*-Butyl Alcohol in Carbon Tetrachloride at 50.5 ± 0.5 °C

$$RNCO + CH_3(CH_2)_3OH \rightarrow RNHCO_2(CH_2)_3CH_3$$

R	Light-assisted[a] (no ferrocene present) k_{obsd},[d] L mol^{-1} s^{-1}	k_{rel}	Light-assisted[b] ferrocene catalyzed k_{obsd},[d] L mol^{-1} s^{-1}	k_{rel}	Dabco[c] catalyzed k_{obsd},[d] L mol^{-1} s^{-1}	k_{rel}	$Fe(acac)_3$[b] catalyzed k_{obsd},[d] L mol^{-1} s^{-1}	k_{rel}
Methyl	$(3.52 \pm 0.09) \times 10^{-5}$	1.00	$(3.9\pm 0.78) \times 10^{-2}$	1.00	$(1.29 \pm 0.14) \times 10^{-2}$	1.00	$(8.18 \pm 0.52) \times 10^{-2}$	1.00
Ethyl	$(3.28 \pm 0.11) \times 10^{-5}$	0.93	$(3.4\pm 0.07) \times 10^{-2}$	0.87	$(7.40 \pm 0.60) \times 10^{-3}$	0.57	$(9.30 \pm 0.50) \times 10^{-2}$	1.14
Isopropyl	$(3.74 \pm 0.82) \times 10^{-5}$	1.06	$(2.1\pm 0.40) \times 10^{-2}$	0.55	$(4.60 \pm 0.40) \times 10^{-3}$	0.36	$(6.80 \pm 0.20) \times 10^{-2}$	0.83
tert-Butyl	$(2.65 \pm 0.04) \times 10^{-5}$	0.75	$(4.21 \pm 0.90) \times 10^{-3}$	0.11	$(7.00 \pm 0.60) \times 10^{-4}$	0.054	$(2.43 \pm 0.08) \times 10^{-2}$	0.30

[a] [RNCO] = [n-C_4H_9OH] = 0.125 M. [b] [RNCO] = [n-C_4H_9OH] = 0.0484; [catalyst] = 3.22×10^{-4} M. [c] [RNCO] = 0.25 M; [n-C_4H_9OH] = 0.125 M; [Dabco] = 1.0×10^{-2} M. [d] Average second-order rate constant from two or more runs.

Table III. Rate Data for the Light-Assisted Reaction of Cyclohexyl Isocyanate with Various Alcohols in Carbon Tetrachloride at 50.5 ± 0.5 °C with Ferrocene as Catalyst[a]

Alcohol	k, L mol^{-1} s^{-1} [b]	k_{rel}
Methyl alcohol	$(8.80 \pm 0.63) \times 10^{-2}$	1
Ethyl alcohol	$(3.84 \pm 2.87) \times 10^{-2}$	0.44
n-Butyl alcohol	$(3.58 \pm 0.30) \times 10^{-2}$	0.41
Isopropyl alcohol	$(1.43 \pm 0.01) \times 10^{-2}$	0.16
tert-Butyl alcohol	$(4.25 \pm 1.24) \times 10^{-4}$	0.0048

[a] [$C_6H_{11}NCO$] = [ROH] = 0.0484 M; [ferrocene] = 3.23×10^{-4} M. [b] Average second-order rate constant from two or more runs.

To assess the potential synthetic utility of the reaction, two tertiary alcohols were selected for reaction with cyclohexyl isocyanate under photochemical conditions. In a Rayonet photochemical reactor, a carbon tetrachloride solution of *tert*-butyl alcohol reacted smoothly with cyclohexyl isocyanate giving nearly a quantitative yield of carbamate based on conversion. Under the same conditions, triphenylmethanol was not converted to a carbamate and was recovered unchanged.

Discussion

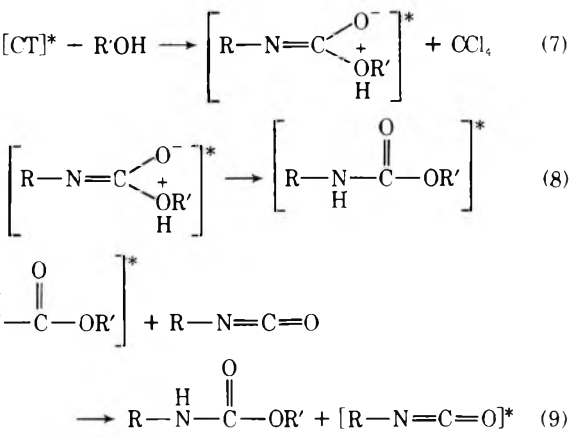
The finding of a light-assisted alcohol–isocyanate reaction is interesting and without a close precedent; many of our observations, however, do have precedent. We will now treat various possible mechanisms which are suggested based on the data available.

Ferrocene and carbon tetrachloride are both known for their ability to form charge transfer complexes[30] (CT) and, in fact, they form a charge transfer complex with each other.[31] Thus the possible involvement of charge transfer complexes in these processes is suggested. With ferrocene absent, one could envision charge transfer formation between the isocyanate and carbon tetrachloride. The absorption of light by the complex could lead to an excited state complex; see eq 5. Alternatively, exciplex formation, as shown in eq 6, could occur.

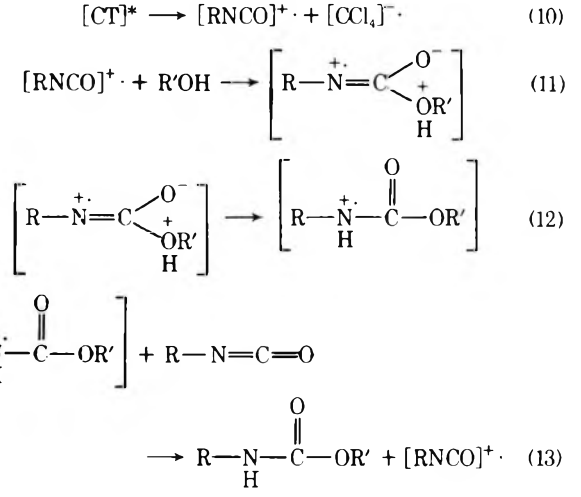
$$RN{=}C{=}O + CCl_4 \rightarrow [CT] \xrightarrow{h\nu} [CT]^* \quad (5)$$

$$RN{=}C{=}O \xrightarrow{h\nu} [RN{=}C{=}O]^* \xrightarrow{CCl_4} [CT]^* \quad (6)$$

Two modes of reaction are conceivable for the [CT]* species. There may be sufficient charge transfer in the complexed species to cause it to react faster with an alcohol, e.g., by eq 7–9, in comparison with an unactivated isocyanate. This sequence of reactions is written as a chain process. Alternatively, complete electron transfer may occur yielding the isocyanate



cation radical; see eq 10. This species would certainly be activated toward reaction with alcohols. Thus, eq 11–13 form a chain process that could account for the observed product.



A cursory search for evidence supporting the reactions shown in eq 5 revealed nothing favorable as no CT absorption band was found in the electronic spectrum[32,33] of cyclohexyl isocyanate in carbon tetrachloride or in solutions of cyclohexyl isocyanate and carbon tetrachloride in cyclohexane or in heptane;[34] alkyl isocyanates show a λ_{max} at ca. 260 nm. However, the reaction of electronically excited isocyanate with carbon tetrachloride to give the excited state CT complex, e.g., eq 5, is not inconsistent with the absence of a CT absorption band.

Although there is some evidence which might favor a chain process, a chain mechanism is not required by the available

Table IV. Rate Data for the Light-Assisted Reaction of Cyclohexyl Isocyanate with *n*-Butyl or *tert*-Butyl Alcohol in Carbon Tetrachloride at 50.5 ± 0.5 °C with Various Ferrocene Derivatives as Catalyst [a]

Alcohol	Catalyst	k, L mol^{-1} s^{-1} [b]	k_{rel}
n-Butyl alcohol	*n*-Butylferrocene	$(1.20 \pm 0.21) \times 10^{-1}$	3.35
n-Butyl alcohol	Acetyl-1,1′-dimethylferrocene	$(9.14 \pm 0.74) \times 10^{-2}$	2.55
n-Butyl alcohol	Ferrocene	$(3.58 \pm 0.30) \times 10^{-2}$	1.00
n-Butyl alcohol	Acetylferrocene	$(2.32 \pm 0.49) \times 10^{-2}$	0.65
n-Butyl alcohol	1,1′-Diacetylferrocene	$(5.83 \pm 1.01) \times 10^{-2}$	0.16
tert-Butyl alcohol	Ferrocene	$(4.28 \pm 1.24) \times 10^{-4}$	1
tert-Butyl alcohol	1,1′-Diacetylferrocene	(9.23)[c] $\times 10^{-4}$	0.22

[a] $[C_6H_{11}NCO] = [ROH] = 0.0484$ M; [cat.] $= 3.23 \times 10^{-4}$ M. [b] Average second-order rate constant from two or more runs. [c] Represents only one kinetic run.

evidence. For example, as evidence for a chain process, the induction period in the light-assisted reaction in the absence of ferrocene, see Figure 1, could be the result of a preequilibrium step to form a species which is kinetically important; alternatively, it may be the result of the destruction of some species which acts as an inhibitor. Thus, while the reaction sequences represented by eq 5 or 6–9 and 5 or 6, 10–13 offer possible explanations for some of our observations, the chain propagating steps, especially the sequence in eq 7–9, are highly unusual. In fact, the sequence of reactions 7–9 is very unlikely.

The ferrocene-catalyzed reaction[35] is all the more interesting. From the data in Table I it can be seen that the process is complicated by the occurrence of three reactions simultaneously. At the concentration tested, ferrocene increases the second-order rate constant of the thermal reaction by a factor of nearly 100. Furthermore, in the presence of light, ferrocene further enhances the rate constant of the ferrocene-catalyzed thermal reaction by a factor of 47.5. Thus, the observed second-order rate constant is a sum of the three individual rate constants, eq 14, but only ferrocene-catalyzed reactions would appear to be kinetically important.

$$k_{obsd} = k_{FcH,light} + k_{FcH,thermal} + k_{thermal} \quad (14)$$

The intensity of the CT absorption band for the ferrocene and carbon tetrachloride[31] suggests its involvement here; see eq 15 and 16. In the mechanistic schemes discussed earlier, eq 14 and 15 fit nicely in an overall scheme with eq 10–13.

$$FcH + CCl_4 \rightarrow [CT] \xrightarrow{h\nu} [CT]^* \xrightarrow{h\nu} FcH^+ \cdot + CCl_4^- \cdot \quad (15)$$

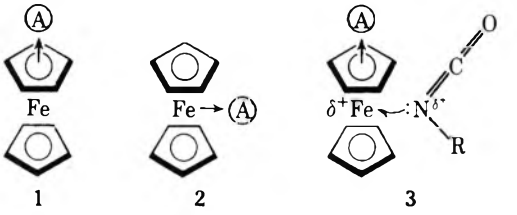
(FcH = ferrocene)

$$FcH^+ \cdot + R\text{-}N{=}C{=}O \rightarrow FcH + [R\text{-}NCO]^+ \cdot \quad (16)$$

The observation that the light-assisted reaction occurs in some solvents but not in others confirms the postulated involvement of solvent. Since *o*-dichlorobenzene, a charge transfer acceptor, is an acceptable solvent for the light-assisted reaction, it apparently is acting in the same role as carbon tetrachloride. Although we have not evaluated an extensive list of acceptors (solvents or solutes), one would assume that a host of acceptors would suffice in the light-assisted process. Indeed it would be interesting to see if there is a correlation of rate with acceptor effectiveness and reduction potential since such would be expected if eq 6 is important in determining the overall rate.

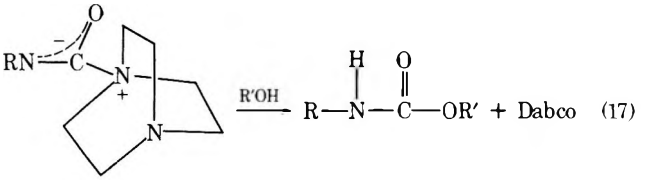
Varying the steric environment of the isocyanate is shown to hardly affect the measured second-order rate constant in the light-assisted reaction (Table II). This result differs from that obtained from the other catalyzed reactions studied. This result can be interpreted to confirm that, if an isocyanate species is involved in the rate-determining step, a very reactive isocyanate derivative is involved. This, of course, is not inconsistent with eq 7 or 11.

In the light-assisted reaction with ferrocene present, the observed trend (Table II) would tend to be evidence of a reaction between a ferrocene species and isocyanate in the rate-limiting step. Consistent with the required transfer of an electron from the ferrocenium ion to the isocyanate species, e.g., eq 16, one might expect steric factors to be important depending on the geometry required. It has been demonstrated[36] that ferrocene and its derivatives interact with acceptors (A) as shown in structure **1** and not as **2**. However, electron transfer may occur by approach of the isocyanate as pictured in **3**. Accordingly, the transfer would be much slower for isocyanates with large alkyl groups.



1 2 3

The effect on rate of varying the R group in alkyl isocyanates in alcohol–isocyanate reactions catalyzed by the common catalysts 1,4-diazabicyclo[2.2.2]octane (Dabco) and ferric acetylacetonate [Fe(acac)$_3$] (Table II) serves as a basis for comparison. The Dabco-catalyzed process is thought to involve rate-limiting reaction of **4** with the alcohol, eq 17.[13-15]

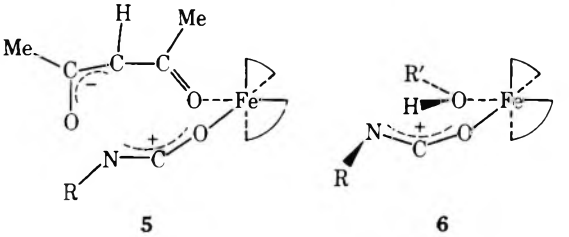


(17)

4

Obviously, the bulk of the Dabco–isocyanate complex should render the reaction more sensitive to steric factors and this is observed.

The catalytically active complex in the Fe(acac)$_3$-catalyzed reaction of isocyanates with alcohols is a 1:1 complex of the isocyanate and Fe(acac)$_3$.[37] This species most likely involves oxygen coordination to the metal as in **5**. If the alcohol also becomes coordinated to iron, e.g., as shown in **6**,[13,37] then the



5 6

alkyl group in RNCO is not in the pathway for an approaching reactant. The data in Table II show that the $Fe(acac)_3$-catalyzed reactions are not unusually sensitive to a change of R in RNCO.

With cyclohexyl isocyanate as the isocyanate reactant, we have investigated the sensitivity of the ferrocene-catalyzed light-assisted reaction to a change in steric bulk of the alcohol (Table III). The trend is quite impressive and reminiscent of the data obtained from similar studies of the thermal reaction of alcohols with phenyl isocyanate.[38] Interestingly, the fact that a trend is present conflicts with the conclusion suggested above that a ferrocenium species and isocyanate are involved in the rate-limiting step.

The effects on rate of varying the electronic and steric factors of the catalyst (Table IV) are significant. The mechanism involving eq 15 and 16 would be supported by electron-donating groups enhancing the rates (ferrocenium ion stabilizing)[39] and this is the case as alkyl substitution on the ferrocene ring provides a modest rate acceleration. Interestingly, acetyl 1,1′-dimethylferrocene is not effective in slowing the rate in agreement with complex formation with the electron-rich ring of the type depicted by structure 1 but somewhat contradictory to the involvement of structure 3.

While there is some evidence supporting the mechanistic equations presented above, the weight of the evidence is weak and unconvincing. For example, the nature of the induction period is puzzling and its origin is speculative. Although it could be used as evidence for a radical chain reaction, the requirement of ca. 30 min to build up steady-state concentrations of apparently reactive intermediates, e.g., $(CT)^*$ and $RNCO^{+}\cdot$, seems odd.

There are other observations that lead us to believe that the reaction is not a simple radical chain process as we have shown in our mechanistic equations above. Since the light-assisted reaction is first order both in alcohol and in isocyanate[40] one would assume that there is a rate-determining step involving these species in some form. Nevertheless, we have shown that the rate constant of the catalyzed reaction is sensitive to ferrocene concentration (Table I), to substituents on the ferrocene rings (Table IV), and to alcohol structure (Table III). Furthermore, the catalyzed light-assisted reaction and the light-assisted reaction show a difference in their sensitivity to changes in the steric environment of the isocyanate (Table II). Therefore, we cannot reconcile all of these facts with the radical chain mechanism discussed above or any other simple mechanism.

Mechanistic considerations aside, it seemed appropriate to consider the synthetic utility of the light-assisted reaction. Although many catalysts are known which accelerate alcohol–isocyanate reactions, light is unique among them. It has advantages since it leaves no catalyst residue. Its use also has disadvantages since the reactor must be of a design which allows the input of light. We have explored the use of this process for causing otherwise difficult reactions to occur with mixed results. Under thermal conditions, tertiary alcohols react very slowly with isocyanates and often give large quantities of elimination products.[21] However, we have found that *tert*-butyl alcohol reacts smoothly with cyclohexyl isocyanate in carbon tetrachloride in a Rayonet photochemical reactor. The yield of carbamate is nearly quantitative based on conversion. On the other hand, we were not able to convert triphenylmethanol to a carbamate by this procedure.

Experimental Section[41]

Materials. The isocyanates were purchased from Aldrich and were distilled and stored in a desiccator prior to use. Alcohols, except ethanol, were Fisher certified reagent grade and were distilled prior to use. Absolute ethanol was used as obtained from USI. Ferrocene, obtained from Ventron, was doubly sublimed, acetylferrocene[42] was sublimed, 1,1′-diacetylferrocene, obtained from Arapahoe, was recrystallized from petroleum ether (bp 60–90 °C), *n*-butylferrocene, obtained from Arapahoe, was distilled prior to use, and acetyl-1,1′-dimethylferrocene, obtained as a mixture of isomers from the Ethyl Corp., was used without further purification. Ferric acetylacetonate, obtained from Ventron, was recrystallized from a mixture of benzene and petroleum ether, and diazobicyclo[2.2.2]octane (Dabco) was used as obtained from Aldrich. Solvents were spectrograde and were used without further purification.

Kinetic Method. All reactions, except those specified, were run in a water-jacketed 10-cm quartz cell with the water temperature controlled to ±0.5 °C by circulating the water from a thermostated (Haake Model FJ) bath maintained at 50.0 ± 0.1 °C. The kinetics of the reactions were followed by observing the decrease in alcohol concentration in the near infrared (1.406 μ for 1-butanol) with a Cary 14 spectrophotometer.[43] A product peak also appeared in each case at about 1.480 μ and was recorded only as a measure of product formation. Measurements were made at convenient time intervals and the reactions were treated as second order for the purpose of calculating the rate constant. The reported rate constants were generally derived from treatment of all the data obtained for thermal reactions and the data for light-assisted reaction obtained after an initial induction period. Generally, data were obtained through the first reaction half-life.

The near-infrared light source in the Cary 14 spectrophotometer is a GE CPR tungsten filament projector lamp operating at 18 A and 6 V. The light passes through the sample prior to going through the monochromator. The wavelength of light passing through the sample was limited in certain cases by the use of Corning filters.

The lamp was turned on only for obtaining datum points for slow reactions unless otherwise stated. For fast reactions, the light remained on constantly. With the lamp constantly on, the sample temperature increases by 1–2 °C in some cases (i.e., $t_{1/2} \gtrsim 20$–30 min). Thus, the k values for the reactions run with the lamp constantly on are more appropriately at 51 ± 1 °C.

The standard solutions of alcohol and of isocyanate in the designated solvent were separately preheated to 50 °C in a thermostated bath prior to mixing in the reaction cell. After mixing, the solutions were degassed and the cells were back-filled with dry nitrogen since the rates of the photoreactions were found to be affected by the presence of oxygen.

Product Studies. In addition to verifying the appearance of a product band in the near infrared as mentioned above, at least one run with each catalyst system and alcohol–isocyanate combination was checked for product formation by an alternate method. These included the use of GLC to monitor the disappearance of isocyanate and the stripping of solvent to isolate product. Routinely, a trace amount of a yellow side product was observed in the photoassisted reactions. This material was not identified but it may be the result of isocyanate self-photoreactions.[28,29]

Samples of the carbamates were recrystallized for positive (NMR, melting point) identification. Yields were consistent only with nearly quantitative alcohol–isocyanate reaction for the alcohol or isocyanate converted. A preparative scale reaction is detailed below.

***tert*-Butyl *N*-Cyclohexylcarbamate. A. By Irradiation.** Fifty milliliters of 0.10 M cyclohexyl isocyanate in carbon tetrachloride was mixed with 5 mL of 1.0 M *tert*-butyl alcohol in carbon tetrachloride in a 5 × 35 cm single-necked, cylindrical quartz round-bottom flask. The solution was degassed and the flask back-filled with dry nitrogen. The solution was irradiated for 12 h in a Rayonet photochemical reactor equipped with 12 mercury lamps with predominant output at ca. 3120 Å. The solvent was stripped in vacuo to yield a slightly yellow crystalline product, mp 76.5–77.5 °C, 92% yield. Recrystallization from petroleum ether (bp 30–60 °C) gave colorless crystals, mp 78.5–79 °C (lit. 78[44] and 76–78 °C[45]). The IR and NMR were consistent with the assigned structure.

B. Without Irradiation. A vial containing a solution of the reactants in the same proportions as above was degassed, back-filled with nitrogen, and completely covered with black tape to exclude light. The vial was stored in the photochemical reactor during the reaction period of the solution in paragraph A above. After 12 h the vial was opened and the contents were analyzed. No reaction was apparent by GLC analysis.

In another trial a solution of 30 mL of 0.10 M cyclohexyl isocyanate in carbon tetrachloride and 3 mL of 1.0 M *tert*-butyl alcohol in carbon tetrachloride was prepared in a 100-mL round-bottom flask. The solution was degassed and the flask was back-filled with dry nitrogen. The flask was covered with aluminum foil and heated under nitrogen at 76 °C for 9 days. Analysis for unreacted alcohol after that period

revealed 84% conversion. The solvent was stripped off to give a solid, mp <74 °C, which was revealed to be impure carbamate.

Attempted Photoreaction of Triphenylmethanol with Cyclohexyl Isocyanate. A solution of 0.125 g of cyclohexyl isocyanate and 0.260 g of triphenylmethanol in 200 mL of carbon tetrachloride was prepared and irradiated as described in paragraph A of the reaction above. IR, NMR, and GLC analysis revealed negligible conversion of the alcohol or isocyanate.

Acknowledgments. We kindly acknowledge the technical assistance of Mr. Doug May and fruitful discussions with R. A. Abramovitch, H. C. Allen, R. Bruner, W. D. Stephens, and K. J. Thomas. We also thank C. C. Wamser and P. S. Engel for helpful suggestions.

Registry No.—*n*-Butyl alcohol, 71-36-3; *tert*-butyl alcohol, 75-65-0; *tert*-butyl *N*-cyclohexylcarbamate, 3712-40-1; cyclohexyl isocyanate, 3173-53-3; methyl isocyanate, 624-83-9; ethyl isocyanate, 109-90-0; isopropyl isocyanate, 1795-48-8; *tert*-butyl isocyanate, 1609-86-5; butyl *N*-methylcarbamate, 5461-30-3; butyl *N*-ethylcarbamate, 16246-07-4; butyl *N*-isopropylcarbamate, 18312-36-2; butyl *N*-*tert*-butylcarbamate, 22815-64-1; butyl *N*-cyclohexylcarbamate, 17671-80-5; methyl alcohol, 67-56-1; ethyl alcohol, 64-17-5; isopropyl alcohol, 67-63-0.

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(1) (a) Supported, in part, by The University of Alabama in Huntsville Research Grants Committee and the U.S. Army Missile Command, Redstone Arsenal, Ala., through Contract DAAH01-72-C-0662. (b) Presented in part at the First Chemical Congress of North America, Mexico City, Mexico, Dec 1975.
(2) (a) M.O. expresses her appreciation to the Universidad Nacional de Colombia, S.A., for a graduate fellowship which made her studies possible. (b) Abstracted, in part, from the M.S. Thesis of M.O., The University of Alabama in Huntsville, May 1973.
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(24) The thermal reaction is sometimes called the spontaneous reaction and is known to be quite complex; cf. ref 13–15. We have determined experimentally that product catalysis is not a significant factor in any of the observations reported here.
(25) This is assumed to be a photooxidation. From the intensity of the green color, it was assumed that the oxidation was facile. Accordingly, a rate decrease was evident and reproducible rate constants were not obtained.
(26) This reactor and the Hg lamps are available from Southern New England Ultraviolet Co.
(27) This filter allows only wavelengths longer than 650 nm to pass through the sample.
(28) The yellow color may be from isocyanate trimer or polymer; it is known, for example, that ferrocene catalyzes the polymerization of isocyanates in the presence of light, cf. Japanese Patent 049 221 (Feb 28, 1973); V. V. Korshak and L. A. Datskevich, *Plast. Massy*, 11 (1971).
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(39) Actually, this is oversimplified as electron-donating groups should indeed speed up reaction 10 yet the added stability of $FcH^{+}\cdot$ would cause eq 11 to be slowed. Thus if both eq 10 and 11 are important, eq 10 is the more sensitive to electronic effects.
(40) The kinetic dependence of rate on isocyanate concentration in the light-assisted reaction was shown by experiment.
(41) All melting points are uncorrected. NMR were recorded in $CDCl_3$ or CCl_4 with a Me_4Si internal standard on a Bruker HFX-10 90-MHz spectrometer. IR were recorded as KBr disks or as Nujol mulls on a Beckman IR-10 spectrophotometer. GLC was performed on a Varian A-90P chromatograph equipped with a thermal conductivity detector.
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Conformational Analysis of 1-Substituted 2,3-Epoxypropanes. A Carbon-13 Nuclear Magnetic Resonance Study

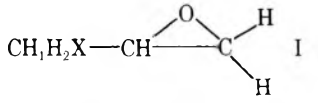
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Received October 18, 1976

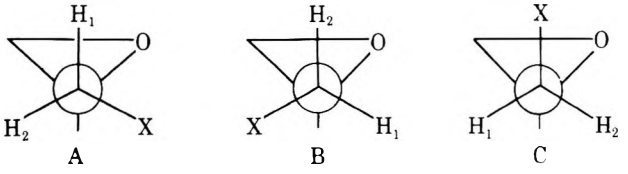
The ^{13}C NMR shift data for nine 1-substituted-2,3-epoxypropanes were obtained and analyzed. It was found that the γ shift was useful in evaluating rotational preferences of the CH_2X moiety. Comparison with 1-substituted propane data is also presented. Solvent effects on rotational populations were found to be unimportant.

The 1-substituted 2,3-epoxypropanes, of general formula I, pose an interesting problem in conformational analysis



I

because the barrier to rotation of the CH_2X moiety is expected to be small. The problem involving rotational populations can be more simply analyzed if all eclipsed conformations are ignored, leaving only rotamers A, B, and C to be considered.



A B C

The stereochemistry of the epoxypropanes, particularly the halogenated derivatives, has been previously investigated using electron diffraction spectroscopy,[1] ab initio calculations,[2] dipole moments,[3] and ^1H NMR spectroscopy.[3,4] However, the conclusions concerning the relative importance of conformations A, B, and C are not in complete agreement. For instance, Thomas[4b] concluded that rotamer C was the least populated state for X = fluorine, while Reynolds[3] reported that B is the minor conformer. The gas-phase diffraction data apparently indicate that for X = chlorine and bromine A and B are of equal importance,[1] while Reynolds states that A is the major conformation.[3] In view of this controversy, it was felt that ^{13}C NMR shift data would provide useful information such that the above situation could be clarified.

The application of ^{13}C NMR spectroscopy to the assessment of molecular structure and stereochemical assignment is well documented.[5] These applications are facilitated by empirical correlations of substituent effects generated from systematic studies of closely related compounds.[6] Of particular utility for obtaining stereochemical assignments is the induced upfield shift observed for the resonance of a carbon which is in a gauche disposition to another carbon or heteroatom at the γ position.[7] The "γ effect" is ascribed to induced polarization of the charge along the ^{13}C–H bond caused by nonbonded interactions, through space, such that the carbon in question becomes more electron rich.[8] Some caution must be exercised in this type of evaluation when the compound contains N, O, or F, since these heteroatoms also induce upfield shifts when γ-antiperiplanar to a particular carbon.[9] The proposed mechanism for this effect is amply described elsewhere.[9] Owing to the sensitivity of the carbon-13 chemical shift to this stereochemical probe, the importance of the rotamer populations for the 1-substituted 2,3-epoxypropanes can be evaluated.

Experimental Section

All of the compounds, except where X = I, were commercially available and of high purity. These compounds were used as received. The iodo derivative was prepared by literature procedures.[3] The carbon-13 magnetic resonance spectra were obtained in the Fourier transform mode on a JEOL FX-60 spectrometer system equipped with a Texas Instruments computer with a 24K memory. The spectra were obtained at an observing frequency of 15.03 MHz. Sample concentrations were ca. 10% w/v in the appropriate solvent in 10-mm o.d. sample tubes. General NMR spectral and instrumental parameters employed follow: internal deuterium lock to solvent; spectral width of 2500 Hz; a pulse width of 4 μs, corresponding to a 36° pulse angle; and a pulse repetition time of 1.8 s. All shifts reported are estimated to be accurate to ±0.05 ppm.

Results

The carbon-13 chemical shift data for the 1-substituted 2,3-epoxypropanes are given in Table I. The shift assignments were readily determined by examination of the proton-coupled spectra. The methylene carbons were readily differentiated by the size of the one-bond coupling constants, that for the ring methylene carbon being invariably larger than the substituted methylene carbon.[5] All of the one-bond coupling constants are given in Table II. Complete analysis of the coupled spectrum was not attempted because the splitting patterns were highly second order.

Discussion

Conformations A, B, and C can be described in terms of the γ interaction of the substitutent X with the oxygen and methylene carbon, respectively. (These interactions can be classified as either γ-syn, γ-syn′, or γ-anti.) For example, in rotamer A the substituent X is γ-syn to oxygen and γ-anti to the methylene moiety. Judging from molecular models and consideration of the angle and distance factors, which control the magnitude of the "γ effect",[8] the γ-syn′ interaction with the methylene should cause larger upfield shifts than the γ-syn interaction. Based upon the simplistic fundamentals of conformational analysis,[10] rotamer C (γ-syn′,γ-syn′) is expected to make the smallest relative contribution to the observed geometry of the epoxypropanes. However, this rotamer should prove important to the observed γ shift because of the large interaction of the substituent X and the methylene carbon. In the instance of X = OH rotamer C could be stabilized by hydrogen bonding and thus be the major conformation.[4d] In cyclopropylcarbinol, a similar compound, the γ-syn′,γ-syn′ conformation was found to present to about 25% of the rotamer population.[11] Conformations A and B are seen to be similar to the two dominant conformations of 1-substituted propanes. Thus it may prove instructive to compare the data obtained for the epoxypropanes with that found for 1-halopropanes. (See Table III.)

Preliminary comparison of the propane and epoxypropane data indicates that the α shift is similar for both systems while the β and γ shifts in the epoxypropanes are much smaller in magnitude. The reduction in the β shift is probably a consequence of "saturation" phenomena previously noted in other systems.[12] The smaller magnitude of the γ shift may also be associated with "saturation" effects; however, in those cases

Table I. Carbon-13 Chemical Shift and Substituent Shift Data for the 1-Substituted 2,3-Epoxypropanes[a]

Registry no.		C_1	C_2	C_3	α	β	γ
75-56-9	H	18.1[b]	47.9	48.1			
		(18.3)[c]	(47.7)	(48.1)	0.2	−0.2	0.0
503-09-3	F	83.6	49.8	43.6	65.5	1.9	−4.5
		(85.1)	(50.3)	(43.5)	(67.0	(2.4)	(−4.6)
106-89-8	Cl	45.2	51.3	46.9	27.1	3.4	−1.2
		(46.5)	(51.9)	(46.9)	(28.4)	(4.0)	(−1.2)
3132-64-7	Br	32.8	51.3	48.5	14.7	3.4	0.4
		(34.4)	(51.8)	(48.6)	(16.3)	(3.9)	(0.5)
624-57-7	I	5.2	52.3	50.5	−12.9	4.4	2.4
556-52-5	OH	62.4	52.6	44.4	44.3	4.7	−3.7
		(63.3)	(52.9)	(44.3)	(45.2)	(5.0)	(−3.8)
122-60-1	OPh	69.6	50.2	44.5	51.5	2.3	−3.6
		(70.6)	(50.6)	(44.3)	(52.5)	(2.7)	(−3.8)
106-88-7	CH_3	25.5	53.3	46.7	7.4	5.4	−1.4
4436-24-2	Ph	38.8	52.5	46.9	20.7	4.6	−1.2

[a] In parts per million from Me_4Si. [b] 10% w/v in $CDCl_3$. [c] 10% w/v in acetone-d_6.

Table II. One-Bond Carbon–Hydrogen Coupling Constants for the 1-Substituted 2,3-Epoxypropanes[a]

	H	F	Cl	Br	OH	OPh	CH_3
J_{11}	176.2	165.3	151.5	153.1	142.5	142.8	128.3
J_{22}	166.3	181.2	183.7	181.2	174.9	170.6	173.0
J_{33}	173.3	176.2	177.1	176.2	175.5	170.5	173.3

[a] ±0.3 Hz.

Table III. Carbon-13 Chemical Shift and Substituent Shift Data for 1-Substituted Propanes

	C_1	C_2	C_3	α	β	γ
H[a]	15.6	16.1	15.6			
Cl[b]	46.6	26.5	11.4	31.0	10.4	−4.2
Br[b]	35.7	26.8	13.2	20.1	10.7	−2.4
I[c]	9.2	26.8	15.3	−6.4	10.7	−0.3
OH[c]	64.0	26.3	10.5	48.4	10.2	−5.1
OCH_3[d]	75.5	24.1	11.0	59.9	8.0	−4.6
CH_3[d]	25.0	25.0	13.2	9.4	8.9	−2.4
Ph[b]	39.0	25.2	14.1	23.4	9.1	−1.5

[a] E. G. Paul and D. M. Grant, *J. Am. Chem. Soc.*, 86, 2984 (1964). Original data converted using $\delta_c^{C_6H_6}$ 128.7. [b] J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972. [c] L. F. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra", Wiley-Interscience, New York, N.Y., 1972. [d] T. Yonemoto, *J. Magn. Reson.*, 13, 153 (1974).

where there is a *sign* difference, changes in conformational populations are probably in operation.

As previously mentioned, the nature of the γ shift should give indication to the rotational preference of the CH_2X fragment. In the instance of the 1-halopropanes it has been noticed that as the halogen becomes larger the relative population of the gauche rotamer decreases. Concomitant with this change is a decrease of the "γ effect".

Unfortunately, no clear correlation of the "γ effect" and substituent size has been established. Since the propane data analysis may be crucial in determining the rotamer populations in the epoxypropanes, the conclusions concerning group size should be examined more closely. The propane shift data can be evaluated by consideration of the carbon-13 substituent effects obtained from low-temperature spectra of appropriate monosubstituted cyclohexanes.[13] When the substituent is in an axial disposition, corresponding to the gauche interaction in the propanes, the γ shifts for Cl, Br, and I are −6.6, −5.5, and −4.2 ppm, respectively. For the equatorial disposition, corresponding to the anti interaction, the γ shifts are −0.1, 1.4, and 2.3 ppm, respectively. Based on these data, the relative population of the gauche and anti conformation in the propanes can be obtained. In the case of chloropropane, a close to statistical population of conformers is observed (63% gauche). For bromopropane and iodopropane, the gauche population decreases to 55 and 35%, respectively. These calculations confirm the accepted results.

In the evaluation of the γ shifts observed for the halogenated epoxypropanes (Cl, Br, and I) an interesting, although not unpredictable, pattern emerges. As the substituent becomes larger the γ shift passes from an upfield to a downfield value. This observation appears quite analogous to the propane situation. The conclusion concerning the rotational preference of the CH_2X moiety structured on this result can be best explained if rotamer C makes a significant contribution to the γ shift. As the substituent becomes larger, rotamer A increases at the expense of rotamer C and probably to a small extent at the expense of rotamer B. For X = Cl, the relatively small "γ effect" indicates that A is the major conformation. Using the cyclohexane data, as was done for the simple propanes, a minimum value (saturation effects unimportant) for the sum of rotamers B and C is about 20%. Similarly, for X = Br a value of 15% is obtained. Judging from the magnitude of the γ shift, it appears that when X = CH_3 or phenyl, the rotational populations are similar to the chlorine derivative.

Table IV. Solvent Effects on the Carbon–Fluorine Coupling Constants in 1-Fluoro-2,3-epoxypropane.[a]

Solvent	J_{1F}	J_{2F}	J_{3F}
Benzene	169.6	23.8	8.6
Chloroform	170.3	23.8	8.6
Acetone	166.6	23.2	9.2
Acetonitrite	166.0	22.6	9.2

[a] ±0.6 Hz.

An analysis similar to that used above can not be used when X = F, OH, or OPh because these groups induce upfield shifts from both γ-syn and γ-anti orientations. The evaluation of the rotamer populations when X = F was made on the basis of solvent shifts and long-range ^{13}C–F coupling constants (Table IV).

It was indicated by Thomas (X = F) that as the solvent polarity is increased, the relative population of conformation A increases at the expense of B.[4b] This conclusion was based partly on the analysis of the proton chemical shifts. However, reevaluation of that data indicates an inconsistency in the reasoning. As the population of rotamers changes from B to A, the proton chemical shift of H_1 should move to higher field, owing to this proton being in the face of the oxirane ring for a greater fraction of the time.[14] This is observed. In concert, the proton chemical shift of H_2 should move to lower field. However, this does not occur, suggesting that the conclusions regarding solvent effects are not correct.

Solvent effects on the carbon-13 chemical shifts in many of the compounds were studied in order to ascertain if rotamer populations could be changed. Except for the C_1 carbon shifts, no substantial solvent effects were observed. These results indicate that the solvent plays at best a minor role in determining rotamer populations. Further insight regarding the role of solvent can be obtained from the ^3J ^{13}C–F coupling constant. The geometrical dependence upon the three-bond ^{13}C–F coupling constants can be seen in the low-temperature spectrum of fluorocyclohexane.[13] In the fluorine axial conformation (dihedral angle 60°) the $^3J_{CF}$ coupling constant is about 1 Hz, while in the fluorine equatorial conformation (dihedral angle 180°) the $^3J_{CF}$ is 11.5 Hz. A population change from conformation B to conformation A in polar solvents would require an increase in $^3J_{CF}$. Similarly, a change from rotamer B to C should increase $^3J_{CF}$ if a Karplus-like equation were to operate. From a consideration of the constancy of $^3J_{CF}$ with solvent polarity and the magnitude of the coupling constant value, it is concluded that the major conformation when X = F is A with C being the next most populated. This result is in complete agreement with Reynolds ^1H NMR investigation.

The remaining substituents to be considered are X = OH and X = OPh. From ^1H NMR studies it was concluded that for X = OH, the order of rotamer population is C > A > B.[4d] A major consideration in determining the relative populations of A and B was the ease of hydrogen bonding. Since hydrogen bonding cannot occur for X = OPh, the comparison of the γ shift should be informative. In the propane series, where hydrogen bonding is unimportant, the γ shift for X = OH and X = OCH_3 is similar in magnitude. The same observation applies to the epoxypropanes. Unless one assumes that the similar γ shifts in the epoxypropanes are fortuitous, an accident of the averaging of various conformations, a reasonable conclusion is that both X = OH and OPh reside in similar environments. It is concluded from the carbon-13 shift data that the order of conformational stability for X = OH and OPh is A > C > B.

Acknowledgment. I would like to thank the Robert A. Welch Foundation for their generous financial support, and Paul D. Bartlett for encouragement given.

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Cyclopropylcarbinyl Cation Chemistry and Antihomoaromaticity in the Cycloprop[2,3]inden-1-yl Cation System

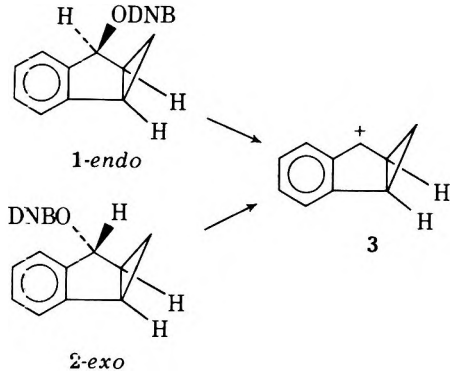
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Received November 3, 1976

A detailed investigation of the solvolytic behaviors of the *endo*- and *exo*-cycloprop[2,3]inden-1-yl 3,5-dinitrobenzoates in 80% aqueous acetone has been carried out. Both esters exhibited closely similar rates of hydrolysis and gave identical mixtures of *endo*- and *exo*-cycloprop[2,3]inden-1-ol products. From kinetic comparisons with model systems, it could be concluded that antihomoaromatic effects cause a rate retardation at 80 °C of approximately 10^3 for the cycloprop[2,3]inden-1-yl 3,5-dinitrobenzoate hydrolyses. Also, in accord with the postulation of antihomoaromatic interactions in the cycloprop[2,3]inden-1-yl activated complexes, the effects of methyl substituents on rate indicated that considerable charge is delocalized at C-10 but little at C-3.

For comparison with some of the results of previous work in our laboratory involving studies of stereochemical and electronic effects upon the nature and behavior of cyclopropylcarbinyl cations[1] and free radicals,[2] we have carried out a detailed investigation of the solvolytic behavior of the *endo*- and *exo*-cycloprop[2,3]inden-1-yl 3,5-dinitrobenzoates (**1** and **2**) in 80% aqueous acetone. Reactions of these compounds are also of considerable interest for their own sakes because the cycloprop[2,3]inden-1-yl cation intermediate **3** which should be formed in hydrolyses of **1** and **2** is formally a benzo analogue of the monohomocyclopentadienyl cation. Thus, we wished to investigate whether the rates of formation of **3** from **1** or **2**, and the further reactions of **3**, were influenced to a measurable



extent by antihomoaromatic effects.[3] Although some studies of potentially antihomoaromatic systems involving charge delocalization through cyclopropane rings have been reported,[4] most of these were not done under neutral solvolytic conditions

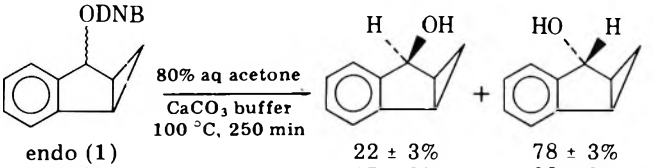
Results and Discussion

Unsubstituted Cycloprop[2,3]inden-1-yl Esters. Synthesis of the isomerically pure *endo*-cycloprop[2,3]inden-1-ol precursor of the 3,5-dinitrobenzoate **1** was accomplished in 41% yield directly through reaction of inden-1-ol[5] with methylene iodide and a zinc–copper couple.[6] Reduction of cycloprop[2,3]inden-1-one[7] with aluminum isopropoxide in 2-propanol[8] gave a 76% yield of a 73:27 exo–endo mixture of cycloprop[2,3]inden-1-ols, from which a 15% yield of the isomerically pure exo alcohol precursor of **2** could be isolated via spinning band distillation followed by fractional recrystallization.

The rates of hydrolysis of **1** and **2** were measured in 80% aqueous acetone both at 80.0 and at 100.0 °C, and the results are listed in Table I. Controls indicated that during the course of hydrolysis both dinitrobenzoates isomerized to small extents due to ion-pair return. Thus, after periods of time sufficient for 50% acid production, the initially pure endo dinitrobenzoate **1** had isomerized to a 75:25 mixture of **1** and **2**, and the initially pure exo dinitrobenzoate **2** had isomerized to a 90:10 mixture of **2** and **1**. However, these amounts of isomerization do not result in producing significant differences between the actual and measured solvolytic rate constants.

As is seen from the data in Table I, the hydrolytic reactivities of **1** and **2** are almost identical. This is in contrast to what we expected from examination of molecular models where it appeared that rate-retarding antihomoaromatic interactions resulting from charge delocalization along the 2,3-cyclopropane bond might be more important when the leaving group has an endo orientation. Apparently, the same types of stabilizing or destabilizing factors are encountered by both isomers owing to sufficient flexibility being present in their activated complexes such that similar types of C-1 orbital overlap with the cyclopropane and benzene ring orbitals can occur. However, from these kinetic results alone it is not possible to conclude if the activated complexes are actually affected by any antihomoaromatic destabilization.

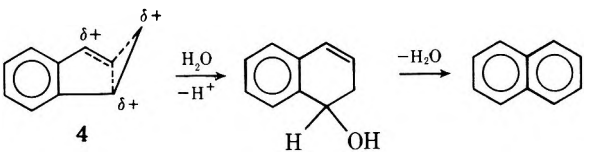
The hydrolysis products of **1** and **2** were determined in 80% aqueous acetone buffered with calcium carbonate at 100 °C after about 5 half-lives for acid production. As is shown below, both isomeric dinitrobenzoates yielded an essentially identical mixture of products within experimental error. Controls run on both the *endo*- and *exo*-cycloprop[2,3]inden-1-ols under



endo (1)	22 ± 3%	78 ± 3%
exo (2)	17 ± 3%	83 ± 3%

the solvolytic conditions indicated that less than 5% isomerization or rearrangement to other materials had occurred. Thus, it is clear that a common carbonium ion intermediate must be involved in product formation from both **1** and **2**.

It should be noted that the exclusive formation of products of solvent attack at C-1, and less than 1% of products such as 1,2-dihydronaphthalen-1-ol or naphthalene expected if solvent attack occurred at C-3, indicates that a delocalized species such as **4** is not important in product formation.



Analogous behavior was observed by Berson and co-workers[4b] in their studies of the methanolysis of the 2-deuterio-*endo*- and -*exo*-bicyclo[3.1.0]hex-3-en-2-yl trifluoroacetates. This

Table I. Rates of Hydrolysis of *endo*- and *exo*-Cycloprop[2,3]-inden-1-yl 3,5-Dinitrobenzoates (1 and 2) in 80% Aqueous Acetone

Compd	Concn, 10^3 M	Temp, °C	$10^5 k_1$, s^{-1}
1 (endo)	8.5	100.0	22.0 ± 0.4
	10.0	80.0	2.77 ± 0.09[a]
2 (exo)	6.5	100.0	25.7 ± 0.7
	4.2	80.0	3.29 ± 0.04[b]

[a] $\Delta H^{\ddagger}$ = 26.4 ± 0.7 kcal mol^{-1}, $\Delta S^{\ddagger}$ = −5.0 ± 2.1 eu. [b] $\Delta H^{\ddagger}$ = 26.2 ± 0.5 kcal mol^{-1}, $\Delta S^{\ddagger}$ = −5.2 ± 1.4 eu.

result thus provides support for an antiaromatic effect in the cycloprop[2,3]inden-1-yl cation. In the absence of an antihomoaromatic effect, considerable delocalization of positive charge at the C-3 position might have been predicted. For example, under conditions identical with those used in the present work, Friedrich and Saleh[1] found that the *endo*- and *exo*-2-bicyclo[3.1.0]hexyl 3,5-dinitrobenzoates yielded ca. 27% of cyclohexen-4-ol from solvent attack at C-5 of the 2-bicyclo[3.1.0]hexyl cation, which corresponds to solvent attack at C-3 in our system.

Kinetic Comparisons with Model Systems. In order to gather more information regarding whether there are destabilizing antihomoaromatic interactions in the cycloprop[2,3]-inden-1-yl activated complexes, and to assess the magnitude of the effects, the rates of hydrolysis of the cycloprop[2,3]-inden-1-yl 3,5-dinitrobenzoates (1 and 2) were compared with those of various model compounds. The structures of these are shown in Table III. The model compounds were selected so as to provide an estimate of the reactivities of 1 and 2 expected in the absence of antihomoaromatic effects.

Of the model compounds selected for these comparisons, the indan-1-yl (**5**), *endo*-5,5-dimethyl-3,4-benzobicyclo[4.1.0]hepten-1-yl (**6**), 4,4-dimethyl-2,3-benzocyclohexen-1-yl (**7**), and phenylcyclopropylcarbinyl (**8**) 3,5-dinitrobenzoates had to be prepared and their solvolytic kinetics studied for the present work. The geminal dimethyl groups were included in **6** and **7** for synthetic convenience, but should have no effects on their rate comparisons with the other systems. The procedures used for synthesis of compounds **5**–**8** are reported in the Experimental Section. For the other model compounds, suitable kinetic data for the *endo*-2-bicyclo[3.1.0]hexyl (**9**), *endo*-2-bicyclo[4.1.0]heptyl (**10**), 1-cyclopropylethyl (**11**), 1-phenylethyl (**12**), cyclopentyl, cyclohexyl, and isopropyl 3,5-dinitrobenzoates could be estimated from data already available in the literature.

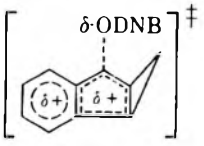
The rate constants for hydrolysis in 80% aqueous acetone of the model compounds **5**–**8** studied are given in Table II, and the relative rate comparisons of these with the *endo*-cycloprop[2,3]inden-1-yl and other model 3,5-dinitrobenzoates are given in Table III. It is apparent that the cycloprop[2,3]-inden-1-yl system (**1**) on the average is about 10^2 less reactive than either the 5,5-dimethyl-3,4-benzobicyclc[4.1.0]hepten-1-yl (**6**) or phenylcyclopropylcarbinyl (**8**) systems in which antihomoaromatic effects cannot be operating. Also, from comparison of the cumulative effects on rate of phenyl and cyclopropyl substitution in the five-ring, six-ring, and open-chain systems, one can estimate that on the average **1** is about 10^3 less reactive than would be predicted in the absence of antihomoaromatic effects. This rate retardation is not very large. However, it should be pointed out that in potentially antihomoaromatic systems possible molecular distortions which tend to minimize destabilizing cyclic antihomoaromatic orbital overlap would be energetically favorable.[3] Thus, the destabilizing effects might be very much larger in a fully delocalized antihomoaromatic system with normal geometry.

Table II. Rates of Hydrolysis of Some 3,5-Dinitrobenzoates in 80% Aqueous Acetone

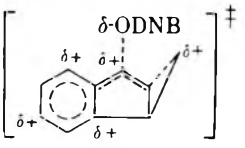
Compd	Concn, 10^3 M	Temp, °C	$10^5 k_1$, s^{-1}
5	7.8	100.0	30.6 ± 0.4
	11.5	80.0	4.35 ± 0.07[a]
6		80.0	(3.12 × 10^3)[b]
	2.4	39.9	6.10 ± 0.7
	2.7	20.0	5.80 ± 0.09
7	4.7	100.0	10.0 ± 0.5
	4.3	80.0	1.28 ± 0.07[c]
8		80.0	(2.38 × 10^2)[d]
	10.5	60.0	31.3 ± 0.8
	6.7	39.9	3.01 ± 0.03

[a] $\Delta H^{\ddagger}$ = 24.3 ± 0.4 kcal mol^{-1}, $\Delta S^{\ddagger}$ = −9.9 ± 1.1 eu. [b] $\Delta H^{\ddagger}$ = 21.0 ± 0.3 kcal mol^{-1}, $\Delta S^{\ddagger}$ = −6.2 ± 1.1 eu. [c] $\Delta H^{\ddagger}$ = 26.2 ± 1.4 kcal mol^{-1}, $\Delta S^{\ddagger}$ = −7.1 ± 4.1 eu. [d] $\Delta H^{\ddagger}$ = 23.5 ± 0.4 kcal mol^{-1}, $\Delta S^{\ddagger}$ = −4.2 ± 1.3 eu.

Methyl Substituent Effects. If molecular distortions which minimize cyclic antihomoaromatic orbital overlap are truly operating in the activated complexes for ionization of the cycloprop[2,3]inden-1-yl 3,5-dinitrobenzoates, then one might predict little delocalization of charge along the endocyclic cyclopropane bond from C-1 to C-3 as in structure **13**. However, charge delocalization along the exocyclic cyclopropane bond from C-1 to C-10 as in structure **14** would still



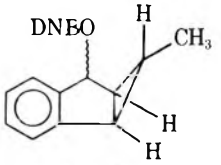
13



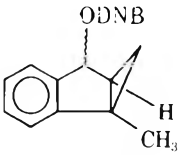
14

appear to be allowed. Thus, to assess these possibilities, a study of the effects on rate of introducing electron-releasing methyl substituents at C-3 and at C-10 in the cycloprop[2,3]-inden-1-yl system were initiated. The methyl group should have a rate-accelerating effect at a carbon where charge is delocalized, but have little or no effect at a carbon where there is no charge delocalization.

Synthesis of the isomerically pure alcohol precursor of the *anti*-10-methyl-*endo*-cycloprop[2,3]inden-1-yl 3,5-dinitrobenzoate (**15**) was accomplished in 34% yield via reaction of



(anti-endo) **15**
(anti-exo) **16**

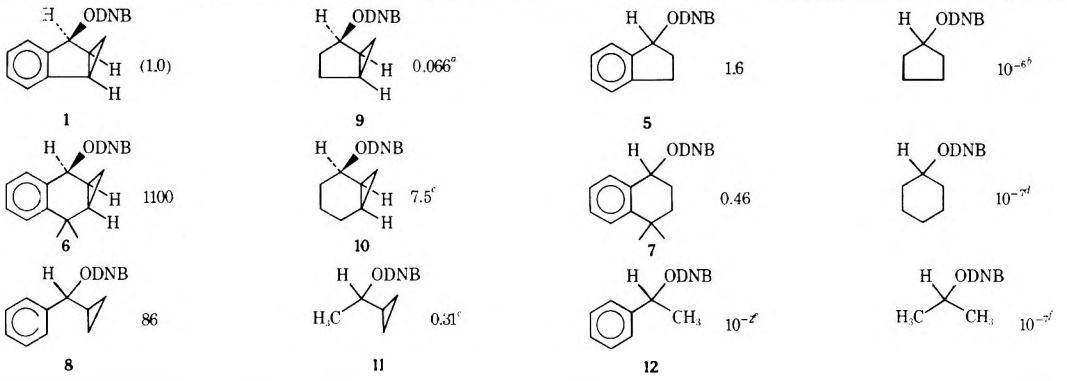


(endo) **17**
(exo) **18**

inden-1-ol[5] with ethylidine iodide[14] and ethylzinc iodide[15] in ether followed by fractional recrystallization of the initially obtained mixture of anti-endo and syn-endo-10 methyl alcohols. The anti-endo alcohol was isomerized using aluminum isopropoxide in 2-propanol to give a 66:34 mixture of anti-exo to anti-endo alcohols. Preparation of the 3,5-dinitrobenzoates from this alcohol mixture followed by fractional recrystallization gave a 54% yield of a 90% isomerically pure sample of the anti-exo 10-methyl 3,5-dinitrobenzoate **16**.

Preparation of the 3-methyl-*endo*-cycloprop[2,3]inden-1-ol precursor of **11** proved to be rather difficult as several reasonable approaches were found to be unsatisfactory. One of these approaches involving the anticipated conversion of 3-methylindan-1-one (**19**) to 3-methylinden-1-one (**20**), how-

Table III. Relative Rates of Hydrolysis of Some 3,5-Dinitrobenzoates in 80% Aqueous Acetone at 80 °C



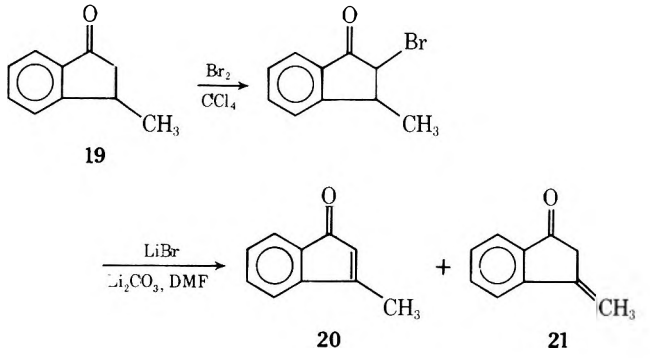
[a] Calculated from data in ref 1. [b] Estimated from data in ref 9. [c] Calculated from data in ref 10. [d] Estimated from data in ref 11. [e] Estimated from data in ref 12. [f] Estimated from data in ref 13.

Table IV. Rates of Hydrolysis of *anti*-10-Methyl- and 3-Methyl-*endo*- and -*exo*-cycloprop[2,3]inden-1-yl 3,5-Dinitrobenzoates in 80% Aqueous Acetone

Compd	Concn, 10^3 M	Temp, °C	$10^5 k_1$, s^{-1}
15 (*anti*-10-Me-*endo*)	6.0	80.0	47.3 ± 1.5
	5.1	60.0	5.72 ± 0.08[a]
16 (*anti*-10-Me-*exo*)	3.2	80.0	52.6 ± 0.7
	2.8	60.0	5.56 ± 0.09[b]
17 (3-Me-*endo*)	5.2	100.0	23.7 ± 1.0
	5.8	80.0	3.52 ± 0.06[c]
18 (3-Me-*exo*)	5.2	100.0	30.3 ± 0.5
	3.4	80.0	3.83 ± 0.08[d]

[a] $\Delta H^{\ddagger} = 24.0 \pm 0.6$ kcal mol^{-1}, $\Delta S^{\ddagger} = -6.1 \pm 1.8$ eu. [b] $\Delta H^{\ddagger} = 25.6 \pm 0.3$ kcal mol^{-1}, $\Delta S^{\ddagger} = -1.4 \pm 1.0$ eu. [c] $\Delta H^{\ddagger} = 24.3 \pm 0.8$ kcal mol^{-1}, $\Delta S^{\ddagger} = -10.4 \pm 2.3$ eu. [d] $\Delta H^{\ddagger} = 26.4 \pm 0.5$ kcal mol^{-1}, $\Delta S^{\ddagger} = -4.3 \pm 1.5$ eu.

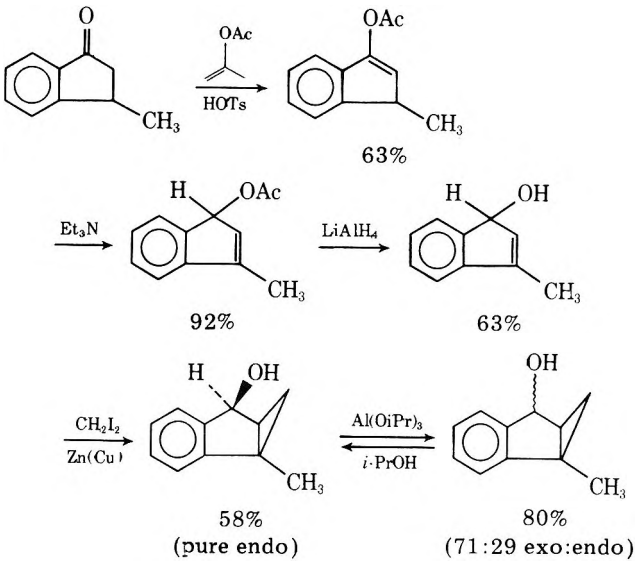
ever, was quite interesting in that it led to a 2:1 mixture of 3-methylinden-1-one (**20**) and 3-methyleneindan-1-one (**21**).



Treatment of this 2:1 mixture of ketones with pyridine at 103 °C for 10 h caused isomerization to a 1:2 mixture in which **21** predominated. The observed thermodynamic instability of the α,β-unsaturated **20** as compared to the β,γ-unsaturated **21** can be attributed to antiaromatic destabilization of **20**.

Thus, a synthesis of the alcohol precursor of **17** had to be devised which avoided **20** as an intermediate. The approach chosen, which proved successful, is shown in Scheme I. Synthesis of the exo alcohol precursor of **18** was then accomplished by aluminum isopropoxide in 2-propanol equilibration with the endo alcohol. Preparation of the 3,5-dinitrobenzoates of the resulting 71:29 exo–endo mixture of 3-methylcycloprop[2,3]inden-1-ols followed by fractional recrystallization provided an isomerically pure sample of the *exo*-3,5-dinitrobenzoate **18**.

Scheme I



The results of studies on the rates of hydrolysis of the *anti*-10-methyl- and 3-methyl-*endo*- and -*exo*-cycloprop[2,3]inden-1-yl 3,5-dinitrobenzoates **15**, **16**, **17**, and **18** are given in Table IV. Controls run under the solvolytic conditions showed that none of these dinitrobenzoates rearranged to more than about 10% of isomeric dinitrobenzoates after 1 half-life for acid production. From the data in Table IV, it is seen that both in the *anti*-10-methyl and 3-methyl systems the rates of reaction are essentially independent of leaving group geometry. Similar behavior was observed in the non-methyl-substituted systems. Also, from comparison of the data in Tables I and IV, it is seen that substitution of a methyl group at C-10 of the cycloprop[2,3]inden-1-yl 3,5-dinitrobenzoate has an accelerating effect of about 15 for both the endo and exo isomers. However, substitution of a methyl group at C-3 has virtually no effect on rate.

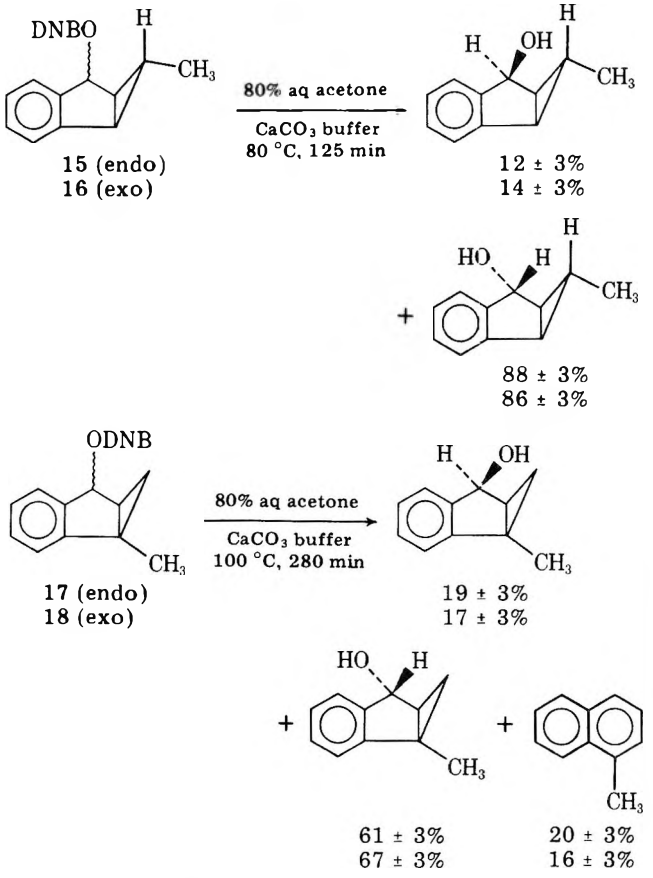
By comparison to the above results, previous work of ours[1] showed that substitution of a methyl group at C-5 in the simple 2-bicyclo[3.1.0]hexyl 3,5-dinitrobenzoates produced rate accelerations of about 20 in 80% aqueous acetone at 100 °C for both the endo and exo isomers. This corresponds to substitution at C-3 in the cycloprop[2,3]inden-1-yl system.

Thus, one can conclude from these methyl substituent effect studies that there can be little or no delocalization of positive charge at C-3 in the cycloprop[2,3]inden-1-yl activated complexes. However, there is considerable charge delocalization at C-10. These solvolytic data agree with the results of the recently reported NMR studies of Olah and co-

workers[4c] of the cycloprop[2,3]inden-1-yl cation generated from cycloprop[2,3]inden-1-ol in either FSO_3H–SO_2ClF or FSO_3H–SbF_5. Under both our and Olah's conditions it must be concluded that the cycloprop[2,3]inden-1-yl cation is not a fully delocalized antiaromatic species, but that potential antiaromaticity does in some manner prevent otherwise normal charge delocalization to C-3.

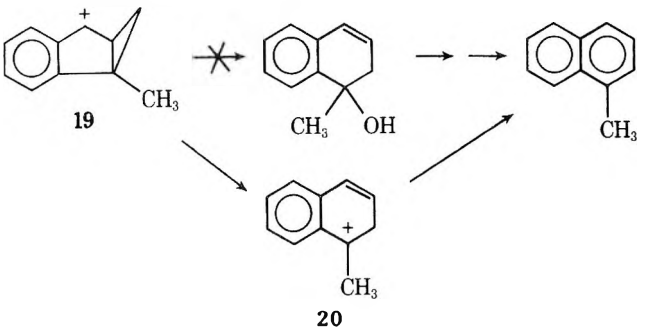
Although the kinetic results from the hydrolysis of the 3-methyl- and *anti*-10-methylcycloprop[2,3]inden-1-yl 3,5-dinitrobenzoates were readily explainable, upon examining their hydrolysis products some possible ambiguities were observed. These data are shown in Scheme II. In both cases

Scheme II



the major products were unrearranged isomeric cycloprop[2,3]inden-1-ols. Also, within experimental error identical product mixtures were obtained starting with either the endo or the exo dinitrobenzoates. This behavior is similar to that observed with the non-methyl-substituted esters **1** and **2**. However, from the 3-methylcycloprop[2,3]inden-1-yl 3,5-dinitrobenzoates (**17** and **18**), significant amounts of 1-methylnaphthalene are formed. On the other hand, no 3-hydroxymethylindene is observed from hydrolyses of the *anti*-10-methylcycloprop[2,3]inden-1-yl 3,5-dinitrobenzoates (**15** and **16**). Controls run on the 3-methyl- and *anti*-10-methyl-*endo*-cycloprop[2,3]inden-1-ols under the solvolytic conditions indicated that these underwent less than 5% isomerization or other reactions.

The observation that no 3-hydroxymethylindene is observed from hydrolysis of **15** and **16** is not surprising considering the fact that the C-1 position where major solvent attack occurs is both secondary and benzylic, while even with a methyl substituent the C-10 position is simple secondary. However, formation of 1-methylnaphthalene from **17** and **18** was unexpected and would appear to contradict the interpretation of the results of the kinetic studies that little positive charge is delocalized at the C-3 position in the activated complexes for ionization of **17** and **18**. On the other hand, a possible explanation for the formation of 1-methylnaphthalene may be that it does not result directly via solvent attack on a delocalized version of the initially formed cyclopropylcarbinyl cation intermediate **19**, but from another carbonium ion species **20** formed by subsequent rearrange-



ment. This species, being both benzylic and tertiary, and having less ring strain, should be much more stable than **19**. Reflection of this stability in a lower energy barrier for the rearrangement process of **19** to **20** as compared to the corresponding processes in the unsubstituted and *anti*-10-methyl substituted systems provides an explanation for the lack of formation of naphthalene products from hydrolyses of the latter systems.

Experimental Section

General. Melting points and boiling points are uncorrected. Infrared spectra were recorded with a Perkin-Elmer Model 237B grating spectrophotometer. NMR spectra were obtained on a Varian A-60A instrument with chemical shifts measured in parts per million (δ) downfield from Me_4Si internal standard. GLC analyses and separations were carried out using a Varian Series 1400 instrument. Mass spectra were obtained on a CEC 21-104 single beam mass spectrometer by John Voth. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

***endo*-Cycloprop[2,3]inden-1-ol.** Employing the LeGoff[6] modification of the Simmons–Smith reaction, 24 g (0.37 mol) of 30 mesh zinc–copper couple, 103 g (0.38 mol) of methylene iodide, and 20 g (0.15 mol) of inden-1-ol[5] in 250 mL of ether was stirred at reflux for 10 h. After addition of ammonium chloride and extraction with ether, the combined ether solution was washed with saturated sodium chloride solution and dried over magnesium sulfate. Removal of the ether followed by vacuum distillation gave 16.7 g of cycloprop[2,3]-inden-1-ol, bp 100–103 °C (0.6 mm). Recrystallization of the white solid yielded 9.0 g (41%) of white needles of cycloprop[2,3]inden-1-ol: mp 86.5–87.5 °C; NMR ($CDCl_3$) δ 0.5 (m, 1 H, cyclopropyl), 0.9 (m, 1 H, cyclopropyl), 1.9 (m, 1 H, cyclopropyl), 2.3 (m, 1 H, cyclopropyl), 2.8 (s, 1 H, CHOH), 5.5 (d, J = 6 Hz, 1 H, CHOH), and 7.15 ppm (m, 4 H, aromatic); IR (KBr) 3325 (O–H) and 1015 cm^{-1} (C–O); mass spectrum (70 eV) *m/e* (rel intensity) 146 (20), 145 (38), 131 (48), 128 (64), 117 (100), 116 (39), 115 (50).

Anal. Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.90. Found: C, 81.99; H, 7.05.

***endo*-Cycloprop[2,3]inden-1-yl 3,5-Dinitrobenzoate.** This was prepared by treatment of 1.8 g (0.012 mol) of cycloprop[2,3]inden-1-ol with 3.8 g (0.017 mol) of 3,5-dinitrobenzoyl chloride in pyridine at 0 °C for 2 h. Workup was followed by recrystallization of the solid to yield 1.6 g (38%) of *endo*-cycloprop[2,3]inden-1-yl 3,5-dinitrobenzoate: mp 150–152 °C; NMR ($CDCl_3$) δ 1.0 (m, 2 H, cyclopropyl), 2.5 (m, 2 H, cyclopropyl), 6.8 (d, J = 6 Hz, 1 H, CHODNB), 7.4 (m, 4 H, aromatic), and 9.3 ppm (s, 3 H, aromatic); IR (KBr) 1695 (C=O) and 1235 cm^{-1} (C–O).

Anal. Calcd for $C_{17}H_{12}N_2O_6$: C, 60.00; H, 3.55. Found: C, 60.17; H, 3.70.

Cycloprop[2,3]inden-1-one. This material was prepared through the reaction of aluminum chloride with 46.1 g (0.26 mol) of 2-phenylcyclopropanecarboxylic acid chloride[7] in 225 mL of 1,2-dichloroethane at 0 °C for 1 h, 25 °C for 10 h, and 65 °C for 1.5 h. After workup, the mixture was extracted with ether and the ether solution was washed with saturated sodium chloride, then dried over anhydrous magnesium sulfate. Following solvent removal, vacuum distillation yielded 24.5 g (65%) of cycloprop[2,3]inden-1-one: bp 103–105 °C (0.7

mm); n^{23}D 1.5870 [lit.[7] bp 68 °C (0.06 mm)]; NMR (CCl_4) δ 1.1 (m, 1 H, cyclopropyl), 1.5 (m, 1 H, cyclopropyl), 2.2 (m, 1 H, cyclopropyl), 2.8 (m, 1 H, cyclopropyl), and 7.2 ppm (m, 4 H, aromatic).

***exo*-Cycloprop[2,3]inden-1-ol.** Following the method of Eliel,[8] 14.4 g (0.10 mol) of cycloprop[2,3]inden-1-one was stirred with aluminum isopropoxide in isopropyl alcohol for 5 h. The usual workup was followed by vacuum distillation affording 12.4 g (85%) of a light yellow oil, bp 88–91 °C (0.1 mm), which was a 73:27 exo–endo mixture. Spinning band distillation of 7.11 g followed by recrystallization from 20 ml of 1:1 ether–petroleum ether (bp 30–60 °C) yielded 1.24 g (15%) of *exo*-cycloprop[2,3]inden-1-ol: mp 67–68.5 °C; NMR (CCl_4) δ 0.0 (m, 1 H, cyclopropyl), 1.1 (m, 1 H, cyclopropyl), 2.0 (m, 1 H, cyclopropyl), 2.1 (bs, 1 H, OH), 2.4 (m, 1 H, cyclopropyl), 4.8 (bs, 1 H, CHOH), and 7.2 ppm (m, 4 H, aromatic); IR (mineral oil) 3220 cm^{-1} (O–H); mass spectrum (70 eV) *m/e* (rel intensity) 146 (18), 145 (37), 131 (45), 128 (38), 127 (23), 117 (100), 116 (35), 115 (44).

Anal. Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.89. Found: C, 82.10; H, 6.80.

***exo*-Cycloprop[2,3]inden-1-yl 3,5-Dinitrobenzoate.** This was prepared in the usual manner by the reaction of 0.65 g (0.0045 mol) of exo-cycloprop[2,3]inden-1-ol and 1.4 g (0.0062 mol) of 3,5-dinitrobenzoyl chloride in pyridine at 0 °C. Workup and recrystallization of the dinitrobenzoate from ether produced 0.63 g (41%) of *exo*-cycloprop[2,3]inden-1-yl 3,5-dinitrobenzoate: mp 113–115 °C; NMR ($CDCl_3$) δ 0.3 (m, 1 H, cyclopropyl), 1.4 (m, 1 H, cyclopropyl), 2.8 (m, 2 H, cyclopropyl), 6.4 (d, *J* = 2 Hz, 1 H, CHODNB), 7.4 (m, 4 H, aromatic), and 9.2 ppm (bs, 3 H, aromatic); IR (mineral oil) 1725 cm^{-1} (C=O).

Anal. Calcd for $C_{17}H_{12}N_2O_6$: C, 60.00; H, 3.55. Found: C, 60.13; H, 3.55.

Indan-1-ol. Reduction of 9.1 g (0.069 mol) of indan-1-one with 1.22 g (0.032 mol) of lithium aluminum hydride in ether followed by workup, distillation, and recrystallization from petroleum ether (bp 30–60 °C) produced 4.1 g (68%) of white needles of indan-1-ol: mp 53–55 °C (lit.[17] mp 53–54 °C); NMR (CCl_4) δ 2.0 (m, 2 H, $CHOHCH_2$), 2.7 (m, 2 H, CH_2 aromatic), 3.8 (s, 1 H, OH), 4.9 (t, *J* = 6 Hz, 1 H, CHOH), and 7.1 ppm (m, 4 H, aromatic).

Indan-1-yl 3,5-Dinitrobenzoate. In the usual manner 2.05 g (0.015 mol) of indan-1-ol was treated with 4.4 g (0.019 mol) of 3,5-dinitrobenzoyl chloride in pyridine at 0 °C for 2 h. Workup and recrystallization from acetone–petroleum ether (bp 30–60 °C) yielded 4.2 g (85%) of indan-1-yl 3,5-dinitrobenzoate: mp 115.5–119 °C (lit.[18] mp 119–120 °C): NMR ($CDCl_3$) δ 2.6 (m, 2 H, $CHODNBCH_2$), 3.2 (m, 2 H, CH_2 aromatic), 6.6 (t, *J* = 5 Hz, 1 H, CHODNB), 7.4 (m, 4 H, aromatic), and 9.1 ppm (m, 3 H, aromatic).

4,4-Dimethyl-1,4-dihydronaphthalen-1-one. This was prepared from 4,4-dimethyl-2-bromo-1-tetralone[19] by the method of Corey.[20] A mixture of 17.1 g (0.068 mol) of 2-bromo-4,4-dimethyl-1-tetralone, 14.2 g (0.16 mol) of lithium bromide, and 20.0 g (0.27 mol) of lithium carbonate in dry dimethylformamide was heated at 120–125 °C for 60 min. The mixture was poured into ice and extracted with ether. The ethereal solution was washed with saturated sodium chloride and dried over anhydrous magnesium sulfate. Removal of the ether followed by recrystallization from mixed hexanes yielded 9.85 g (84%) of 4,4-dimethyl-1,4-dihydronaphthalen-1-one: mp 69–70 °C (lit.[19] mp 69.5–70.5 °C); NMR (CCl_4) δ 1.5 (s, 6 H, CH_3 and CH_3), 6.3 (d, *J* = 10 Hz, 1 H, CH=CH), 6.7 (d, *J* = 10 Hz, 1 H, CHC=O), 7.4 (m, 3 H, aromatic), and 8.0 (m, 1 H, aromatic).

5,5-Dimethylbenzobicyclo[4.1.0]hepten-1-one. This material was prepared from 4,4-dimethyl-1,4-dihydronaphthalen-1-one employing the cyclopropanation procedure of Corey.[21] In a flame-dried flask under nitrogen, 1.31 g (0.030 mol) of sodium hydride and 6.9 g (0.030 mol) of trimethylsulfoxonium iodide were combined and dimethyl sulfoxide was added. After 20 min of stirring, 5.2 g (0.030 mol) of 4,4-dimethyl-1,4-dihydronaphthalen-1-one was added. Workup followed by distillation afforded 5.3 g (95%) of 5,5-dimethylbenzobicyclo[4.1.0]hepten-1-one as a colorless liquid: bp 106.5–107.5 °C (1 mm); n^{23}D 1.5637; NMR (CCl_4) δ 0.6 (m, 1 H, cyclopropyl), 1.2 (m, 4 H, CH_3 and cyclopropyl), 1.5 (m, 4 H, CH_3 and cyclopropyl), 2.0 (m, 1 H, cyclopropyl), 7.1 (m, 3 H, aromatic), and 7.4 ppm (m, 1 H, aromatic); IR (neat) 1750 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 186 (26), 172 (14), 171 (100), 152 (12), 146 (18), 144 (19), 143 (29), 131 (22), 129 (12), 128 (36), 127 (11), and 115 (25).

5,5-Dimethylbenzobicyclo[4.1.0]hepten-1-ol. Fourteen milliliters of 0.55 M potassium tri-*sec*-butylborohydride in tetrahydrofuran was utilized to reduce 1.17 g (0.0063 mol) of 5,5-dimethylbenzobicyclo[4.1.0]hepten-1-one at 0 °C. Oxidative workup followed by vacuum distillation yielded 1.02 g (87%) of 5,5-dimethylbenzobicyclo[4.1.0]-hepten-1-ol (greater than 90% endo): bp 104–105 °C (1.0 mm); NMR (CCl_4) δ 0.1 (m, 2 H cyclopropyl), 1.3 (m, 4 H, CH_3 and cyclopropyl), 1.6 (m, 4 H, CH_3 and cyclopropyl), 3.7 (bs, 1 H, OH), 5.1 (bs, 1 H, CHOH), 7.1 (m, 3 H, aromatic), and 7.5 (m, 1 H, aromatic).

5,5-Dimethyl-*endo*-benzobicyclo[4.1.0]hepten-1-yl 3,5-Dinitrobenzoate. The usual procedure involving the reaction of 0.63 g (0.0034 mol) of 5,5-dimethylbenzobicyclo[4.1.0]hepten-1-ol with 1.1 g (0.0048 mol) of 3,5-dinitrobenzoyl chloride in pyridine was used. Workup and recrystallization gave 0.45 g (29%) of 5,5-dimethyl-*endo*-benzobicyclo[4.1.0]hepten-1-yl 3,5-dinitrobenzoate: mp 88–90 °C; NMR ($CDCl_3$) δ 0.5 (m, 2 H, cyclopropyl), 1.3 (s, 3 H, CH_3), 1.5 (s, 4 H, CH_3 and cyclopropyl) 1.8 (m, 1 H, cyclopropyl), 6.7 (d, *J* = 5 Hz, 1 H, CHODNB), 7.3 (m, 4 H, aromatic), and 9.3 ppm (s, 3 H, aromatic); IR (mineral oil) 1725 cm^{-1} (C=O).

Anal. Calcd for $C_{20}H_{18}N_2O_6$: C, 62.82; H, 4.74. Found: C, 62.62; H, 4.78.

4,4-Dimethyl-1-tetralol. This was prepared in 75% yield by lithium aluminum hydride reduction of 4,4-dimethyl-1-tetralone: bp 107–109 °C (1.9 mm); n^{22}D 1.5465 [lit.[22] bp 102–104 °C (15 mm)]; NMR (CCl_4) δ 1.2 (s, 3 H, CH_3), 1.2 (s, 3 H, CH_3), 1.7 (m, 4 H, CH_2CH_2), 3.5 (bs, 1 H, OH), 4.3 (bs, 1 H, CHOH), and 7.1 ppm (m, 4 H, aromatic).

4,4-Dimethyl-1-tetralyl 3,5-Dinitrobenzoate. A mixture of 0.60 g (0.0035 mol) of 4,4-dimethyl-1-tetralol and 1.1 g (0.0048 mol) of 3,5-dinitrobenzoyl chloride in pyridine was stirred at 0 °C. Workup and recrystallization from 1:10 benzene–mixed hexanes produced 0.45 g (36%) of 4,4-dimethyl-1-tetralyl 3,5-dinitrobenzoate: mp 123–125 °C; NMR ($CDCl_3$) δ 1.3 (s, 3 H, CH_3), 1.4 (s, 3 H, CH_3) 2.1 (m, 4 H, CH_2CH_2), 6.2 (t, *J* = 4 Hz, 1 H, CHODNB), 7.2 (m, 4 H, aromatic), and 9.0 ppm (s, 3 H, aromatic).

Anal. Calcd for $C_{19}H_{18}N_2O_6$: C, 61.62; H, 4.90. Found: C, 61.43; H, 4.90.

Phenylcyclopropylcarbinol. A sample of 5.30 g (0.036 mol) of phenyl cyclopropyl ketone was reduced with lithium aluminum hydride in ether. Workup by pouring into 100 ml of ice-cold 1 M sulfuric acid was followed by ether extraction and drying. Subsequent vacuum distillation yielded 4.81 g (89%) of phenylcyclopropylcarbinol: bp 78–79 °C (1.0 mm); n^{22}D 1.5405 [lit.[23] bp 121 °C (12 mm); n^{25}D 1.5390]; NMR (CCl_4) δ 0.2 (m, 4 H, cyclopropyl), 0.9 (m, 1 H, cyclopropyl), 3.4 (bs, 1 H, OH), 4.8 (d, *J* = 8 Hz, CHOH), and 7.1 ppm (s, 5 H, aromatic).

Phenylcyclopropylcarbinyl 3,5-Dinitrobenzoate. Through the reaction of 1.62 g (0.010 mol) of phenylcyclopropylcarbinol and 3.0 g (0.013 mol) of 3,5-dinitrobenzoyl chloride in pyridine at 0 °C, this dinitrobenzoate was prepared. The usual workup followed by recrystallization from 10:1 methylcyclohexane–chloroform yielded 2.10 g (64%) of phenylcyclopropylcarbinyl 3,5-dinitrobenzoate: mp 92–93 °C; NMR ($CDCl_3$) δ 0.7 (m 4 H, cyclopropyl), 1.6 (m, 1 H, cyclopropyl), 5.5 (d, *J* = 9 Hz, 1 H, CHODNB), 7.4 (m, 5 H, aromatic), and 9.2 ppm (m, 3 H, aromatic).

Ethylidene Iodide. Following the method of Letsinger and Kammeyer,[14] 15.9 g (0.16 mol) of ethylidene chloride was refluxed with 70.7 g (0.45 mol) of ethyl iodide and 0.3 g of aluminum chloride. Workup and vacuum distillation afforded 30.7 g (67%) of ethylidene iodide: bp 70–72 °C (17 mm); n^{22}D 1.6703 [lit.[14] bp 75–76 °C (25 mm)]; NMR (neat) δ 3.7 (d, *J* = 7 Hz, 3 H, CH_3) and 6.0 ppm (q, *J* = 7 Hz, 1 H, CHI_2).

***anti*-10-Methyl-*endo*-cycloprop[2,3]inden-1-ol.** The procedure of Krug and Tang[15] was followed to prepare ethylzinc iodide. After the reaction of 23.4 g (0.070 mol) of cupric citrate monohydrate with 132.0 g (2.0 mol) of powdered zinc, 80 mL (1.0 mol) of ethyl iodide was added. After refluxing in ether, 215 mL of 3.56 M ethylzinc iodide was obtained: NMR (ether) δ 0.4 (m, 2 H, CH_2) and 1.1 ppm (m, 3 H, CH_3). Under a nitrogen atmosphere 5.35 g (0.040 mol) of inden-1-ol was added to 45 mL of 3.56 M ethylzinc iodide. Then 23.0 g (0.081 mol) of ethylidene iodide was added dropwise and refluxing was continued for 12 h. Workup with ammonium chloride and extraction with ether was followed by washing with saturated sodium bicarbonate and saturated sodium chloride solutions and drying over anhydrous magnesium sulfate. Distillation produced 5.2 g of impure *anti*-10-methyl-*endo*-cycloprop[2,3]inden-1-ol, bp 81–92 °C (0.7 mm). Recrystallization from 100 mL of 3:1 pentane–ether afforded 2.2 g (34%) of *anti*-10-methyl-*endo*-cycloprop[2,3]inden-1-ol, mp 82–85 °C. Further recrystallization from pentane gave white crystals of *anti*-10-methyl-*endo*-cycloprop[2,3]inden-1-ol: mp 86.5–87.0 °C; NMR (CCl_4) δ 0.8 (m, 1 H, cyclopropyl), 1.0 (d, *J* = 5 Hz, 3 H, CH_3), 1.6 (m, 1 H, cyclopropyl), 2.0 (m, 1 H, cyclopropyl), 2.4 (d, *J* = 7 Hz, 1 H, OH), 5.5 (m, 1 H, CHOH), and 7.2 ppm (bs, 4 H, aromatic); IR (mineral oil) 3350 (O–H) and 3250 cm^{-1} (O–H); mass spectrum (70 eV) *m/e* (rel intensity) 160 (29), 145 (100), 142 (32), 141 (31), 131 (80), 128 (27), 127 (21), 117 (27), 116 (44), 115 (61), and 91 (20).

Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.61; H, 7.63.

***anti*-10-Methyl-*endo*-cycloprop[2,3]inden-1-yl 3,5-Dinitrobenzoate.** Employing the usual procedure, 1.0 g (0.0063 mol) of *anti*-10-methyl-*endo*-cycloprop[2,3]inden-1-ol was treated with 1.7 g (0.0075 mol) of 3,5-dinitrobenzoyl chloride in pyridine at 0 °C. Workup and recrystallization from 1:1 chloroform–pentane produced 0.95 g (42%) of *anti*-10-methyl-*endo*-cycloprop[2,3]inden-1-yl 3,5-dinitrobenzoate: mp 148–149 °C; NMR ($CDCl_3$) δ 1.1 (bs, 4 H, $CHCH_3$), 2.2 (m, 2 H, cyclopropyl), 6.6 (d, J = 6 Hz, 1 H, CHODNB), 7.1 (bs, 4 H, aromatic), and 9.0 ppm (s, 3H, arom); IR (mineral oil) 1710 (C=O) and 1355 cm^{-1} (C–O).

Anal. Calcd for $C_{18}H_{14}N_2O_6$: C, 61.02; H, 3.98. Found: C, 61.11; H, 4.01.

***anti*-10-Methyl-*exo*- and -*endo*-cycloprop[2,3]inden-1-ols.** This material was prepared using the method of Eliel.[8] A mixture of 1.25 g (0.0078 mol) of *anti*-10-methyl-*endo*-cycloprop[2,3]inden-1-ol, 2.6 g (0.0127 mol) of aluminum isopropoxide, 50 mg of acetone, and 75 mL of isopropyl alcohol was heated at reflux for 148 h. Then the mixture was cooled, treated with aqueous sodium hydroxide, and extracted with ether. The ethereal solution was dried over anhydrous magnesium sulfate and, after removal of the solvent, distillation produced 1.12 g of a 1:1 endo–exo mixture of *anti*-10-methylcycloprop[2,3]inden-1-ols: bp 108–110 °C (3.4 mm); NMR (CCl_4) δ 0.3 [m, 0.5 H, cyclopropyl (exo isomer)], 1.0 [m, 3.5 H, CH_3 and cyclopropyl (endo isomer)], 1.6 (m, 1 H, cyclopropyl), 2.0 (m, 1 H, cyclopropyl), 3.2 (bs, 1 H, OH), 4.6 [bs, 0.5 H, CHOH (exo isomer)], 5.3 [d, J = 6 Hz, 0.5 H, CHOH (endo isomer)], and 7.1 ppm (m, 4 H, aromatic). Also, when the above mixture was recrystallized from pentane part of the endo isomer was removed to leave 0.62 g (50%) of oil which was a 66:34 exo–endo mixture of *anti*-10-methylcycloprop[2,3]inden-1-ols.

***anti*-10-methyl-*exo*- and -*endo*-cycloprop[2,3]inden-1-yl 3,5-Dinitrobenzoates.** This mixture of dinitrobenzoates was prepared in the usual manner from a 66:34 exo–endo mixture of *anti*-10-methylcycloprop[2,3]inden-1-ols. A sample of 0.62 g (0.0039 mol) of the mixture of alcohols was treated with 1.1 g (0.0048 mol) of 3,5-dinitrobenzoyl chloride in pyridine. Workup and recrystallization from 10:1 pentane–chloroform yielded 0.74 g (54%) of an 87:13 exo–endo mixture of *anti*-10-methylcycloprop[2,3]inden-1-yl 3,5-dinitrobenzoates: NMR ($CDCl_3$) δ 0.6 (m, 1 H, cyclopropyl), 1.2 (d, J = 6 Hz, 3 H, CH_3), 2.0 (m, 1 H, cyclopropyl), 2.5 (m, 1 H, cyclopropyl), 6.4 [s, 0.87 H, CHODNB (exo isomer)], 6.7 [d, J = 6 Hz, 0.13 H, CHODNB (endo isomer)], 7.3 (m, 4 H, aromatic), and 9.2 ppm (m, 3 H, aromatic).

Anal. Calcd for $C_{18}H_{14}N_2O_6$: C, 61.02; H, 3.98. Found: C, 60.90; H, 4.00.

1-Methylinden-3-yl Acetate. This was prepared by heating a mixture of 20.3 g (0.14 mol) of 3-methylindan-1-one, 21.9 (0.22 mol) of isopropenyl acetate, and 0.3 g of *p*-toluenesulfonic acid at reflux for 10 h. After cooling the solution, 5 g of anhydrous sodium carbonate was added and distillation afforded 15.3 g (63%) of 1-methylinden-3-yl acetate: bp 100–101 °C (1.9 mm); NMR (CCl_4) δ 1.4 (d, J = 8 Hz, 3 H, CH_3CH), 2.3 (s, 3 H, CH_3C=O), 3.7 (quartet of doublets, J = 3 and 8 Hz, 1 H, $CHCH_3$), 6.7 (d, J = 3 Hz, 1 H, CHOAc), and 7.7 ppm (m, 4 H, aromatic); IR (neat) 1760 (C=O) and 1190 cm^{-1} (C–O); mass spectrum (70 eV) *m/e* (rel intensity) 188 (10), 147 (11), 146 (100), 145 (22), 131 (58), 117 (10), 115 (19).

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.32; H, 6.57.

3-Methylinden-1-ol. Upon treatment of 13.1 g (0.074 mol) of 1-methylinden-3-yl acetate with 1 mL of trimethylamine in 5 mL of ether at reflux for 1 h, rearrangement occurred resulting in an 92:8 ratio of 3-methylinden-1-yl acetate and 1-methylinden-3-yl acetate. After removal of the triethylamine and ether under vacuum, the remaining mixture of acetates was dissolved in ether, cooled to 0 °C, and reduced with lithium aluminum hydride. Workup by pouring the mixture into 1 N sulfuric acid was followed by extraction with ether and drying over anhydrous magesium sulfate. Removal of the ether left a white solid which was recrystallized from 1:1 ether–petroleum ether (bp 30–60 °C) to yield 6.9 g (63%) of short needles, mp 68–71 °C. Further recrystallization from the same solvent mixture yielded 3-methylinden-1-ol: mp 70.5–71.0 °C; NMR (CCl_4) δ 2.0 (t, J = 2 Hz, 3 H, CH_3), 3.2 (bs, 1 H, OH), 4.8 (bs, 1 H, CHCH), 5.8 (q, J = 2 Hz, 1 H, CHCHOH), and 7.0 ppm (m, 4 H, aromatic); IR (mineral oil) 3280 cm^{-1} (O–H); mass spectrum (70 eV) *m/e* (rel intensity) 147 (10), 146 (92), 145 (32), 132 (10), 131 (100), 128 (17), 127 (13), 117 (14), 115 (25), 103 (18), 77 (12).

Anal. Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.89. Found: C, 82.34; H, 6.93.

3-Methyl-*endo*-cycloprop[2,3]inden-1-ol. To 25.0 g (0.39 mol) of a zinc–copper couple, prepared by the LeGoff[6] procedure, in ether was added 27.2 g (0.19 mol) of 3-methylinden-1-ol and 80 g (0.30 mol) of methylene iodide in ether over a 30-min period. This solution was refluxed for 4 h, and workup by the usual method was followed by ether extraction and drying over magnesium sulfate. Distillation afforded 18.6 g of 3-methylcycloprop[2,3]inden-1-ol, bp 92–97 °C (0.8 mm), which was recrystallized from ether–petroleum ether (bp 30–60 °C) to yield 17.4 g (58%) of white crystals, mp 78–80 °C. Further recrystallization from pentane yielded 3-methyl-*endo*-cycloprop[2,3]-inden-1-ol: mp 79–80 °C; NMR (CCl_4) δ 0.6 (m, 2 H, cyclopropyl), 1.5 (s, 3 H, CH_3), 1.7 (m, 1 H, CHCHOH), 1.9 (bs, 1 H, OH), 5.4 (bs, 1 H, CHOH), and 7.1 ppm (bs, 4 H, aromatic); IR (mineral oil) 3345 and 3250 cm^{-1} (O–H); mass spectrum (70 eV) *m/e* (rel intensity) 145 (100), 142 (34), 141 (28), 131 (66), 130 (22), 129 (25), 128 (38), 127 (25), 117 (50), 116 (24), 115 (58), 91 (24).

Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.59; H, 7.63.

3-Methyl-*endo*-cycloprop[2,3]inden-1-yl 3,5-Dinitrobenzoate. In the usual manner, 1.14 g (0.071 mol) of 3-methyl-*endo*-cycloprop[2,3]inden-1-ol was cooled to 0 °C in pyridine and treated with 2.0 g (0.088 mol) of 3,5-dinitrobenzoyl chloride. Workup and recrystallization from 1:1 chloroform–pentane gave 1.36 g (64%) of 3-methyl-*endo*-cycloprop[2,3]inden-1-yl 3,5-dinitrobenzoate: mp 118–120 °C; NMR ($CDCl_3$) δ 1.0 (m, 2 H, cyclopropyl), 1.6 (bs, 3 H, CH_3), 2.1 (m, 1 H, cyclopropyl), 6.6 (d, J = 6 Hz, 1 H, CHODNB), 7.1 (m, 4 H, aromatic) and 9.0 ppm (m, 3 H, aromatic); IR (mineral oil) 1725 (C=O) and 1275 cm^{-1} (C–O).

Anal. Calcd for $C_{18}H_{14}N_2O_6$: C, 61.02; H, 3.98. Found: C, 60.98; H, 3.82.

3-Methyl-*exo*- and -*endo*-cycloprop[2,3]inden-1-ols. Again using the method of Eliel,[8] a mixture of 10.1 g (0.063 mol) of 3-methyl-*endo*-cycloprop[2,3]inden-1-ol, 15.1 g (0.073 mol) of aluminum isopropoxide, and 0.1 g of acetone in 2-propanol was heated at reflux for 48 h. Workup by pouring the cooled mixture into ice-cold 2 M hydrochloric acid and extraction with ether was followed by drying over anhydrous magnesium sulfate. Vacuum distillation afforded 8.1 g (80%) of a colorless liquid, bp 89–92 °C (1.0 mm), which was a 75:25 exo–endo mixture of 3-methylcycloprop[2,3]inden-1-ols: NMR (CCl_4) δ 0.0 [t, J = 4 Hz, 0.75 H, cyclopropyl (anti proton of exo isomer)], 0.7 (m, 1.25 H, cyclopropyl), 1.4 (m, 4 H, CH_3 and cyclopropyl), 3.3 (bs, 1 H, OH), 4.4 [s, 0.75 H, CHOH (exo isomer)], 5.2 [d, J = 6 Hz, 0.25 H, CHOH (endo isomer)], and 7.3 ppm (m, 4 H, aromatic).

3-Methyl-*exo*-cycloprop[2,3]inden-1-yl 3,5-Dinitrobenzoate. To 1.83 g (0.01 mol) of a 75:25 exo–endo mixture of 3-methylcycloprop[2,3]inden-1-ol cooled to 0 °C in pyridine was added 3.0 g (0.013 mol) of 3,5-dinitrobenzoyl chloride. Workup and recrystallization produced 2.10 g (52%) of whitish crystals, mp 109–117 °C. Recrystallization twice more from 1:1 methylene chloride–pentane yielded 3-methyl-*exo*-cycloprop[2,3]inden-1-yl 3,5-dinitrobenzoate: mp 118–120 °C; NMR ($CDCl_3$) δ 0.4 (t, J = 4 Hz, 1 H, cyclopropyl), 1.2 (doublet of doublets, J = 4 and 8 Hz, 1 H, cyclopropyl), 1.7 (s, 3 H, CH_3), 2.0 (doublet of doublets, J = 4 and 8 Hz, 1 H, cyclopropyl), 6.3 (s, 1 H, CHODNB) 7.3 (m, 4 H, aromatic), and 9.2 ppm (s, 3 H, aromatic); IR (mineral oil) 1725 (C=O) and 1285 cm^{-1} (C–O).

Anal. Calcd for $C_{18}H_{14}N_2O_6$: C, 61.02; h, 3.98. Found: C, 61.13; H, 4.08.

Kinetic Procedures. Acetone (Mallinckrodt AR) was dried by allowing it to slowly drain through a 50 by 2.6 cm column packed with 1/16 in. pellets of Linde 4A molecular sieve. The acetone was distilled from powdered type 4A molecular sieve through a 40-cm Widmer column. The 80 vol % aqueous acetone was then prepared by combining 800 mL of the dry acetone with 200 mL of redistilled water.

As an example of the usual kinetic procedure, 0.1724 g (5.07×10^{-4} mol) of *endo*-cycloprop[2,3]inden-1-yl 3,5-dinitrobenzoate was dissolved in 50 mL of 80% aqueous acetone in a 50-mL volumetric flask. This solution was then divided into nine portions of ca. 5.5 mL and sealed in ampules. The set of ampules was immersed in a thermostated 5-gal constant-temperature oil bath and at regular intervals they were removed and cooled quickly in ice. After equilibrating to room temperature, a 5-mL aliquot was taken and titrated for acid formed with ca. 0.01 N sodium methoxide in methanol using 2 drops of a 1% methanolic solution of bromothymol blue as the indicator. Infinity titers were determined in duplicate after about 10 half-lives for reaction. All runs were carried out in duplicate and the reported values are the average of two runs. Rate constants were calculated by use of the standard first-order integrated rate equation[23] and thermodynamic parameters were obtained using the Eyring equation.[24] Errors reported for the rate constants represent in each case the standard deviation of the mean. Error values recorded for the activation parameters were determined based on the errors mentioned

above for the rate constants.

Controls on Kinetic Materials. As a typical example of the method employed, 0.0428 g (1.21×10^{-4} mol) of 3-methyl-*endo*-cycloprop[2,3]inden-1-yl 3,5-dinitrobenzoate was dissolved in 5.0 mL of 80% aqueous acetone. The sample was sealed in an ampule and heated for 15 min (time for hydrolysis of ca. 25% of the ester) at 100.0 °C. The sample was cooled, poured into water, and extracted with ether. The ethereal solution was washed with saturated sodium bicarbonate solution and dried over anhydrous magnesium sulfate. All traces of solvent were removed on the vacuum pump and the sample was analyzed for 3-methyl-*exo*- and -*endo*-cycloprop[2,3]inden-1-yl 3,5-dinitrobenzoates by NMR.

Hydrolysis Products. As an example of the procedure, a sample of 0.2902 g (8.52×10^{-4} mol) of *endo*-cycloprop[2,3]inden-1-yl 3,5-dinitrobenzoate and 0.20 g (2×10^{-3} mol) of calcium carbonate were combined with 5 mL of 80% aqueous acetone and sealed in an ampule. After heating for 250 min at 100.0 °C, the mixture was cooled and poured into 50 mL of ether which contained a weighed amount of indan-1-ol internal standard. The ether solution was washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was removed using a Widmer column and the products analyzed by GLC using a 5 ft × 0.25 in. 20% diethylene glycol succinate (DEGS) column on Chromosorb W and by NMR.

Controls on Hydrolysis Products. In an example of the general case, 0.0277 g (1.73×10^{-4} mol) of 3-methyl-*endo*-cycloprop[2,3]-inden-1-ol 0.0406 g (4.06×10^{-4} mol) of calcium carbonate, and 0.0285 g (1.41×10^{-4} mol) of 3,5-dinitrobenzoic acid were combined in 5 mL of 80% aqueous acetone and sealed in an ampule. The ampule was heated at 100.0 °C for 281.0 min (ca. 5 half-lives of the corresponding ester) and then cooled to room temperature. The sample was poured into ether containing indan-1-ol (internal standard) and water was added. After ether extraction, the ethereal solution was washed with saturated sodium bicarbonate and dried over anhydrous sodium sulfate. The solution was concentrated to ca. 0.5 mL using a Widmer column and the sample was analyzed by GLC using a 5 ft × 0.125 in. SF-96/Carbowax on Chromosorb G column and by NMR.

Acknowledgment. The authors wish to thank the Committee on Research of the University of California, Davis, for a Faculty Research Grant providing partial support for this study.

Registry No.—1, 61463-14-7; 2, 61490-56-0; 5, 61463-15-8; 6, 61463-16-9; 7, 61463-17-0; 8, 61463-18-1; 15, 61463-19-2; 16, 61490-57-1; 17, 61463-20-5; 18, 61490-58-2; 19, 6072-57-7; *endo*-cycloprop[2,3]inden-1-ol, 57378-75-3; methylene iodide, 75-11-6; inden-1-ol, 61463-21-6; 3,5-dinitrobenzoyl chloride, 99-33-2; cycloprop[2,3]inden-1-one, 5771-62-0; 2-phenylcyclopropanecarboxylic acid chloride, 5685-36-9; 1,2-dichloroethane, 107-06-2; *exo*-cycloprop[2,3]inden-1-ol, 57378-74-2; indan-1-ol, 6351-10-6; indan-1-one, 83-33-0; 4,4-dimethyl-1,4-dihydronaphthalen-1-one, 16020-16-9; 4,4-dimethyl-2-bromo-1-tetralone, 17426-90-3; dimethylformamide, 68-12-2; 5,5-dimethylbenzobicyclo[4.1.0]hepten-1-one, 61463-22-7; dimethyl sulfoxide, 67-68-5; 5,5-dimethylbenzobicyclo[4.1.0]hepten-1-ol, 61463-23-8; 4,4-dimethyl-1-tetralol, 53952-18-4; 4,4-dimethyl-1-tetralone, 2979-69-3; phenylcyclopropylcarbinol, 1007-03-0; phenyl cyclopropyl ketone, 3481-02-5; ethylidene iodide, 594-02-5; ethylidene chloride, 75-34-3; ethyl iodide, 75-03-6; *anti*-10-methyl-*endo*-cycloprop[2,3]inden-1-ol, 61463-24-9; *anti*-10-methyl-*exo*-cycloprop[2,3]inden-1-ol, 61490-59-3; 1-methylinden-3-yl acetate, 61463-25-0; isopropenyl acetate, 108-22-5; 3-methylinden-1-ol, 23417-85-8; 3-methyl-*endo*-cycloprop[2,3]inden-1-ol, 61463-26-1; 3-methyl-*exo*-cycloprop[2,3]inden-1-ol, 61490-60-6.

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Thermodynamics of Vinyl Ethers. 19. Alkyl-Substituted Divinyl Ethers[1]

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Received November 12, 1976

Chemical equilibration studies of isomeric alkyl-substituted divinyl ethers have been carried out. The thermodynamic data obtained are used for discussions concerning the spatial structure of the C=C–O–C=C system in these compounds. Divinyl ethers unsubstituted in the α position probably exist mainly in the planar (or nearly planar) s-trans,s-trans form, the planar s-cis,s-trans form being in any case excluded as the most stable structure. The latter structure is possible for an α-substituted but not for an α,α'-dialkyl-substituted divinyl ether, which assumes a nonplanar structure. The same structure applies to most α,β-dialkyl- and α,β-polyalkyl-substituted divinyl ethers. Electron distribution in the divinyloxy system is rather sensitive to the number and position of alkyl groups present, as revealed by the ^{1}H NMR shift data.

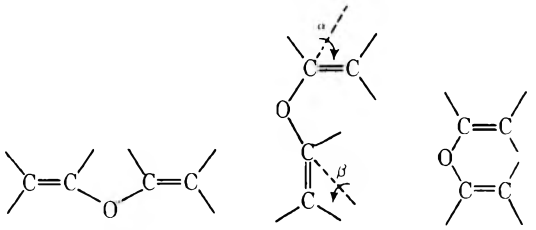
The spatial structure of divinyl ether (**1**) has been of interest ever since the finding of Dolliver et al.[2] that the conjugation energies of **1** and ethyl vinyl ether (**2**) are equal (ca. 15 kJ mol^{-1}). Since the oxygen atom of **1** is interposed between

$CH_2{=}CH{-}\ddot{O}{-}CH{=}CH_2$ (**1**) $Et{-}\ddot{O}{-}CH{=}CH_2$ (**2**)

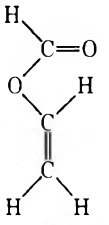
two unsaturated linkages, the stabilization due to p–π interaction in **1** might be expected to be higher than that in **2**. The similar conjugation energies of **1** and **2** thus suggest that either the O atom of **1** conjugates effectively with just one of the two vinyl groups or it conjugates with both C=C bonds but with reduced efficiency. The former alternative is reasonable if **1** is markedly nonplanar so that the p orbitals of the O atom can

effectively overlap with the π orbital of only one C=C bond. The spatial structure (conformation) of **1** has been the subject of several investigations with contradictory results. From an electron diffraction study,[3] a slightly nonplanar structure (not far from the planar s-trans,s-trans configuration shown in Scheme I) was proposed for the only stable form of **1**. The

Scheme I



existence of at least two rotamers of **1** has been observed by other investigators. On the basis of IR and Raman spectra studies, Glague and Danti[4] suggested the planar s-cis,s-trans structure ($\alpha = \beta = 0$ in Scheme I) for the most stable rotamer, whereas the less stable rotamer was believed to have a "gauche" structure in which the two vinyl groups are not coplanar. The microwave studies of Hirose and Curle[5] gave evidence for a nonplanar s-cis,s-trans structure ($\alpha = 40$–$50°$, $\beta = 10$–$20°$ in Scheme I) for the most stable rotamer of **1** (the planar s-cis,s-trans structure has been proposed[6,7] for vinyl formate **3**). However, the IR and Raman spectra studies of

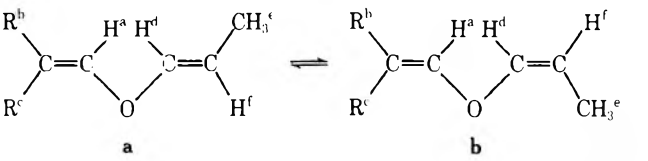


3

Cadioli et al.[8] showed that the low-energy rotamer of **1** has the planar s-trans,s-trans form, whereas the high-energy rotamer assumes a nonplanar s-cis,s-trans structure with $\alpha = 45°$ and $\beta = 20°$. The enthalpy difference between the rotamers was obtained as ca. 2.5 kJ mol^{-1}. None of the above investigators observed the existence of the planar s-cis,s-cis rotamer, which is sterically crowded.

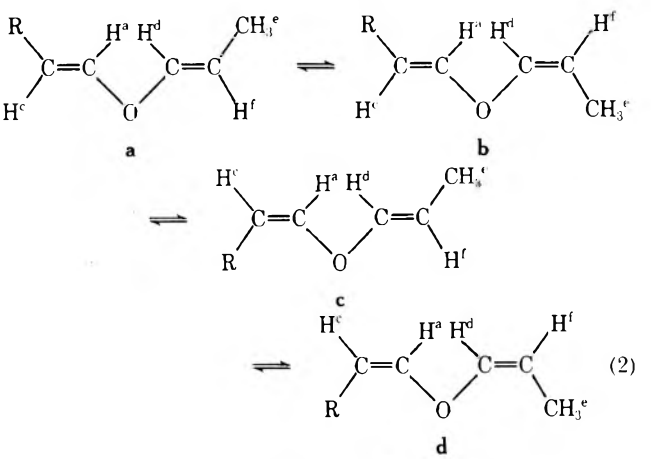
Besides these studies concerned with the spatial structure of the unsubstituted divinyl ether molecule, a study of the conformation of (*Z*,*Z*)-dipropenyl ether (**6d**, see below) has been published.[9] The planar s-trans,s-trans structure was given to the only stable form of **6d** as well as to the parent divinyl ether.

As an extension of our studies on the structure–stability relationship in compounds containing the vinyl ether moiety (–OC=C), thermodynamics of geometric and prototropic (double bond positional) isomerization reactions on alkyl-substituted divinyl ethers have now been investigated. Clarification of the spatial structures of these compounds was not our primary goal; however, it is evident that if a reaction involves a change in the conformation of the C=C–O–C=C system, the change is reflected in the values of the thermodynamic parameters of isomerization, thus providing experimental background for conclusions concerning the possible conformations of the species involved. In addition to the thermodynamic results, interesting information on the effects of alkyl substituents on electron distribution in the divinyl ether system was obtained from ^{1}H NMR shift data of protons bound to the C(sp^2) atoms. The reactions (1–4) studied in this



a **b**

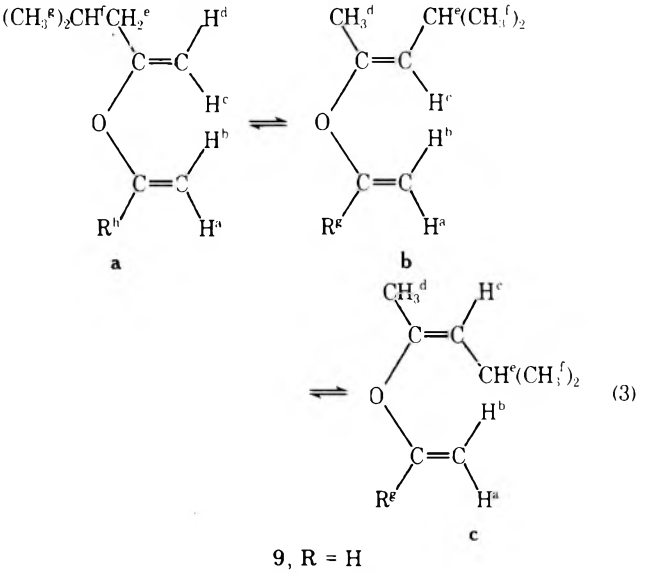
4, R = H
5, R = CH_3 (1)



a **b** **c** **d**

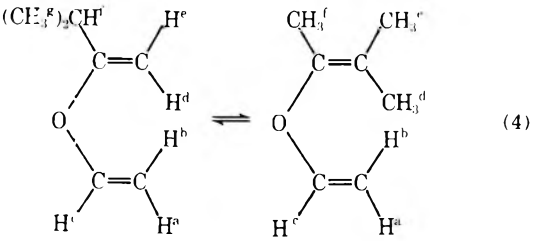
6, R = CH_3[b] (**6b** ≡ **6c**)
7, R = CH_3[g]CH_2[b]
8, R = $(CH_3$[g]$)_2CH$[b]

(2)



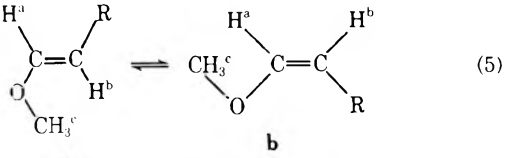
a **b** **c**

9, R = H
10, R = CH_3 (3)



11a **11b**

(4)



a **b**

12, R = CH_3[e]CH_2[d]
13, R = $(CH_3$[e]$)_2CH$[d] (5)

Table I. Thermodynamic Data (Liquid Phase, 298.15 K) for the Reactions Studied in This Work[a]

Reaction	$\Delta G°$/kJ mol^{-1}	$\Delta H°$/kJ mol^{-1}	$\Delta S°$/J K^{-1} mol^{-1}
4a → 4b	−2.33 ± 0.03	−1.5 ± 0.2	2.6 ± 0.4
5a → 5b	−1.79 ± 0.05	−2.0 ± 0.3	−0.7 ± 0.8
6a → 6b	−3.64 ± 0.06	−1.7 ± 0.3	6.5 ± 0.7
6b → 6d	−0.20 ± 0.02	−2.0 ± 0.1	−6.2 ± 0.2
6a → 6d	−3.83 ± 0.06	−3.7 ± 0.3	0.3 ± 0.8
7a → 7b	−2.03 ± 0.11	−2.7 ± 0.6	−2.2 ± 1.6
7a → 7c	−0.75 ± 0.10	−1.3 ± 0.5	−2.0 ± 1.5
7a → 7d	−2.75 ± 0.07	−3.6 ± 0.4	−2.9 ± 1.0
8a → 8b	−2.20 ± 0.01	−2.6 ± 0.1	−1.4 ± 0.1
8a → 8c	0.18 ± 0.02	−0.5 ± 0.1	−2.1 ± 0.3
8a → 8d	−1.73 ± 0.05	−2.6 ± 0.3	−3.0 ± 0.7
9a → 9b	−0.35 ± 0.04	−1.0 ± 0.2	−2.0 ± 0.6
9b → 9c	−0.08 ± 0.05	0.6 ± 0.2	2.1 ± 0.7
9a → 9c	−0.43 ± 0.04	−0.4 ± 0.2	0.1 ± 0.5
10a → 10b	−2.58 ± 0.06	−4.7 ± 0.3	−7.1 ± 0.9
10b → 10c	−3.82 ± 0.05	−5.4 ± 0.2	−5.4 ± 0.6
10a → 10c	−6.39 ± 0.09	−10.1 ± 0.5	−12.4 ± 1.1
11a → 11b[b]	−8.25 ± 0.02	−3.3 ± 0.3	16.5 ± 1.0
12a → 12b	1.67 ± 0.09	3.8 ± 0.5	7.1 ± 1.4
13a → 13b	2.62 ± 0.02	4.3 ± 0.1	5.7 ± 0.3

[a] Solvents: neat for **4–8** and **12–13**, cyclohexane for **9–11**. The errors are twice the standard errors. [b] $\Delta C_p° = -44 \pm 6$ J K^{-1} mol^{-1}.

Table II. Thermodynamic Data (Gas Phase, 298.15 K) for the Reactions Studied in This Work

Reaction	$\Delta H°$/kJ mol^{-1}	$\Delta S°$/J K^{-1} mol^{-1}
4a → 4b	−2.3 ± 0.4	1.5 ± 0.6
5a → 5b	−2.7 ± 0.4	−1.5 ± 0.9
6a → 6b	−2.3 ± 0.4	5.8 ± 0.9
6b → 6d	−2.9 ± 0.3	−7.2 ± 0.6
6a → 6d	−5.1 ± 0.4	−1.4 ± 0.9
7a → 7b	−3.3 ± 0.7	−2.9 ± 1.7
7a → 7c	−2.2 ± 0.6	−3.1 ± 1.6
7a → 7d	−5.5 ± 0.5	−5.1 ± 1.1
8a → 8b	−3.1 ± 0.3	−2.0 ± 0.6
8a → 8c	−1.7 ± 0.3	−3.4 ± 0.6
8a → 8d	−4.8 ± 0.4	−5.4 ± 0.9
9a → 9b	−0.1 ± 0.4	−0.9 ± 0.8
9b → 9c	−0.4 ± 0.4	1.0 ± 0.9
9a → 9c	−0.4 ± 0.4	0.1 ± 0.7
10a → 10b	−4.3 ± 0.4	−6.7 ± 1.0
10b → 10c	−6.6 ± 0.4	−6.7 ± 0.8
10a → 10c	−10.9 ± 0.6	−13.3 ± 1.2
11a → 11b	−1.4 ± 0.4	18.9 ± 1.1
12a → 12b	2.2 ± 0.6	4.9 ± 1.5
13a → 13b	3.3 ± 0.3	4.4 ± 0.6

work are shown (the superscripts refer to the NMR spectra; see Experimental Section).

Many of these reactions involve $E \rightarrow Z$ transfers of alkyl groups (alkyl = Me, Et, or *i*-Pr). For comparison, reaction 5 was studied for R = Et and R = *i*-Pr (the case R = Me has been studied previously[10]).

Results and Discussion

1. Results. For most reactions ln K (K = the mean equilibrium constant at temperature T) proved to be a linear function of T^{-1}, justifying the use of the van't Hoff equation for determining the values of $\Delta G°$, $\Delta H°$, and $\Delta S°$ at 298.15 K. For **11a ⇌ 11b**, however, a plot of ln K vs. T^{-1} was considerably curved (i.e., $\Delta C_p° \neq 0$), and in this case the values of K were fitted to eq 6[11]

$$\ln K = A + BT^{-1} + C \ln T \qquad (6)$$

Table III. Thermodynamic Data (Gas Phase, 298.15 K) for Reaction 7

R (confign)	$\Delta H°$/kJ mol^{-1}	$\Delta S°$/J K^{-1} mol^{-1}
Me (*E*)	−2.3	0.0[a]
Me (*Z*)	−2.9	−1.4[a]
Et (*E*)	−3.3	−2.9
Et (*Z*)	−3.3	−2.0
i-Pr (*E*)	−3.1	−2.0
i-Pr (*Z*)	−3.1	−2.0

[a] Statistically corrected.

Table IV. Thermodynamic Data (Gas Phase, 298.15 K) for Reaction 8

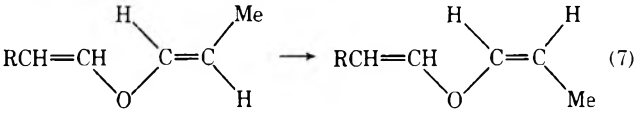
R	Configurational position of Me	$\Delta H°$/kJ mol^{-1}	$\Delta S°$/J K^{-1} mol^{-1}
Me	*E*	−2.3	0.0[a]
Me	*Z*	−2.9	−1.4[a]
Et	*E*	−2.2	−3.1
Et	*Z*	−2.2	−2.2
i-Pr	*E*	−1.7	−3.4
i-Pr	*Z*	−1.7	−3.4

[a] Statistically corrected.

from which the value of $\Delta C_p°$ (independent of T) could also be evaluated. The values of the thermodynamic functions of isomerization in the liquid phase at 298.15 K are given in Table I. The gas-phase values of $\Delta H°$ and $\Delta S°$ (Table II) were estimated from the corresponding liquid phase values and the normal boiling point data as described previously.[12]

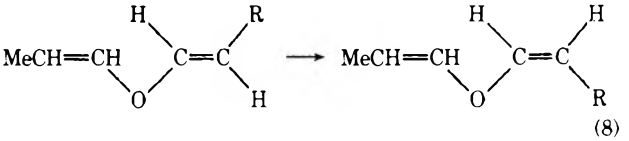
2. Thermodynamic Data. Compound **6b** (≡ **6c**) is favored at equilibrium by a statistical factor of 2. To eliminate the effects of the statistical factor on the values of $\Delta G°$ and $\Delta S°$ for **6a → 6b**, the terms RT ln 2 (= 1.72 kJ mol^{-1} at 298.15 K) and $-R$ ln 2 (= −5.8 J K^{-1} mol^{-1}) should be added to the experimental $\Delta G°$ and $\Delta S°$ values, respectively. On the other hand, the terms $-RT$ ln 2 and R ln 2 should be added to the experimental $\Delta G°$ and $\Delta S°$ values for **6b → 6d.**

The thermodynamic data of Table III (obtained from the data of Table II) reveal that the values of $\Delta H°$(g) and $\Delta S°$(g) of reaction 7 are (within experimental error) independent of



(7)

the size and configurational position (*E*,*Z*) of R. Similarly, the values of $\Delta H°$(g) and $\Delta S°$(g) of reaction 8 are essentially in-

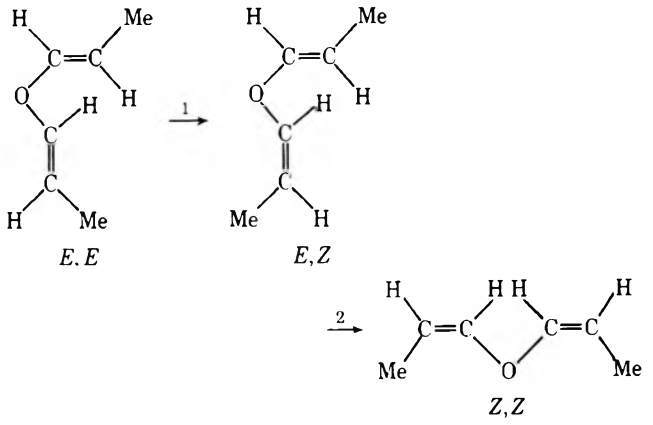


(8)

dependent of the configurational position of the Me group; however, $\Delta H°$(g) becomes less negative and $\Delta S°$(g) more negative with increasing size of R (Table IV).

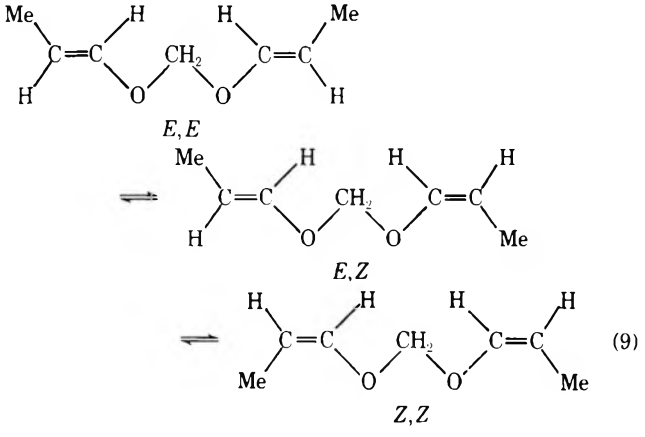
The facts given above exclude the planar s-cis,s-trans structure as the most stable conformation of any of these β,β'-dialkyl-substituted divinyl ethers, as shown by the following reasoning concerning (for simplicity) the β,β'-dimethyl-substituted divinyl ether **6**. Assuming that the *E*,*E* (**a**) and *E*,*Z* (**b**) isomers exist in the planar s-cis,s-trans form, the reactions *E*,*E* → *Z*,*Z* and *E*,*Z* → *Z*,*Z* necessarily involve

changes in the spatial structure of the C=C-O-C=C system, since it is evident that the *Z,Z* isomer cannot assume the planar s-cis,s-trans form because of strong repulsive Me···H interactions between the two vinyl groups (experimental evidence[9] supports the planar s-trans,s-trans structure for the *Z,Z* isomer). The stereochemical course of the reaction *E,E* → *E,Z* → *Z,Z* would thus be as follows:



The assumed course of the above reaction requires that $\Delta H_2° > \Delta H_1°$ since $\Delta H_2°$ includes the enthalpy term (>0) for the change in the conformation of the C=C-O-C=C system. This is not, however, supported by experimental facts, since $\Delta H_2°$ is slightly more negative than $\Delta H_1°$. Moreover, the statistically corrected $\Delta G°(1)$ values for steps 1 and 2 of the above reaction are equal (−1.90 kJ mol^{-1}). Hence it appears that the spatial structure of the C=C-O-C=C system remains unchanged on going from the *E,E* to the *Z,Z* isomer.

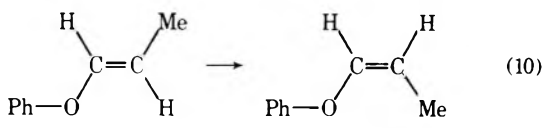
Reaction 9 was studied in a previous work.[1] The values of



(9)

$\Delta G°$, $\Delta H°$, and $\Delta S°$ for all steps of reaction 9 are practically identical with the corresponding steps of the analogous reaction 2 with R = Me; for example, $\Delta G°(1) = -4.06 \pm 0.03$ kJ mol^{-1}, $\Delta H°(1) = -4.0 \pm 0.2$ kJ mol^{-1}, and $\Delta S°(1) = 0.3 \pm 0.4$ J K^{-1} mol^{-1} for the *E,E* → *Z,Z* isomerization (reaction 9). Since all the isomeric species of reaction 9 were found to exist mainly in the planar s-trans,s-trans form, the similarity between the thermodynamic data for reactions 9 and 2 (R = Me) suggests that the same spatial structure should also apply to the divinyl ethers in question.

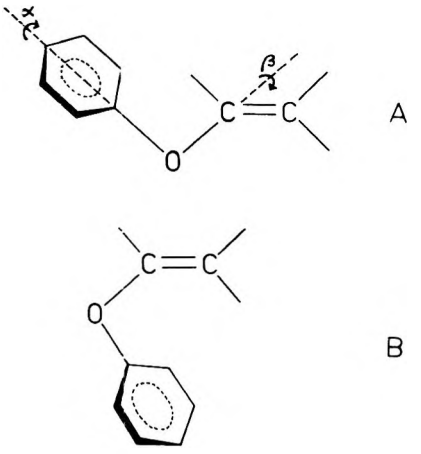
The values of $\Delta H°$(g) and $\Delta S°$(g) for **4a** → **4b** (Table II) correspond closely to those for reaction 10, for which $\Delta H°$(g) = −2.3 ± 0.3 kJ mol^{-1} and $\Delta S°$(g) = 2.7 ± 0.6 J K^{-1} mol^{-1}.[10] Phenyl vinyl ether, the parent compound of PhOCH=CHMe,



(10)

is known[13-16] to exist as a mixture of rotamers, the most stable of which has the nonplanar structure A shown in Scheme II

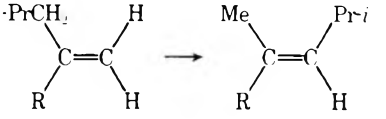
Scheme II



(according to Donnay and Garnier,[16] α = 40–50° and β = 10–20°; other values have also been suggested). Considering rotamer A alone, it is apparent that an *E* → *Z* transfer of a substituent on the β carbon of the vinyl group does not necessitate any change in the spatial structure of the phenyl vinyl ether skeleton. The practically equal values of $\Delta H°$(g) and $\Delta S°$(g) for the two reactions concerned thus give the idea that also the divinyl ether skeletons in **4a** and **4b** remain essentially unchanged in the reaction **4a** → **4b**. Hence the planar s-cis,s-trans structure is excluded as the most stable form of **4a** (for **4b** this structure is not likely because of steric factors).

Let us compare the thermodynamics of the *E* → *Z* transfer of R in MeOCH=CHR (reaction 5) with that in MeCH=CHOCH=CHR (reaction 2). In the former reaction the spatial orientation of the MeO group changes from the s-cis to the s-trans[10] giving rise to the more positive enthalpy changes. It would seem reasonable to expect the differences in the values of the thermodynamic parameters for the two reactions in question to be independent of R. However, this is not the case: the values of $\Delta H°$(g) of reaction 5 are 3.0 (R = Me[10]), 4.4 (R = Et), and 5.0 kJ mol^{-1} (R = *i*-Pr) more positive than those of reaction 2 (the mean $\Delta H°$ values for the **a** → **c** and **b** → **d** reactions). Similarly, the $\Delta S°$(g) values of reaction 5 are ca. 4 (R = Me[10]), 8 (R = Et), and 8 J K^{-1} mol^{-1} (R = *i*-Pr) more positive than those of reaction 2. The origin of these facts is not clear.

The values of $\Delta H°$(g) of reaction 11 depend on R as shown



(11)

in Table V. This reaction involves an increase in the number of alkyl substituents attached to the double bond and the highest stabilization due to the increased degree of substitution is achieved in the case R = H, i.e., in ordinary olefins. The weak stabilizing ability of alkyl groups on the C=C bond of vinyl ethers is probably due to the reduced double-bond character of the olefinic linkage (see ref 18 and references cited therein). The data of Table V thus suggest that the double-bond character of the olefinic bond in the product of reaction 11 increases on going from the top (R = MeO) to the bottom (R = H). The enthalpy change for R = CH_2=C(Me)O (i.e., for **10a** → **10b**) leads to the conclusion that the C=C bond of the product (**10b**) behaves almost like an ordinary olefinic bond. This leads to the idea that conjugation between the lone electron pairs of the O atom and the C=C bond of the

Table V. Enthalpy Data (Gas Phase, 298.15 K) for Reaction 11

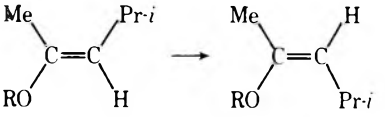
R	$\Delta H°$/kJ mol^{-1}
MeO	0.6 ± 0.4 (ref 17)
CH_2=CHO—	−0.1 ± 0.4 (this work)
CH_2=C(Me)O—	−4.3 ± 0.4 (this work)
H	≈−6.2 (ref 17)

Table VI. Enthalpy Data (Gas Phase, 298.15 K) for Reaction 12

R	$\Delta H°$/kJ mol^{-1}
Me	11.46 ± 0.35 (ref 17)
CH_2=CH—	−0.4 ± 0.4 (this work)
CH_2=C(Me)—	−6.6 ± 0.4 (this work)

–OC(Me)=CHPr-*i* fragment of **10b** is weak, suggesting a markedly nonplanar structure for this molecule. This result is already evident from an inspection of molecular models, since any planar structure of **10b** (or of its two isomers) would be sterically crowded. On the other hand, molecular models reveal that of the planar s-trans,s-trans and s-cis,s-trans forms, the latter is possible for **9a** and **9b**, whereas the former would lead to considerable steric strain between the α H atom of the unsubstituted vinyl group and the α substituent of the other vinyl group. The enthalpy change for reaction 11 with R = CH_2=CHO is indeed reasonable for planar molecules. The third isomer **9c** would, however, be sterically crowded in any planar structure.

The above conclusions are substantiated by the values of $\Delta H°$(g) for reaction 12 (Table VI). The high positive enthalpy



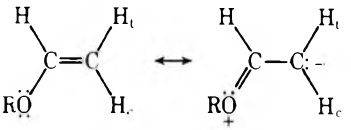
(12)

change for the case R = MeO is a result of the s-cis → gauche reorientation of the MeO group on going from the reactant to the product.[19] On the other hand, assuming no change in the spatial orientation of the R group during the reaction, the expected enthalpy change could be obtained as follows. The reactant is destabilized by the Me···*i*-Pr cis interaction (ca. 4.0 kJ mol^{-1}, ref 20) and the product stabilized by the attractive *i*-Pr···O cis interaction, which may be evaluated as ca. 1.7 kJ mol^{-1} from the values of $\Delta H°$(g) for reactions **8a** → **8c** and **8b** → **8d**. The predicted enthalpy change for reaction 12 would thus be ca. −5.7 kJ mol^{-1}, in moderate agreement with the experimental value for R = CH_2=C(Me)O, which supports the nonplanarity of the C=C–O–C=C skeleton in the two isomers concerned. However, for R = CH_2=CHO the planar s-cis,s-trans structure is possible for the reactant (**9b**), since the enthalpy change is considerably more positive than that expected for nonplanar molecules.

The values of $\Delta S°$(g) (in J K^{-1} mol^{-1}) for reaction 11 are −6.4 ± 0.8 (R = MeO, ref 17), −0.9 ± 0.8 (R = CH_2=CHO), and −6.7 ± 1.0 [R = CH_2=C(Me)O]. Since there is no apparent reason for a change in the spatial orientation of the R group during the reaction, the entropy changes should be equal for all these reactions, as shown previously for a series of related reactions.[19] However, the entropy change for R = CH_2=CHO is ca. 6 J K^{-1} mol^{-1} less negative than those for the other reactions. A possible explanation is that **9a** exists in the planar s-cis,s-trans form, whereas **9b** prefers a slightly nonplanar s-cis,s-trans structure, which gives rise to two enantiomers whereby the entropy of **9b** is increased by the entropy of mixing, $R \ln 2$ (= 5.8 J K^{-1} mol^{-1}). The reason for the suggested slight nonplanarity of the C=C–O–C=C system of **9b** is not clear, although it possibly originates from the increase in double-bond substitution on going from **9a** to **9b**, which leads to changes in electron distribution in the divinyloxy system (see discussion of ^{1}H NMR shift data).

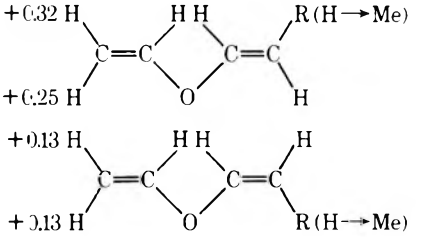
Reaction **11a** → **11b** involves a considerable change in $C_p°$. Somewhat smaller $\Delta C_p°$ values have been previously[21] recorded for related reactions with alkoxy groups substituted for the vinyloxy group of the present compounds. The **b** isomer is favored by a high entropy value. The planar s-cis,s-trans structure seems likely for **11a** and a nonplanar structure for **11b**.

3. ^{1}H NMR Shift Data. The ^{1}H NMR signals of the β protons of the vinyl group of alkyl vinyl ethers (ROCH=CH_2) are found ca. 1 ppm upfield from the corresponding signals of 1-alkenes (RCH=CH_2). This is due to the increased electron density on the β carbon of vinyl ethers,[22,23] which arises from the p–π conjugation:

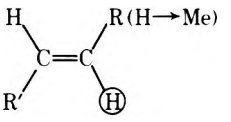


Thus it appears that the chemical shifts of the β protons of alkyl vinyl ethers could be used as an approximate measure of the extent of conjugation in the vinyloxy system. High τ values suggest enhanced conjugation and vice versa. Of the two β protons, the one trans to the RO group (H_t) is to be preferred for shift comparison since, owing to its longer distance from RO, H_t is less susceptible to the differences in the shielding effects of varying alkyl groups than the cis proton. As an example, the H_t signal of ethyl vinyl ether is found at τ 6.14 and that of divinyl ether at τ 5.79.[24] The different shift values are reasonable, since, although the conjugation energies of these compounds are equal,[2] conjugation in the latter is distributed between two vinyl groups, i.e., the conjugation energy of divinyl ether is 7.5 kJ mol^{-1} per vinyl group.

Against this background, the chemical shift data of the present compounds reveal many interesting facts. When one of the β protons of divinyl ether is replaced by a Me group, the shifts (expressed in τ values) of the β′ protons change as follows (the data are from ref 24 and this work):



Moreover, the effect of methyl substitution on the shift of the proton encircled depends on R′ as follows (ref 10, 24, 25, and this work):

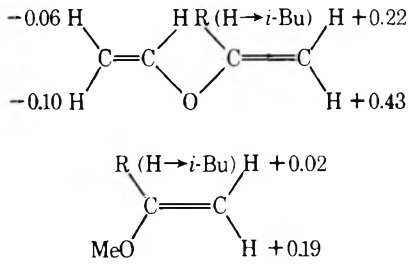


−0.29 ppm (R′ = Me)
−0.58 ppm (R′ = CH_2=CHO)
−0.64 ppm (R′ = MeO)

Accordingly, in divinyl ethers the effect of a β Me group is to increase conjugation in the unsubstituted vinyl group, and to decrease conjugation in the substituted vinyl group as shown by the high decrease in τ value for the case R′ = CH_2=CHO relative to that for R′ = Me.

The effect of an alkyl group in the α position on the shifts

of the β protons in substituted divinyl and methyl vinyl ethers is shown below (ref 17, 24, and this work):



It is seen that in divinyl ethers conjugation decreases slightly in the unsubstituted vinyl group but increases considerably in the substituted vinyl group.

In summary, electron distribution in alkyl-substituted divinyl ethers is markedly sensitive to the number and position of the substituents.

Experimental Section

Materials. (*E*)- and (*Z*)-Propenyl Vinyl Ether (4a and 4b, Respectively). A mixture of allyl alcohol (75 cm^3), ethyl vinyl ether (300 cm^3), and mercuric acetate (15 g) was allowed to stand for 7 days at room temperature, after which it was washed with water and dried ($CaSO_4$). Fractionation gave 45 g of allyl vinyl ether containing some ethyl vinyl ether, bp 60–66 °C (743 Torr). Pure allyl vinyl ether boiled at 66 °C (743 Torr). A mixture of allyl vinyl ether (17 g), Me_2SO (25 cm^3), and KOBu-*t* (4 g) was allowed to stand for 7 days at room temperature, followed by distillation. The product (13 g, **4a**:**4b** ≅ 1:20) was collected at 62 °C (760 Torr). An about 1:1 mixture of the two isomers was obtained by treating the synthetic product (10 g) with $Hg(OAc)_2$ (1.5 g) for 2 weeks at 50 °C followed by fractionation. These two mixtures of **4a** and **4b** were used for the equilibrations and for recording the NMR spectra.

(*E*)- and (*Z*)-Propenyl Isobutenyl Ether (5a and 5b, Respectively). Isobutyraldehyde diallyl acetal was prepared by heating a mixture of isobutyraldehyde (72 g), allyl alcohol (120 g), hexane (100 cm^3), and *p*-toluenesulfonic acid (1 g) in a water-removal assembly until the evolution of water ceased. After cooling, the mixture was made alkaline with NaOMe in MeOH and distilled to give 124 g of the acetal, bp 56–57 °C (8 Torr). It was isomerized to the corresponding dipropenyl acetal by KOBu-*t* in Me_2SO as described above for **4**. The yield of the product, bp 49–50 °C (7 Torr), was 85%. About 0.1 g of *p*-toluenesulfonic acid was added to 26 g of the acetal, and the mixture was heated in a distillation apparatus until the formation of propionaldehyde (rearrangement product of the unstable primary reaction product MeCH=CHOH) ceased. The residual was distilled to give 10 g of a 30:70 mixture of **5a** and **5b**, bp 117–118 °C (751 Torr).

(*E,E*)-, (*E,Z*)-, and (*Z,Z*)-Dipropenyl Ether (6a, 6b, and 6d). Diallyl ether (Fluka AG) was isomerized to dipropenyl ether (mainly **6d**) by KOBu-*t* in Me_2SO as described above (see **4**). A rapid and vigorous conversion occurred when the reactants were heated to ca. 70 °C. The product, obtained in 85% yield, was collected at 85–93 °C (774 Torr). A mixture of the synthetic product (27 g) and $Hg(OAc)_2$ (1.4 g) was refluxed for 115 h. The ratio **6a**:**6b**:**6d** was then 1:3.9:3.6. The mixture was distilled and the pure isomers separated from the distillate by preparative GLC.

(*E,E*)-, (*E,Z*)-, (*Z,E*)-, and (*Z,Z*)-1-Butenyl Propenyl Ether (7a, 7b, 7c, and 7d, Respectively). Butyraldehyde diallyl acetal [bp 181 °C (760 Torr)] was prepared from butyraldehyde and allyl alcohol in 55% yield as described above for isobutyraldehyde diallyl acetal (see **5**). The product was isomerized to the corresponding dipropenyl acetal by KOBu-*t* in Me_2SO. The reaction mixture was extracted with hexane, and the combined extracts were washed with water, dried (K_2CO_3), and distilled to give the acetal in 40% yield, bp 181 °C (760 Torr). Slow distillation of the acetal from a catalytic amount of *p*-toluenesulfonic acid gave first propionaldehyde, and then the desired products in 27% yield, bp 114–116 °C (758 Torr).

(*E,E*)-, (*E,Z*)-, (*Z,E*)-, and (*Z,Z*)-3-Methyl-1-butenyl Propenyl Ether (8a, 8b, 8c, and 8d, Respectively). See preparation of **7** (the starting aldehyde was isovaleraldehyde). Most of the product, bp 131–134 °C (760 Torr), consisted of **8d**.

2-Vinyloxy-4-methyl-1-pentene, (*E*)- and (*Z*)-2-Vinyloxy-4-methyl-2-pentene (9a, 9b, and 9c, Respectively). A mixture of methyl isobutyl ketone dimethyl acetal (30 g, 0.20 mol), 2-bromoethanol (25 g, 0.20 mol), and *p*-toluenesulfonic acid (0.1 g) was heated in a distillation apparatus until the evolution of MeOH ceased. The remainder was cooled, and 30 g (0.28 mol) of KOBu-*t* was added slowly with cooling, after which the mixture was heated. A mixture of *t*-BuOH and mainly **9a** was collected at 40 °C (15 Torr). The alcohol was removed from the mixture as an azeotrope with hexane. Fractionation of the residue gave 7 g (28%) of the desired vinyl ethers, bp 119–124 °C (752 Torr).

2-Isopropenyloxy-4-methyl-1-pentene, (*E*)- and (*Z*)-2-Isopropenyloxy-4-methyl-2-pentene (10a, 10b, and 10c, Respectively). These compounds were prepared from methyl isobutyl ketone dimethyl acetal, 1-chloro-2-propanol, and KOBu-*t* as described above for **9**, bp 132–140 °C (760 Torr).

2-Vinyloxy-3-methyl-1-butene (11a) and 2-Vinyloxy-3-methyl-2-butene (11b). See preparation of **9**. Methyl isopropyl ketone dimethyl acetal served as the starting acetal. The product, obtained in 69% yield, was collected at 99–106 °C (766 Torr).

(*E*)- and (*Z*)-1-Methoxy-1-butene (12a and 12b, Respectively). A mixture of butyraldehyde dimethyl acetal (15 g, 0.127 mol), quinoline (30 cm^3), and some *p*-toluenesulfonic acid was heated in a distillation apparatus. Cleavage of the acetal gave a mixture of MeOH and **12**, which was collected at ca. 64 °C. The alcohol was removed by extraction with water, and the organic layer was dried (K_2CO_3). Three grams (0.035 mol, 27%) of a mixture of **12a** and **12b** remained.

(*E*)- and (*Z*)-1-Methoxy-3-methyl-1-butene (13a and 13b, Respectively). See preparation of **12**. Isovaleraldehyde dimethyl acetal was used as the acetal. The yield was 44%.

In many cases the synthetic route employed gave essentially one of the several possible isomers, although at thermodynamic equilibrium the relative amounts of the other isomers were considerably higher. In those cases the synthetic product was allowed to stand in the presence of a suitable catalyst (mercuric acetate or iodine in cyclohexane) until the thermodynamic equilibrium had been achieved. The product was then distilled, and the isomers were separated from the distillate by preparative GLC if possible. The column used was a Carbowax 20M column.

^{1}H NMR spectra. The spectra were recorded at 60 MHz in CCl_4 solution with Me_3Si as internal standard. In many cases mixtures of isomers were used for recording the spectra, since pure isomers could not always be isolated. The spectra of the unsubstituted vinyl group could be analyzed as AMX spectra, since the geminal coupling constant between the β protons (i.e., the AM portion) was less than one-tenth of the difference in the chemical shifts of the β protons. The chemical shifts are given in τ values and the coupling constants in hertz. **4a:** 3.65 (a), 5.11 (b), 5.74 (c), 3.78 (d), 8.40 (e), 4.91 (f), J_{ab} = 6.4, J_{df} = 12.0, J_{bc} = 0.0, J_{ef} = 6.8. **4b:** 3.59 (a), 5.92 (b), 5.62 (c), 3.88 (d), 8.40 (e), 5.40 (f), J_{ab} = 6.9, J_{ac} = 14.1, J_{bc} = 1.7, J_{df} = 6.8, J_{ef} = 6.8, J_{de} = 1.7. **5a:** 4.13 (a), 8.40 (b, c), 3.86 (d), 8.46 (e), 5.14 (f), J_{df} = 12.4, J_{ef} = 6.9. **5b:** 4.04 (a), 8.44 (b), 8.36 (c), 4.00 (d), 8.40 (e), 5.61 (f), $J_{df} \approx J_{ef}$ = 6.8. **6a:** 3.83 (a, d), 8.46 (b, e), 5.01 (c, f), $J_{ac} = J_{df}$ = 12.3, $J_{ab} = J_{de}$ = 1.4. $J_{bc} = J_{ef}$ = 6.8. **6b:** 3.81 (a), 8.44 (b), 4.99 (c), 3.91 (d), 8.41 (e), 5.46 (f), J_{ac} = 12.9, J_{df} = 6.5, J_{bc} = 6.8, J_{ef} = 7.3. **6d:** 3.92 (a, d), 8.37 (b, e), 5.54 (c, f), $J_{ac} = J_{df}$ = 6.2, $J_{ab} = J_{de}$ = 1.5, $J_{bc} = J_{ef}$ = 7.0. **7b:** 3.79 (a), 8.03 (b), 5.01 (c), 3.97 (d), 8.41 (e), 5.50 (f), 9.00 (g), J_{ac} = 12.4, J_{bc} = 6.8, J_{bg} = 7.3, $J_{df} \approx J_{ef}$ = 6.6, J_{ab} = 1.5. **7d:** 3.99 (a), 7.88 (b), 5.60 (c), 3.99 (d), 8.41 (e), 5.66 (f), 9.03 (g), $J_{ac} \approx J_{bc}$ = 6.6, J_{bg} = 7.5, J_{de} = 1.5. $J_{df} \approx J_{ef}$ = 6.6. **8a:** 3.89 (a), 7.71 (b), 5.03 (c), 3.89 (d), 8.46 (e), 5.09 (f), 9.03 (g), $J_{ac} \approx J_{df}$ = 12.0, J_{bc} = 7.3, J_{de} = 1.5, J_{bg} = 6.9. **8b:** 3.78 (a), 7.70 (b), 5.05 (c), 3.96 (d), 8.44 (e), 5.49 (f), 9.02 (g), J_{ac} = 12.2, J_{bc} = 7.7, J_{bg} = 6.9, $J_{df} \approx J_{ef}$ = 6.8, J_{de} = 1.5. **8c:** 4.09 (a), 7.16 (b), 5.67 (c), 3.80 (d), 8.45 (e), 5.06 (f), 9.04 (g), J_{ac} = 6.2, J_{bc} = 8.7, J_{bg} = 6.9, J_{de} = 1.5, J_{df} = 12.0, J_{ef} = 6.9. **8d:** 4.04 (a), 7.12 (b), 5.71 (c), 3.93 (d), 8.39 (e), 5.54 (f), 9.02 (g), J_{ab} = 0.8, J_{ac} = 6.2, J_{bc} = 8.1, J_{bg} = 7.1, J_{de} = 1.7, $J_{df} \approx J_{ef}$ = 6.7. **9a:** 5.73 (a), 5.39 (b), 5.92 (c), 6.01 (d), 8.05 (e), 9.09 (g), 3.63 (h), J_{ab} = 1.2, J_{ah} = 6.0, J_{bh} = 13.7, J_{cd} = 1.7, J_{ef} = 2.3, J_{fg} = 6.5. **9b:** 5.82 (a), 5.50 (b), 5.50 (c), 8.22 (d), 7.6 (e), 9.02 (f), 3.70 (g), J_{ag} = 6.0, J_{bg} = 13.7, J_{ce} = 9.5, J_{ef} = 6.8. **10a:** 5.7–5.9 (a, b, c, d), 8.04 (e), 8.1 (f), 9.09 (g), 8.18 (h), J_{ef} = 1.8, J_{fg} = 6.9. **10b:** 6.09 (a, b), 5.23 (c), 8.2 (d), 9.00 (f), 8.2 (g), J_{ce} = 9.9, J_{ef} = 6.3. **10c** (only a few signals were detected): 6.1 (a, b), 5.36 (c), J_{ce} = 8.5. **11a:** 5.74 (a), 5.40 (b), 3.63 (c), 5.99 (d, e), 7.66 (f), 8.91 (g), J_{ab} = 1.1, J_{ac} = 6.2, J_{bc} = 13.6, J_{fg} = 6.7. **11b:** 6.03 (a), 5.83 (b), 3.75 (c), 8.35 (d), 8.43 (e), 8.23 (f), J_{ab} = 1.6, J_{ac} = 6.6, J_{bc} = 14.2. **12a:** 3.80 (a), 5.40 (b), 6.59 (c), 8.07 (d), 9.04 (e), J_{ab} = 12.9, J_{bd} = 6.6, J_{de} = 7.5. **12b:** 4.23 (a), 5.78 (b), 6.50 (c), 7.98 (d), 9.08 (e), J_{ab} = 6.2, J_{ad} = 1.3, J_{de} = 7.3. **13a:** 3.80 (a), 5.43 (b), 6.64 (c), ca. 7.8 (d), 9.02 (e), J_{ab} = 12.7, J_{bd} = 7.5, J_{de} = 6.9. **13b:** 4.37 (a), 5.89 (b), 6.49 (c), ca. 7.3 (d), 9.08 (e), J_{ab} = 6.4, J_{bd} = 8.8, J_{ad} = 1.3.

Configurational Assignments. The configurations of the geometric isomers of **4–8** and **12–13** were readily deduced from the magnitude of the vicinal coupling constant across the C=C bond, the

cis coupling constant being 6–7 Hz and the trans coupling constant 12–14 Hz.[26] The configurations of the geometric isomers of **9** were assigned as follows. The first step in the synthesis of **9** involves a reaction between the dimethyl acetal of methyl isobutyl ketone and 2-bromoethanol under acid conditions, which leads to a formation of the isomeric species *i*-BuC(OCH_2CH_2Br)=CH_2 and (*E*)- and (*Z*)-MeC(OCH_2CH_2Br)=CHPr-*i*. From previous thermodynamic studies[12,17,19] it can be inferred that the more stable geometric isomer has the *E* configuration. In the second step, HBr is eliminated from the product of the first stage, and since this process is carried out under basic conditions, no (significant) isomerization occurs during this step. Hence the predominating geometric isomer of the final synthetic mixture must have the *E* configuration. The same arguments were applied for the identification of the geometric isomers of **10**.

Determination of Normal Boiling Points. The standard enthalpies and entropies of vaporization at 298.15 K were estimated from the values of the normal boiling points of the compounds studied. The boiling points were determined by the gas chromatographic method described previously.[12] The values obtained follow (in °C): **4a**, 67.0; **4b**, 62.0; **5a**, 121.3; **5b**, 117.0; **6a**, 101.9; **6b**, 98.5; **6d**, 93.5; **7a**, 125.8; **7b**, 121.8; **7c**, 120.0; **7d**, 113.8; **8a**, 138.5; **8b**, 135.3; **8c**, 131.0; **8d**, 125.0; **9a**, 114.8; **9b**, 120.4; **9c**, 114.8; **10a**, 135.8; **10b**, 138.1; **10c**, 130.8; **11a**, 95.7; **11b**, 107.9; **12a**, 72.6; **12b**, 62.6; **13a**, 86.3; **13b**, 80.0.

Equilibrations. The equilibration experiments on **4**–**8** and **12**–**13** were carried out in the neat liquid with $Hg(OAc)_2$ as catalyst, and those on **9**–**11** in cyclohexane solution with I_2 as catalyst. Whenever available, pure isomers were used as starting materials for the equilibrations. In all cases the position of equilibrium was approached from at least two starting mixtures with sufficiently different isomer compositions to be sure that the true thermodynamic equilibrium had been achieved. The equilibrations were carried out at at least four temperatures between 273 and 423 K. The equilibrated samples were analyzed by GLC using an 8-m Carbowax column. The gas chromatograph was equipped with a HP 3370 B electronic integrator for determining the peak areas. For more details of the equilibration procedure see ref 10 and the previous papers of this series.

Acknowledgment. The authors thank Miss Hannele Kalva, M.S., for some experimental aid.

Registry No.—**4a**, 24268-10-8; **4b**, 24268-09-5; **5a**, 40716-31-2; **5b**, 40716-32-3. **6a**, 4696-28-0; **6b**, 4696-29-1; **6c**, 4696-27-9; **7a**, 61463-28-3; **7b**, 61463-29-4; **7c**, 61463-30-7; **7d**, 61463-31-8; **8a**, 61463-32-9; **8b**, 61463-33-0; **8c**, 61463-34-1; **8d**, 61463-35-2; **9a**, 61463-36-3; **9b**, 61463-37-4; **9c**, 61463-38-5; **10a**, 61463-39-6; **10b**, 61463-40-9; **10c**, 61463-41-0; **11a**, 61463-42-1; **11b**, 61463-43-2; **12a**, 10034-13-6; **12b**, 10034-12-5; **13a**, 31915-76-1; **13b**, 31915-77-2; allyl alcohol, 107-18-6; ethyl vinyl ether, 109-92-2; isobutyraldehyde diallyl acetal, 37406-14-7; isobutyraldehyde, 78-84-2; isobutyraldehyde dipropenyl acetal, 39801-12-2; diallyl ether, 557-40-4; butyraldehyde diallyl acetal, 35020-94-1; butyraldehyde, 123-72-8; isovaleraldehyde, 590-86-3; methyl isobutyl ketone dimethyl acetal, 1112-78-3; 2-bromoethanol, 540-51-2; 1-chloro-2-propanol, 127-00-4; methyl isopropyl ketone dimethyl acetal, 59554-08-4; butyraldehyde dimethyl acetal, 4461-87-4; isovaleraldehyde dimethyl acetal, 57094-35-6.

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Dark Reactions of Halobenzenes with Pinacolone Enolate Ion. Evidence for a Thermally Induced Aromatic $S_{RN}1$ Reaction[1a]

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Received August 31, 1976

Iodo- and bromobenzene react with potassium pinacolone enolate in dimethyl sulfoxide at 25 °C in the dark to form the substitution product, $PhCH_2COC(CH_3)_3$. The reaction behaves in fashion consistent with the $S_{RN}1$ radical chain mechanism but inconsistent with nonchain mechanisms. It is inhibited by the electron scavengers *p*-dinitrobenzene and benzophenone and by the radical scavenger di(*tert*-butyl) nitroxide. It is accelerated by light, and the iodobenzene/bromobenzene reactivity ratio, about 6, is the same in the dark and the photostimulated reactions. Some features of it are not understood: a strange rate law and extraordinary accelerations by O_2, nitrobenzene, and ferric nitrate. Several observations serve to rule out an aryne mechanism, but in the case of *m*-iodoanisole an aryne side reaction was encountered.

In recent years it has been found that halobenzenes, unsubstituted or provided even with electron-releasing substituents, will react with certain nucleophiles under stimulation by electrons or photons to form products of substitution. The behavior of these reactions is consistent with the $S_{RN}1$ mechanism [2] a radical chain mechanism, but not with the longer known S_NAr or benzyne mechanisms. A representative aromatic $S_{RN}1$ reaction is that of phenyl halides with ketone enolate ions[3–6] of which the sort shown in eq 1 will be our present interest.

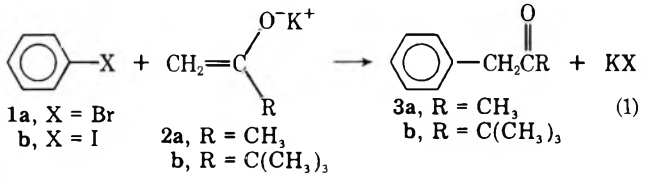
A radical chain mechanism comprises initiation, propagation, and termination steps. Of these, the steps in the propa-

Table I. Reactions of *m*-Iodoanisole with Potassium Pinacolone Enolate (2b) and/or *t*-BuOK in Me_2SO at 25 °C

Expt no.	$[ArI]_0$,[a] M	$[2b]_0$, M	$[t\text{-BuOK}]_0$, M	$[DNB]_0$,[b] M	Time, min	Product yields, % I^-	5b	6	Ratio, 6/5b
1	0.082	0.288	0.038		180	89	58	11	0.19
2	0.0073	0.288	0.038		60	84	51	15	0.29
3	0.0074	0.288	0		60	[c]	58	13	0.22
4	0.0068	0.288	0.038		1	27	26	1	0.05
5	0.0076	0	0.18		45	96		44	
6	0.0066	0.288	0.038	0.0011	10	27	[c]	[c]	
					21	43	16	13	0.84
7	0.0081	0.288	0.038	0.0031	60	[c]	[d]	[d]	1.03

[a] ArI is *m*-iodoanisole. [b] DNB is *p*-dinitrobenzene. [c] Not determined. [d] Because no internal standard was used, only the 6/5b product ratio could be determined.

gation cycle are the most characteristic of a given reaction, for various methods of initiation of the same reaction can often



1a, X = Br
b, X = I

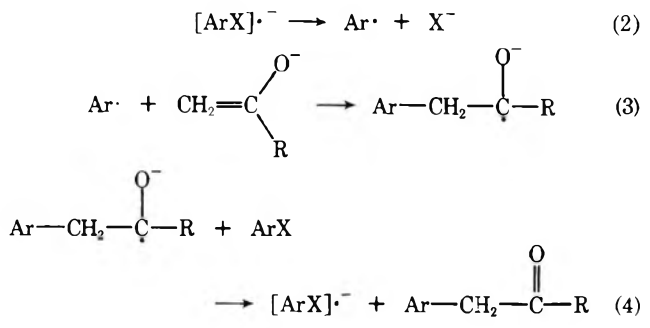
2a, R = CH_3
b, R = $C(CH_3)_3$

3a, R = CH_3
b, R = $C(CH_3)_3$

(1)

be employed and the addition of appropriate substances can often change the termination events. The postulated propagation cycle for the reactions of eq 1 is shown in Scheme I.

Scheme I



(2)

(3)

(4)

In Scheme I, the first propagation step shown is scission of the radical anion of the reacting aryl halide to give an aryl radical and halide ion. The next is combination of the aryl radical with an enolate ion to give a radical anion of the sort sometimes called a ketyl. The last (step 4) is an electron transfer from the ketyl to another aryl halide molecule, furnishing the arylated ketone product as well as the aryl halide radical anion which is the reactant in step 2. Other modes of reaction of the ketyl are also conceivable.

It is plain why solvated electrons in liquid ammonia act to stimulate aromatic $S_{RN}1$ reactions: they convert aryl halides or other substrates to their radical anions, $[ArX]\cdot^-$, which enter the propagation sequence at step 2. Stimulation of these reactions by photons may involve photolysis of the C–X bond[7] or photostimulation of electron transfer from the nucleophile to the substrate.

The initial recognition of aromatic substitution by the $S_{RN}1$ mechanism concerned a reaction, that of some iodopseudocumenes with amide ion in ammonia,[2] that did not depend on stimulation by electrons or photons (unless from the diffuse light of the laboratory). There has, however, been little other evidence of thermally induced aromatic substitution by this mechanism.[8] We recently encountered such a reaction,[9] and now report some of its characteristics.

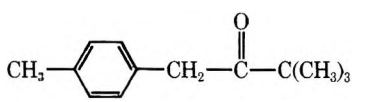
Results

In the course of a brief investigation of photostimulated reactions of bromo- and iodobenzene with ketone enolate ions in dimethyl sulfoxide (Me_2SO) solution, which occur according to eq 1 except that there is also some diphenylation, we observed that substantial reaction also occurs at room temperature without illumination.[10a] For example, iodobenzene (0.1 M) reacted with potassium acetone enolate (0.4 M) at ca. 23 °C to release 31% of iodide ion in only 12 min in the dark.

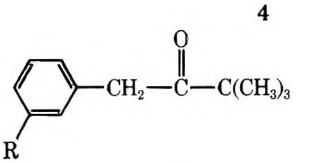
In the photochemical studies it was found that potassium pinacolone enolate (**2b**) reacts about as rapidly as the acetone enolate (**2a**) but gives less diphenylation product and less by-products attributable to aldol condensation. Reactions with **2b** were chosen for principal emphasis in the present work. Iodobenzene (0.1 M) with **2b** (0.4 M) reacting 30 min in the dark released iodide ion in 68% yield. In another experiment, 73% of iodide ion and 70% of 1-phenyl-3,3-dimethyl-2-butanone (**3b**) were formed during 60 min in the dark. In still others, **1b** (0.01M) and **2b** (0.3 M) reacted during 105 min to form **3b** in quantitative yield, and **1b** (0.023 M) with **2b** (0.1 M) afforded 81% of **3b** in a 20-h dark reaction.

Bromobenzene is less reactive. During 90 min in the dark, **1a** (0.1 M) and **2b** (0.4 M) released only 9% of bromide ion. The product of reaction of **1a** with **2b** was shown to be **3b**.

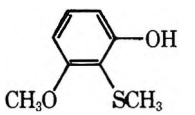
Other aryl iodides were found also to react in the dark in the manner of eq 1. Indeed, we shall report separately on substituent effects on reactivity in such reactions.[10b] We mention here only certain observations that bear on the possibility of an aryne mechanism, either for the main reaction or as a subsidiary reaction pathway. *p*-Iodotoluene reacted with **2b** to give the anticipated *p*-tolyl product (**4**) while *m*-iodotoluene gave its meta isomer (**5a**), each of these isomeric products free of contamination by the other. *m*-Iodoanisole afforded **5b** in 58% yield, but also 13% of a wholly different kind of product, namely, phenol **6**.



4



5a, R = CH_3
b, R = OCH_3



6

Several experiments concerning reactions of *m*-iodoanisole are summarized in Table I. It should be noted (expt 5) that reaction only with *t*-BuOK, **2b** being absent, afforded phenol

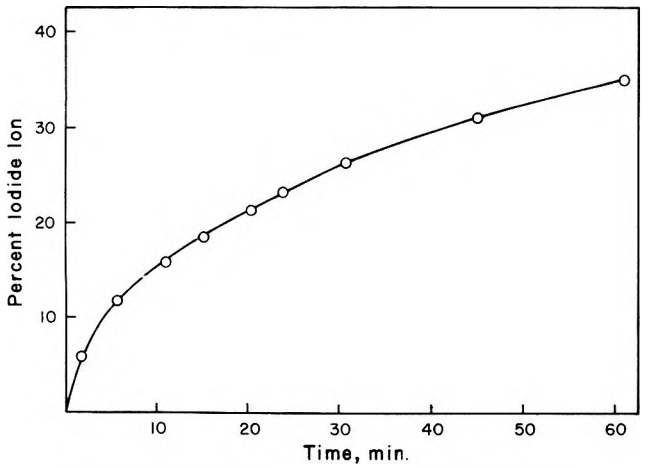


Figure 1. Percent reaction as function of time in dark reaction of iodobenzene (0.0246 M) with **2b** (0.100 M) and *t*-BuOK (0.003 M) in Me_2SO at 25 °C.

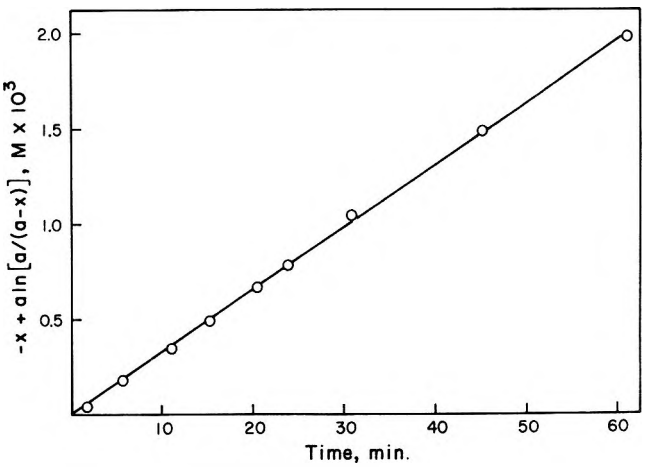


Figure 2. The data of Figure 1 plotted according to eq 6.

6 in substantial amount together with tars and unidentified minor products. In expt 3, no excess *t*-BuOK was present but the yield and proportion of **6** were about the same as in expt 1 and 2. The initial rate of reaction with **2b** is very high, as shown by expt 4; after only 1 min, 27% of iodide ion had been released. Moreover, the products formed in the first minute were richer in ketone **5b** than the products formed during longer periods of reaction.

p-Dinitrobenzene acts to depress overall reaction rate and to increase the fraction of phenol **6** among the products. In expt 6, 17 mol % of *p*-dinitrobenzene was employed and it took 10 min to obtain 27% release of iodide ion whereas the same amount of iodide ion was liberated in only 1 min in the absence of *p*-dinitrobenzene (expt 4). The product ratio of phenol **6** to ketone **5b** was 0.84 in contrast to ratios about 0.2 in the absence of *p*-dinitrobenzene (expt 1–3). With further increase in the amount of *p*-dinitrobenzene present, to 38 mol % (expt 7), there was a small further increase in the phenol/ketone product ratio, to 1.03.

2-Iodomesitylene also reacted with **2b**, but rather slowly. During 3 h in the dark, 20% of iodide ion was released, 15% of 1-mesityl-3,3-dimethyl-2-butanone and 2% of mesitylene were formed, and 80% of 2-iodomesitylene remained unreacted.

Kinetic Studies. Efforts were made to determine the rate law governing the reaction of iodobenzene with **2b**. Reactions were conducted under a blanket of N_2 at 25 °C in flasks wrapped with an opaque covering, and samples were taken at intervals by pipet.

Figure 1 depicts the results of a typical run. Iodide ion release is initially very fast but it slows down remarkably as the reaction progresses toward completion. The data obtained do not fit the simple rate laws appropriate for first- or second-order kinetics or for reaction zero order in reactants but inverse first order in a product. On the other hand they do conform rather well to rate equation 5 in its integrated form (eq 6).

$$dx/dt = k_e[PhI]/[X] \quad (5)$$

$$-x + a \ln \frac{a}{a-x} = k_e t \quad (6)$$

In these equations, a represents the initial concentration of **1b** and x the concentration of iodide ion at any time. The data of Figure 1 are replotted in Figure 2 according to eq 6.

We are unsatisfied by eq 5 and 6 because, as reported below, we find it difficult to ascribe chemical significance to them. Nevertheless, we use the slopes and plots according to eq 6 for the purpose of representing reactivity; they constitute empirical rate constants with units of mol $l.^{-1}$ s^{-1}, symbolized k_e.

Most of our rate measurements are summarized in Table II. The first k_e entry (expt 8) is the average from four runs, the k_e's from which were individually 5.4, 7.0, 7.2, and 5.7 M s^{-1}. Reproducibility was thus good, and remained so throughout this work.

Halving the initial concentration of iodobenzene (expt 9) did not change k_e within experimental error. It ought not to if rate equation 6 is correct, for in its derivation (in eq 5) explicit account is taken of the effect of varying iodobenzene concentration. Equation 6 has some of the characteristics of the rate equation for pseudo-first-order kinetics. As in the case of pseudo-first-order kinetics, iodobenzene is in deficiency with respect to **2b** in all the experiments of Table II, and there is relatively little change in the **2b** concentration during any run.

Doubling the concentration of **2b** doubled k_e; compare expt 10 with expt 8. This again is unexceptional in view of the resemblance to pseudo-first-order kinetics. Halving the **2b** concentration (expt 13) cut k_e by a factor of somewhat more than 2.

The presence of excess potassium *tert*-butoxide (*t*-BuOK) had little effect;[11] compare expt 11 with 9, or expt 12 with 8. However, having molecular pinacolone in excess depressed k_e; compare expt 14 with 13.

Raising the temperature increased the reaction rate. The 10 °C increase from 40 to 50 °C (expt 15 and 16) essentially doubled the rate in almost perfect conformance with the familiar rule of thumb. From expt 15 and 16 and an average k_e at 25 °C of 7.0×10^{-7} M s^{-1}, we calculate the activation enthalpy, $\Delta H^{\ddagger}$, to be 13.2 kcal/mol. Because of the strange units of k_e, we do not undertake to reckon $\Delta S^{\ddagger}$.[12b]

Rate Effects of Added Substances. Addition of KI (expt 17) had little effect. There was a slight induction period, and the k_e was slightly depressed, but the effect was scarcely outside experimental error.

Another candidate for species X in the denominator of eq 5 was the potassium salt of product **3b**, which we symbolize **K3b**. Remarkably, the effect of having **K3b** present together with **2b** was not to retard, but rather to accelerate the liberation of iodide ion. There was an initial burst of iodide ion release, and the overall k_e was approximately doubled in expt 18 and tripled in expt 19. The exaltation was thought perhaps to be due to greater reactivity by **K3b** than by **2b**, but analysis of the organic products formed under the conditions of expt 19 showed that only a small amount of 1,1-diphenyl-3,3-dimethyl-2-butanone had been formed. **K3b** separately appeared to have about the same reactivity as **2b**; compare expt 20 with expt 13.

Table II. Kinetics of the Reaction of Iodobenzene with Pinacolone Enolate Ion in Dimethyl Sulfoxide in the Dark

Expt no.	Temp, °C	$[PhI]_0$, M	$[2b]_0$, M	$[t\text{-BuOK}]_0$, M	Other substance, M	$10^7 k_e$,[a] $M\ s^{-1}$	Comments
8	25	0.023	0.100	0.004		6.3 ± 0.9[b]	
9	25	0.011	0.100	0.004		6.5	
10	25	0.023	0.200	0.006		13.5[c]	
11	25	0.012	0.100	0.106		7.3[c]	
12	25	0.023	0.100	0.060		7.7	
13	25	0.011	0.050	0.054		2.8[c]	
14	25	0.012	0.054		CH_3COCMe_3, 0.046 M	1.3[c]	
15	40	0.024	0.098	0.060		20	
16	50	0.024	0.098	0.060		43	
17	25	0.023	0.100	0.004	KI, 0.12 M	6.3	Slight induction period
18	25	0.023	0.084[d]		**K3b**,[e] 0.02 M	12.5	Initial burst
19	25	0.023	0.100	0.044	**K3b**,[e] 0.016 M	22	Initial burst
20	25	0.024		0.80	**K3b**,[e] 0.063 M	4.2	Initially faster
21	25	0.023	0.100	0.004	$p\text{-}C_6H_4(NO_2)_2$, 0.0060 M	0	
22	25	0.023	0.100	0.004	$p\text{-}C_6H_4(NO_2)_2$, 0.00024 M	0	
23	25	0.023	0.100	0.004	$p\text{-}C_6H_4(NO_2)_2$, 8×10^{-5} M	0.7	
24	25	0.024	0.100	0.060	Ph_2CO, 0.0052 M	1.8	45-min induction period
25	25	0.024	0.100	0.060	Ph_2CO, 0.024 M	1.1	50-min induction period
26	25	0.024	0.100	0.060	$(t\text{-Bu})_2NO$, 0.0024 M	0.3	Initially even slower
27	25	0.023	0.100	0.060	O_2, bubbling	130	
28	25	0.023	0.100	0.004	$PhNO_2$, 0.0034 M	17	Induction period
29	25	0.024	0.100	0.060	$PhNO_2$, 0.006 M	43	Induction period
30	25	0.024	0.100	0.060	$Fe(NO_3)_3$, 0.0025 M	770	
31	25	0.024	0.100	0.060	$Fe(NH_4)_2(SO_4)_2 \cdot 6H_2O$, 0.0025 M	2	
32	25	0.024	0.100	0.060	$Fe_2(SO_4)_3$, 0.0025 M	0.7	
33	25	0.026[g]	0.300	0.037		1.8	

[a] From application of eq 6. [b] Average of four runs; standard deviation is shown. [c] Average of two runs. [d] Pinacolone, 0.016 M, also present. [e] **K3b** is the potassium salt of **3b**. [f] Addition of $Fe(NH_4)(SO_4)_2$ (0.0038 M) after 32 min did not cause noticeable acceleration. [g] Bromobenzene.

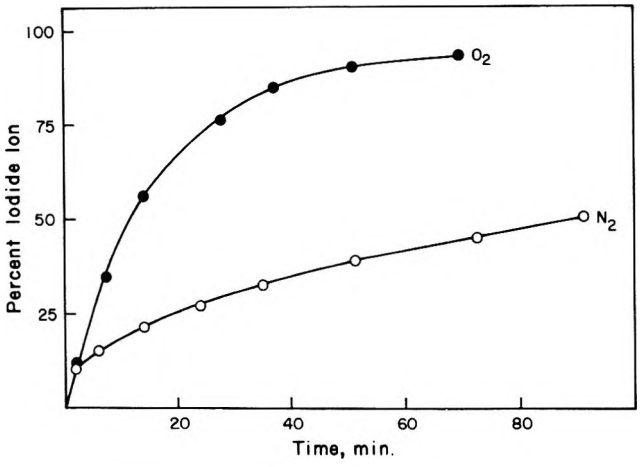


Figure 3. The effect of O_2 on reaction rate. Data of expt 12 and 27, Table II. A plot of the data under O_2 according to eq 6 is linear and steep for the points at 7.4–50.8 min, inclusive.

One would anticipate, on the basis of the mechanism of Scheme I, retardation by reagents that would intercept radicals or act as superior electron acceptors. *p*-Dinitrobenzene has been found to suppress many aliphatic $S_{RN}1$ reactions.[13] In modest concentrations it absolutely stopped the release of iodide ion (expt 21 and 22). Even at the concentration level of 8×10^{-5} M, which represents 0.3 mol with respect to iodobenzene, it reduced k_e tenfold; compare expt 23 with 8.

Benzophenone also inhibits the reaction. At the level of 21 mol % (expt 24) it causes a long induction period and even the subsequent reaction goes at only a quarter of its usual rate. The reaction was still slower in the presence of 100 mol % of benzophenone (expt 25).

Di(*tert*-butyl) nitroxide (expt 26) at the level of 10 mol % severely depressed the rate.

Dioxygen is another familiar radical scavenger. A reaction (expt 27) continuously bubbled with O_2 behaved spectacularly. During the first 5 min iodide ion release occurred about as rapidly as under N_2. But beyond that point iodide ion release remained rapid, whereas it diminished appreciably under N_2; see Figure 3. In terms of k_e values, the reaction under O_2 after the first 5 min was an order of magnitude faster than under N_2. Product analysis on a reaction run under O_2 revealed no formation of **3b**. When a solution of **K3b** in Me_2SO was bubbled with O_2 for 45 min and an attempt was made to recover **3b**, none could be found. In both cases, after esterification of the product mixtures, small amounts (ca. 13%) of methyl benzoate were detected. Ketones are known to undergo autoxidation in basic media.[14]

Nitrobenzene also had an unusual effect. When present to the extent of 14 or 25 mol % in respect to iodobenzene (expt 28 and 29), it inhibited the liberation of iodide ion for a while, but when reaction once started the rate of iodide ion formation was much greater than usual; see Figure 4 for example. Product analysis on a reaction run in the presence of 27 mol % of nitrobenzene showed that iodide ion and **3b** had been formed in yields of 79 and 74%, respectively, and that most of the nitrobenzene had been consumed.

Inasmuch as ferric salts inhibit many radical reactions,[15] the effect of adding various iron salts was investigated. Ferric nitrate (expt 30) strongly stimulated both iodide ion release and the formation of **3b**. However, ferric sulfate and ferric ammonium sulfate (expt 32) as well as ferrous ammonium sulfate (expt 31) mildly inhibited the reaction.

Halogen Mobility. We compared the reactivities of bromo- and iodobenzene by means of competition experiments, several of which are summarized in Table III. The first five concern dark reactions, and among them the **2b** concentration

Table III. Competition between Iodobenzene and Bromobenzene in Reaction with Potassium Pinacolone Enolate (2b) in Me_2SO at 25 °C

Expt no.	$[PhI]_0$, M	$[PhBr]_0$, M	$[2b]_0$, M	$[t\text{-BuOK}]_0$, M	No. of observations	Lighting condition	k_I/k_{Br}
34	0.0050	0.0259	0.288	0.038	4	Dark	7.2
35	0.0051	0.0215	0.288	0.038	3	Dark	7.4
36	0.0075	0.0242	0.098	0.060	4	Dark	6.9
37[a]	0.0080	0.0289	0.049	0.021	6	Dark	6.1
38	0.0072	0.0214	0.049	0.021	4	Dark	5.9
39	0.0075	0.0238	0.049	0.021	4	$h\nu$	5.9
40	0.0094	0.0236	0.049	0.021	3	$h\nu$	5.7

[a] For illustrative detail on expt 37, see Experimental Section and Table IV.

Table IV. Competitive Reactions of 1a and 1b with 2b in Me_2SO at 25 °C;[a] Detail on Expt 37, Table III

Time, min	$[I^-]$, M	$[Br^-]$, M	$\frac{\ln a/(a-x)}{\ln b/(b-y)}$	$\frac{-x + a \ln a/(a-x)}{t}$, $M\,s^{-1} \times 10^8$	$\frac{-y + b \ln b/(b-y)}{t}$, $M\,s^{-1} \times 10^8$
10.0	0.00121	0.00085	5.5	16.2	2.02
20.3	0.00190	0.00121	6.4	20.8	2.03
29.8	0.00206	0.00137	6.2	17.0	1.78
40.0	0.00234	0.00166	5.9	16.8	1.97
60.0	0.00283	0.00194	6.3	17.3	1.80
71.0	0.00303	0.00214	6.2	17.2	1.85
Av			6.1	17.5	1.90

[a] Initial concentration of **1b**, symbolized a, 0.0084 M; initial concentration of **1a**, symbolized b, 0.0304 M; $[I^-]$ and $[Br^-]$ at any time are symbolized x and y, respectively.

varies more than fivefold. Each experiment involved multiple observations; detail on expt 37 is given in Table IV in the Experimental Section. The data suggest a slight dependence of the iodobenzene/bromobenzene rate ratio on **2b** concentration, in the sense that it is higher at higher **2b** concentrations, but the effect is scarcely outside the bounds of experimental error. The average iodobenzene/bromobenzene reactivity ratio from the five experiments under dark conditions is 6.7.

The last two experiments in Table III concern photostimulated reactions conducted in such a way that the dark components of them represent less than 10% of the total. The average iodobenzene/bromobenzene reactivity ratio for the last two, 5.8, is within experimental error identical with that for the preceding two dark experiments (expt 37 and 38) which involved identical concentrations of **2b** and *t*-BuOK. Thus in competition experiments the reactivity ratio is the same for the dark reaction as for the photostimulated reaction.

Relative reactivity in the foregoing experiments was reckoned by means of eq 7

$$\frac{k_I}{k_{Br}} = \frac{\ln([PhI]_0/[PhI]_t)}{\ln([PhBr]_0/[PhBr]_t)} \qquad (7)$$

which is appropriate if some reactive intermediate reacts bimolecularly and competitively with iodo- and bromobenzene.[12a] However, if one evaluates data from a competition experiment by means of eq 6, the data for iodo- and bromobenzene being treated separately, one obtains a different estimate of relative reactivity. Specifically, the data of expt 37 (Table III) give k_I/k_{Br} of 6.1 when reckoned by the standard formula (eq 7), but k_e^I/k_e^{Br} obtained via use of eq 6 was 9.2.

We believe it better to reckon relative reactivity in competition experiments by means of eq 7, despite the fact that eq 6 serves well to represent events in particular runs and even the behavior of iodo- and bromobenzene when reacting admixed (see Table IV, Experimental Section). The basis of this judgment is our belief that step 4 (Scheme I) is the one in which the involvement of iodo- or bromobenzene in the propagation sequence is determined.

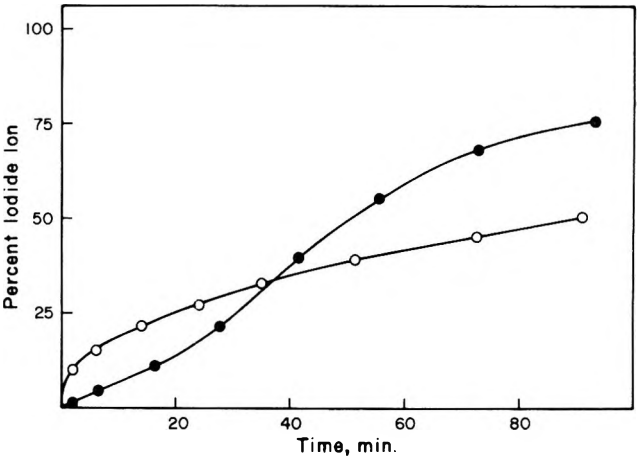


Figure 4. The effect of nitrobenzene on reaction rate. Open circles: without nitrobenzene (expt 12, Table II). Filled circles: with nitrobenzene (expt 29, Table II); a plot of these data according to eq 6 is linear and steep for the points at 41.5–93.0 min, inclusive.

One might anticipate that initiation would be somewhat faster for iodo- than for bromobenzene, and therefore that bromobenzene would react faster in the presence of iodobenzene than in its absence. We have observed that to be the case, as shown in Figure 5. The effect is clear but not spectacular.

In another experiment, iodobenzene was allowed to react completely with excess **2b**, and then bromobenzene was added to the system. The reactivity of bromobenzene under these conditions was the same as in a freshly mixed solution of the same **2b** concentration. Clearly the beneficial effect of iodobenzene is bestowed as iodobenzene reacts; it is not a matter of the iodobenzene reaction destroying some deleterious im-

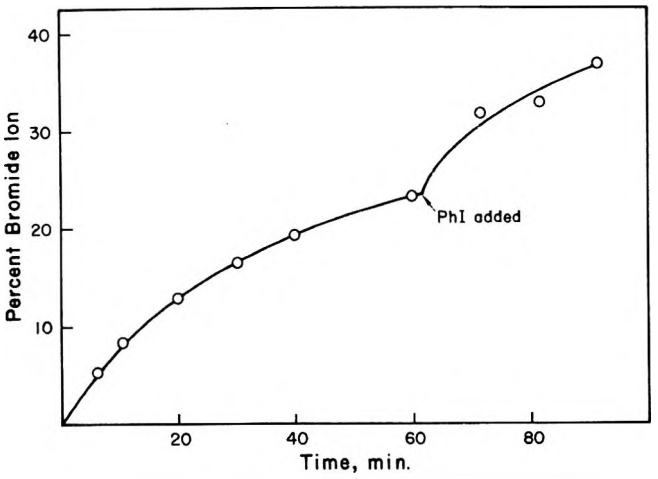


Figure 5. The effect of adding iodobenzene (0.0055 M) on the rate of release of bromide ion in the reaction of bromobenzene with **2b**. Data prior to the time iodobenzene added are treated as expt 33, Table II.

purity or generating some long-lived species that assists the bromobenzene reaction.

Discussion

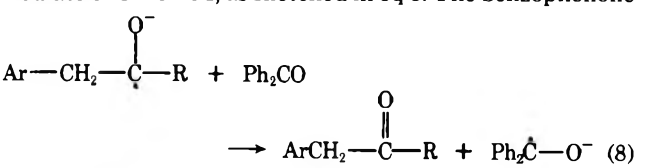
We have found that iodobenzene (**1b**) reacts readily in Me_2SO solution at room temperature with potassium pinacolone enolate (**2b**) to form substitution product **3b**, according to eq 1. Other salient observations are that the reaction appears to obey the peculiar rate law of eq 5 and 6, that it is inhibited by *p*-dinitrobenzene, benzophenone, or di(*tert*-butyl) nitroxide and accelerated by light, and that nitrobenzene, dioxygen, and ferric nitrate have strange kinetic effects. Also, in competition experiments the reactivity of bromobenzene is about one-sixth that of iodobenzene.

These facts constitute compelling evidence that the dark reaction of **1b** with **2b** to form **3b** has a radical chain mechanism. The data are not compatible with a nonchain mechanism.

An important item of evidence toward that conclusion is that the reaction is inhibited by the electron scavenger *p*-dinitrobenzene, being totally stalled even by 1 mol % of this inhibitor in respect to iodobenzene. Inhibition by *p*-dinitrobenzene has often been observed for $S_{RN}1$ reactions at aliphatic sites.[13] In the present case it is possible that **2b** reacts with *p*-dinitrobenzene to form the *p*-nitro derivative of **3b**[16] and that that product or something derived from it is the effective inhibitor. Such reaction would of course consume some **2b**, but the diminution in **2b** concentration would be negligible.

Di(*tert*-butyl) nitroxide is a familiar scavenger of reactive radicals.[17] The fact that, at the level of 10 mol % in respect to **2b**, it reduces the rate to about 5% of its normal value is consistent with a radical chain mechanism.

Inhibition by benzophenone is less familiar. Plausibly, it acts by taking an electron from the postulated ketyl intermediate of Scheme I, as sketched in eq 8. The benzophenone

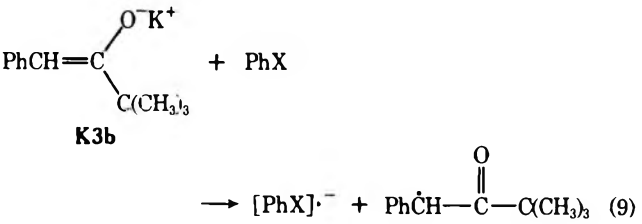


ketyl thereby formed is undoubtedly a more stable species, less able to continue the propagating chain by furnishing an electron to an iodobenzene molecule in the manner of eq 4, more likely to accumulate and to act as a scavenger of reactive radicals.

Acceleration of the reaction of **1b** with **2b** by illumination is also compatible with a radical chain mechanism. Many radical chain mechanisms, including $S_{RN}1$ reactions at aromatic[4] and aliphatic[13] centers, are stimulated by photons, but photoacceleration is not by itself compelling evidence for a radical mechanism.

The fact that the iodobenzene/bromobenzene reactivity ratio is within experimental error identical, about 6, for the thermal and the photostimulated reactions is very important because it is strong evidence that the same mechanism prevails under both sets of conditions.

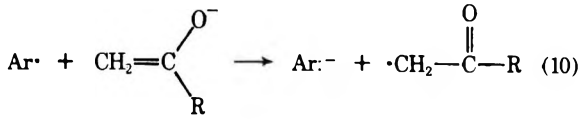
A plausible interpretation can be given for the fact that the potassium enolate of product **3b** accelerates the reaction of **1b** with **2b**. It is that **K3b** is especially effective in initiation of the radical chain. We have no direct evidence of the nature of the initiation process but we think it possible that it involves electron transfer from **2b** to **1b** so as to form the iodobenzene radical anion which enters the propagation sequence (Scheme I) at step 2. If so, **K3b** should be a better electron donor because of resonance stabilization of the resulting radical (eq 9).



K3b

Thus numerous observations deny a nonchain mechanism but are consistent with a radical chain mechanism. The $S_{RN}1$ propagation sequence of Scheme I is compatible with the evidence.[18] Our ideas as to the probable nature of the initiation process are stated immediately above.

The present work provides no evidence as to what the termination steps are. Other work[6b] suggests that termination may involve the occasional reaction of phenyl radical with the enolate ion differently than in step 3, namely, by electron transfer as in step 10. The resulting β-keto alkyl radicals would then dimerize.



The Aryne Mechanism Possibility. Because solutions of enolate ions such as **2b** in Me_2SO are strongly basic and it is known that *t*-BuOK in Me_2SO at 25 °C can generate benzyne from bromobenzene (albeit slowly),[19a] the possibility of an aryne mechanism for reaction 1 needs to be seriously considered.

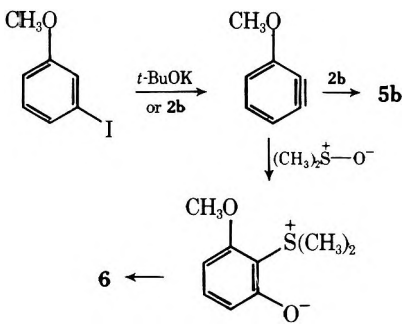
Several items of evidence inveigh against it. First, excess *t*-BuOK does not accelerate the reaction (expt 11, Table II) and the diminution of rate caused by having pinacolone in excess (expt 14) is much less than would be expected if aryne formation were requisite to the reaction. Second, the reaction of *p*-iodotoluene with **2b** gives only the *p*-methyl derivative of **3b**. None of the *m*-methyl derivative, which was obtained separately by reaction of *m*-iodotoluene with **2b**, was detectable as a product from the reaction of *p*-iodotoluene with **2b**. Had the latter reaction gone via the aryne mechanism, addition of **2b** to the intermediate 4-methylbenzyne ought actually to have progressed to somewhat more of the *m*-methyl than of the *p*-methyl derivative of **3b**.[19b] Furthermore, 2-iodomesitylene, a substance incapable of being converted to a benzyne derivative, reacts with **2b** in the manner of eq 1.

However, a side reaction by the aryne mechanism was observed in the case of *m*-iodoanisole. The side reaction forms

phenolic product 6 in yield about 13%. Earlier, phenol 6 had been obtained by Birch, Chamberlain, and Oloyede[20] by the action of dimsyl sodium on o-bromoanisole. It was explained to result from elimination of the elements of HBr from o-bromoanisole to generate 3-methoxybenzyne, addition of a dimethyl sulfoxide molecule with the negatively charged oxygen of the sulfoxide attaching to the arynic position meta to the methoxy group (the position favored for nucleophilic attack), and finally protonation at oxygen and demethylation from sulfur. Previously a similar reaction had been observed from the action of *t*-BuOK in Me_2SO on an aryl bromide, and it was similarly rationalized.[21]

We postulate the genesis of **6** in the reaction of *m*-iodoanisole with **2b** and/or *t*-BuOK to involve the same sort of process, as sketched in Scheme II. Besides adding dimethyl

Scheme II



sulfoxide as mentioned, the postulated aryne intermediate conceivably may add the pinacolone enolate ion from **2b** and then a proton to form **5b**, the major product obtained. Rigorously, we should ask two questions: is *any* of the **5b** actually produced via the aryne route? Is perhaps *all* of the **5b** produced by that route? Our data show that the answers to these two questions are *yes* and *no*, respectively. The data indicate that some **5b** is produced by the aryne route but most by the $S_{RN}1$ mechanism.

The aryne mechanism (Scheme II) is a nonchain, ionic mechanism and should be insensitive to small amounts of the $S_{RN}1$ inhibitor, *p*-dinitrobenzene. Experimentally, the presence of 17 mol % of *p*-dinitrobenzene during the reaction of *m*-iodoanisole with **2b** strongly depressed the overall rate and strongly altered the product proportions so as to increase the **6**/**5b** product ratio (Table I, expt 6). In the presence of a greater amount of *p*-dinitrobenzene (expt 7), the **6**/**5b** product ratio was further elevated by a small amount.

Inasmuch as *p*-dinitrobenzene at the levels used in expt 6 and 7 absolutely stops the reaction of iodobenzene with **2b** (Table II, expt 21 and 22), the products formed from *m*-iodoanisole in the presence of *p*-dinitrobenzene must come totally or nearly so from the aryne route of Scheme II. The data indicate that under the conditions employed the aryne partitions almost equally between the pathways leading to **6** and to **5b**. It follows that in the absence of *p*-dinitrobenzene most of the **5b** is produced by the $S_{RN}1$ route and some by the aryne route; for example, in expt 1 or 3, Table I, about 20% of the **5b** was formed by the aryne route and about 80% by the $S_{RN}1$ route. This is a case of some pedagogical value: within a single reacting system two competing mechanisms, one ionic, the other a radical chain mechanism, lead from the same reactant to the same product.

At a very short reaction time (expt 4, Table I) the product mixture is much richer in ketone **5b** than at longer reaction times. This indicates that phenolic product **6** acts to inhibit the $S_{RN}1$ mechanism, allowing the aryne mechanism a greater share at later stages of the reaction.

Huisgen and Herbig[22] determined the rate of aryne generation from numerous substituted bromobenzenes through the action of lithium piperidide in diethyl ether solution. In the case of *m*-bromoanisole, only formation of 3-methoxybenzyne was detectable; it results from attack on the hydrogen between the bromine and methoxy substituents. The partial rate factor, relevant to attack on one ortho hydrogen in bromobenzene, was 600.

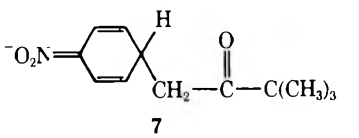
For purposes of discussion, let us assume that the same partial rate factor is applicable to reactions of **2b** with iodobenzene and with *m*-iodoanisole in Me_2SO. Taking account of the facts that about 40% of the reaction of *m*-iodoanisole is by the aryne mechanism, that *m*-iodoanisole reacts with **2b** by the $S_{RN}1$ mechanism about 39 times faster than iodobenzene,[10b] and that iodobenzene has two ortho hydrogens, we estimate that about 8% of the reaction of iodobenzene with **2b** would occur by the aryne mechanism. The estimate warrants low confidence because of uncertainty as to whether the partial rate factor can be transferred from one system to another of rather different character. For what it is worth, it does tend to confirm more direct evidence that the reaction of eq 1 does not occur by the aryne mechanism. It does suggest, however, that the aryne mechanism may have a minor role. Perhaps small amounts (1% or less) of *o*-(methylthio)phenol are produced by a process analogous to Scheme II. If so, inhibition of the $S_{RN}1$ reaction would occur. This may be the origin of the mysterious X in the denominator of eq 5.

Further evidence against the aryne mechanism is the fact that the reaction of bromobenzene with **2b** is slower than of iodobenzene, and that it is also halted by addition of *p*-dinitrobenzene. Bromobenzene is generally more reactive than iodobenzene by the aryne mechanism.[22,23]

New Questions. We report above some extraordinary kinetic effects of nitrobenzene, dioxygen, and ferric nitrate. We cannot explain them, but we wish to comment on their broad significance and their characteristics and to draw attention to them as topics for future attention.

The broad significance of the extraordinary accelerations caused by these additives, sometimes preceded by an induction period, is that they are incompatible with nonchain ionic mechanisms On the other hand, the overall rates of radical chain reactions can in principle be greatly augmented by an added substance if it somehow causes an increased rate of initiation or ties up some substance which otherwise is active in termination. Therefore these extraordinary effects, even though unexplained, support the hypothesis that these reactions occur by a radical chain mechanism.

Nitrobenzene at first inhibited and then accelerated the reaction of **2b** with **1b**; see Figure 4. Observations associated with this spectacular behavior are that a good yield of **3b** was obtained, that most of the nitrobenzene was used up, and that no detectable amount of the *p*-nitro iderivative of **3b** was formed. One cannot be sure whether nitrobenzene itself or some species derived from it, or both, is responsible for the observed effects. Nitrobenzene is a good electron acceptor;[24] its inhibiting action may well involve accepting electrons from the postulated ketyl intermediate (Scheme I) in competition with propagation step 4. It is further possible that nitrobenzene adds the enolate ion to form a σ complex such as **7**. Two-electron oxidation of 7 plus deprotonation would form



7

the *p*-nitro derivative of **3b** which, though not obtained as such, may have been further converted to other substances. Presumably something derived from **7**, from the nitrobenzene radical anion, or from something else in the system acts as an initiator, but we do not know what it is.

Dioxygen in the first few minutes had little kinetic effect but later iodide ion release was faster than usual; see Figure 3. No **3b** was obtained, and it was shown that **3b** is destroyed under reaction conditions by an oxidation reaction which produces some benzoic acid. Hydroperoxides are believed to be intermediates in the oxidation.[14] Conceivably after they have accumulated to some extent they decompose to form radicals which effectively initiate the propagation sequence of Scheme I.

The tremendous accelerating effect of ferric nitrate (expt 30, Table II) defies explanation. The accelerated reaction genuinely forms **3b**, but of the few ferric salts tried the nitrate was the only one with noteworthy effect. Apparently the nitrate ions are somehow involved.

Experimental Section

Materials. The Me_2SO was purified by the method of Steiner and Ritchie[25] except that distillation was from calcium hydride and sodium amide. It was stored under Ar in a foil-wrapped flask fitted with a three-way stopcock. Transfer was carried out by withdrawal through the stopcock using a long needle syringe with Ar flowing through the stopcock via the side arm. In one experiment using Me_2SO distilled only from calcium hydride (but not sodium amide), *m*-iodotoluene was observed to react only half as fast as had been observed several months earlier. When a new batch of Me_2SO was prepared, once again distilled from a mixture of calcium hydride and sodium amide, the rate was the same as observed earlier. The purity of the Me_2SO and care in transfer and handling are critical to good reproducibility of the kinetic data.

Potassium *tert*-butoxide was freshly sublimed just prior to use, quickly weighed, and transferred directly to the nitrogen flushed reaction flask.

Aryl halides were distilled until colorless and stored in foil-wrapped brown bottles.

Aldrich pinacolone was dried over molecular sieves for several days and distilled through a Vigreux column; a forerun of about 40% was discarded. The main fraction (bp 106 °C) was distilled again. A sizable forerun was again discarded and the main fraction, bp 106 °C, was stored over molecular sieves.

GLC Analysis. Gas chromatography was carried out on a Hewlett-Packard 5750 flame ionization instrument. A 3.2 mm × 0.91 m 4% Carbowax 20M on Chromosorb G column was used. Yields of products were determined by usual methods using internal standards. In all cases, the areas were corrected for molar response as determined from standard solutions of the products and the internal standard. Preparative GLC isolations were carried out on a Varian Aerograph A-90P instrument using either a 6.4 mm × 0.61 m 20% SE-30 on Chromosorb G or 6.4 mm × 0.91 m 14% Carbowax 20M on Chromosorb G column.

Dark Reaction of Halobenzene and Pinacolone Enolate in Me_2SO. Typical Procedure. A. Potassium *tert*-butoxide (freshly sublimed) was placed into a 100-ml one-neck flask with a gas inlet side arm and short condenser. The flask and fittings were completely wrapped with opaque tape and all reactions were carried out in a nitrogen atmosphere. Dimethyl sulfoxide (50 ml) was added with a syringe through the condenser and after several minutes of stirring the apparatus was placed in a 25 °C thermostat bath. After equilibration the appropriate amounts (Table I) of aryl halide and pinacolone were added and the flask was well swirled to mix the contents. At the desired time (Table I), the solution was acidified with dilute nitric acid, 150 ml of water was added, and the mixture was extracted with three portions of ether. The combined ether fractions were washed with water and dried. In preparative runs, the ether was removed and the resulting product was purified by preparative GLC and distillation. In analysis runs, an internal standard was added and the ether solution was analyzed by GLC. The aqueous extracts were usually titrated for halide ion.

B. Kinetic measurements were made as in A except that 5-ml aliquots were removed through the condenser at various intervals. In each case, care was taken not to introduce oxygen into the system by purging the pipet with Ar prior to insertion into the flask. The aliquots were delivered into an acidic quenching solution and titrated for free halide ion.

C. Competition experiments were carried out as in B except that bromobenzene was added with the iodobenzene. In one case, a portion of the solution was neutralized and worked up as described in A. Analysis of the ether revealed 0.127 mmol of **3b**. Total halide present was found to be 0.132 mmol, of which 0.042 mmol was bromide and 0.090 mmol iodide ion. This experiment shows that C_6H_5Br as well as C_6H_5I is converted to **3b**.

Detailed data on a representative competition experiment are given in Table IV.

D. Photochemical competition experiments were carried out in the same manner except that the Pyrex flask was not wrapped, and after dissolution of the *t*-BuOK the solution was placed in a Rayonet photochemical reactor which contained a water bath previously adjusted to ca. 25 °C. The reactor was turned on, halides and ketone were added, the flask was swirled, and aliquots quickly removed.

E. Reactions in which added substance effects were studied were carried out as in A and B except that the appropriate inhibitor was added with or just prior to halobenzene and pinacolone addition.

3,3-Dimethyl-1-(*p*-methylphenyl)-2-butanone (4) was prepared from *p*-iodotoluene as described in A above and had mp 35–36 °C; NMR (CCl_4) δ 1.15 (s, 9 H), 2.33 (s, 3 H), 3.67 (s, 2 H), and 7.07 (s, 4 H); IR (film) 1715, 1515, 1475, 1365, 1060, and 770 cm^{-1}; MS *m/e* 190 (molecular ion) and 105 (base peak).

Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.29; H, 9.57.

3,3-Dimethyl-1-(*m*-methylphenyl)-2-butanone (5a) was prepared from *m*-iodotoluene as described in A above and isolated as a colorless liquid: NMR (CCl_4) δ 1.10 (s, 9 H), 2.27 (s, 3 H), 3.58 (s, 2 H), and 6.7–7.1 (m, 4 H); IR (film) 1715, 1615, 1480, 1370, 1060, 760, and 690 cm^{-1}; MS *m/e* 190 (molecular ion) and 105 (base peak).

Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.63, 81.54; H, 9.67, 9.61.

Reaction of *m*-Iodoanisole and Pinacolone Enolate in Me_2SO. The reaction of 1.00 g (4.27 mmol) of *m*-iodoanisole, 1.50 g (15 mmol) of pinacolone, and 1.90 g (17.0 mmol) of *t*-BuOK was carried out for 3 h as described in A above. GLC analysis revealed an unknown product with retention time slightly less than that of the substitution product **5b**. Preparative GLC (SE-30 column) afforded pure **5b** (formed in 58% yield): mp 57.5–58 °C; NMR (CCl_4) δ 1.18 (s, 9 H), 3.67 (s, 2 H), 3.77 (s, 3 H), 6.42–7.33 (m, 4 H); IR (film) 1715, 1585, 1490, 1265, 1055, 765, and 690 cm^{-1}; MS *m/e* 206 (molecular ion) and 121 (base).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.90; H, 8.71.

The other product, collected at 162 °C, was 3-methoxy-2-(methylthio)phenol (**6**) (formed in 11% yield) and had NMR (CCl_4) δ 2.22 (s, 3 H, CH_3S), 3.87 (s, 3 H, CH_3O), and 6.23–7.27 (m, 4 H); IR (film) 3380, 2930, 2840, 1600, 1470, 1450, 1320, 1265, 1220, 1080, and 775 cm^{-1}; MS *m/e* 170 (molecular ion and base peak) and 155.

The 3,5-dinitrobenzoate derivative had mp 146–147.5 °C (three recrystallizations from aqueous ethanol) (lit. 146–148 °C).[20]

Preparation of 3,3-Dimethyl-1-mesityl-2-butanone. Ammonia (250 ml) was distilled from K into a three-neck flask flushed with N_2. Potassium *tert*-butoxide (3.36 g, 0.03 mol), pinacolone (2.00 g, 0.02 mol), and iodomesitylene (2.46 g, 0.01 mol) were added. The flask was irradiated in a Rayonet photochemical reactor for 2 h; then 2.4 g of ammonium nitrate was added. The ammonia was evaporated and the residue was taken up in ether and water. The ether layer was washed with water, dried, and concentrated. Addition of 20 ml of petroleum ether and cooling on dry ice gave crystalline product, mp 79–80 °C (lit.[26] 80–81 °C); the yield in two crops was 1.15 g (53%); NMR (CCl_4) δ 1.23 (s, 9 H), 2.06 (s, 6 H), 2.23 (s, 3 H), 3.72 (s, 2 H), 6.76 (s, 2 H).

This product was identical with that obtained in the reaction of iodomesitylene and **2b** carried out as in A and B above.

Registry No.—**1a**, 108-86-1; **1b**, 591-50-4; **2b**, 51742-96-2; **3b**, 6721-67-1; **4**, 61394-79-4; **5a**, 61394-80-7; **5b**, 61394-81-8; **6**, 33617-66-2; potassium *tert*-butoxide, 865-47-4; *p*-iodotoluene, 624-31-7; *m*-iodotoluene, 625-95-6; *m*-iodoanisole, 766-85-8; 3,3-dimethyl-1-mesityl-2-butanone, 61394-82-9; iodomesitylene, 4028-63-1.

References and Notes

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(18) The radical anion structure presented in steps 3 and 4, Scheme I, shows the extra electron to be located, in effect, in a carbonyl group π^* orbital. Another possible location for it is a benzene ring antibonding π orbital. Transfer of the electron between the two π systems is doubtless rapid; cf. M. Szwarc and J. Jagur-Grodzinski in M. Szwarc, "Ions and Ion Pairs in Organic Reactions", Vol. 2, Wiley, New York, N.Y., 1974, pp 71–85.
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Notes

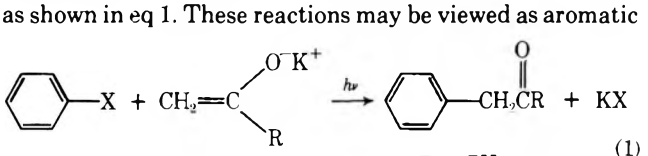
Photostimulated $S_{RN}1$ Reactions of Halobenzenes with Ketone Enolate Ions in Dimethyl Sulfoxide Solution[1a]

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Received August 31, 1976

Many ketone enolate ions react with halobenzenes in liquid ammonia, under Pyrex-filtered irradiation, to form α-phenyl derivatives of the ketones.[2-5] Reactions occur, for example, as shown in eq 1. These reactions may be viewed as aromatic



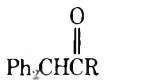
(1)

1a, X = Br **2a**, R = CH_3 **3a**, R = CH_3
b, X = I **b**, R = $C(CH_3)_3$ **b**, R = $C(CH_3)_3$

nucleophilic substitutions, and they are believed to occur by the $S_{RN}1$ mechanism.[6-9]

It has also been observed that reactions according to eq 1 occur in dimethyl sulfoxide (Me_2SO) solution.[4,10] We now describe further observations of the reaction in Me_2SO.

Several experiments of descriptive character are summarized in Table I. The reactions of bromo- and iodobenzene with the enolate ions of both acetone and pinacolone occur readily to give high yields of monophenylation products of type **3** often accompanied by small yields of diphenylation products of type **4**.



4a, R = CH_3
b, R = $C(CH_3)_3$

Some preliminary measurements of the rate of reaction of bromobenzene with **2b** are presented in Table II. In most of these experiments, samples withdrawn at various times were analyzed by titration for bromide ion. Results of a typical experiment are displayed in Figure 1. During about the first 40% of the reaction the absolute rate, in $M\ s^{-1}$, was nearly constant; later it diminished. We were unable to fit the data for entire experiments to simple rate expressions, such as those for first- and second-order kinetics, and therefore tabulate initial zero-order rate coefficients in Table II.

In Table II, one can see that there was considerable variation in rate among experiments conducted identically or nearly so. For example, compare expt 11, 14, 15, and 16. Changing the concentration of bromobenzene or the enolate ion by a factor of 2 affected the rate very little; compare expt 16 with 17, or 12 and 13 with 11, 14, 15, and 16, or 18 with 19. Experiments 18 and 19 were carried out with a lower intensity of irradiation than the rest; they are based on the same batch of solution of **2b** in Me_2SO, and were performed the same day.

In early work efforts were made to determine the rate of photostimulated reaction of iodobenzene with **2a** and **2b**. We found that a substantial fraction of the reaction occurred before irradiation was started. Study of the photostimulated reaction with bromobenzene was more attractive because the dark reaction is much slower. We report elsewhere[11] a study of the kinetics of the dark reaction of **2b** with iodobenzene.

Spectrophotometric studies between 300 and 400 nm showed weak absorption by bromobenzene, strong absorption by **2b**, and very strong absorption ($A > 3$) by the enolate ions of **3a** and **3b** and by the reaction solution from expt 16, Table II, after 27 min irradiation (60% reaction). The very strong absorption by product enolate ions is perhaps a reason for the diminution in zero-order rate at later stages of reaction; see Figure 1.

Also noteworthy is that typical reaction mixtures, although initially colorless to the eye, became yellow on exposure to the atmosphere. This complicates transfer of solution aliquots, as in the dispensing of portions of a master reaction solution into tubes intended to be removed for analysis at different

Table I. Product Yields in Photostimulated Reactions of Halobenzenes with Ketone Enolate Ions in Dimethyl Sulfoxide Solution

Expt no.	Substrate, concn	Enolate, concn	Irradn time, min	Products, % 3[a]	4[b]
1	**1b**,[c] 0.05 M	**2a**,[e] 0.20 M	60	81[g]	11[i]
2	**1b**, 0.03 M	**2a**, 0.25 M	60	88	4
3	**1b**, 0.049 M	**2b**,[f] 0.40 M	62	99	
4	**1a**,[d] 0.10 M	**2b**, 0.40 M	90	87[h]	~9[j]

[a] Product is **3a** if **2a** used, or **3b** if **2b** used. [b] Product **4a** if **2a** used, or **4b** if **2b** used. [c] Registry no., 591-50-4. [d] Registry no., 108-86-1. [e] Registry no., 35648-48-7. [f] Registry no., 51742-96-2. [g] Registry no., 103-79-7. [h] Registry no., 6721-67-1. [i] Registry no., 781-35-1. [j] Registry no., 58343-20-7.

Table II. Rates of Photostimulated Reaction of Bromobenzene with Potassium Pinacolone Enolate in Dimethyl Sulfoxide Solution

Expt no.	[1a], M	[2b], M	Temp,[a] °C	No. of lamps[b]	$10^5 k_0$, M s^{-1}
11	0.05	0.20	26–30	16	1.8
12	0.025	0.20	29–32	16	1.6
13	0.025	0.20	30.5–32.5	16	2.0
14	0.05	0.20	31–34	16	3.0
15	0.05	0.20	35–34	16	4.0
16	0.05	0.20	34	16	1.7
17	0.025	0.10	34–34.5	16	1.7
18[c]	0.025	0.10	34	4	0.88
19[c]	0.127	0.10	34	4	0.77

[a] Temperatures at beginning and end of irradiation are given, in that order. [b] Number of lamps used in photochemical reactor. [c] Experiments 18 and 19 utilized the same batch of solution of **2b** in Me_2SO, and were conducted differently from the rest; see Experimental Section.

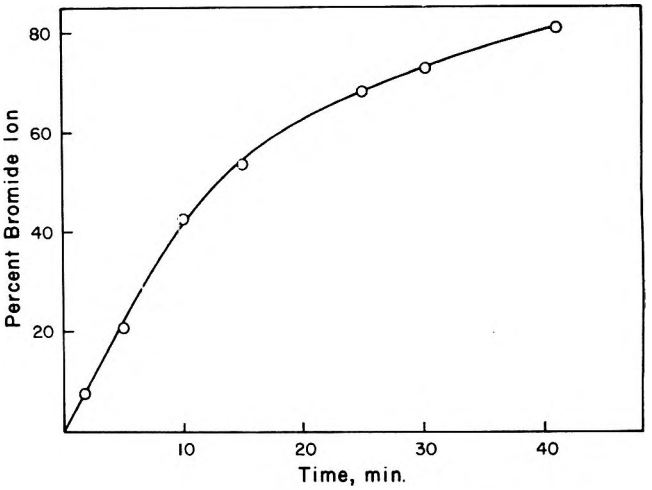


Figure 1. Bromide ion release as a function of time in the reaction of bromobenzene with potassium pinacolone enolate (**2b**) in Me_2SO. Data of expt 17, Table II.

times. In any future experiment of that type, rigorous exclusion of dioxygen during transfer operations should be ensured.

We report elsewhere[11] that, in competitive photostimulated reaction of a mixture of **1a** and **1b** with **2b** in Me_2SO, the iodobenzene/bromobenzene reactivity ratio is about 6.

Investigation of this photostimulated reaction is not being continued.

Experimental Section

Materials and solvents were obtained and purified as described elsewhere.[11] Product determinations were made by GLC as there described.

3,3-Dimethyl-1,1-diphenyl-2-butanone (4b). A flask containing a solution of 2.85 g of iodobenzene, 2.50 g of 3,3-dimethyl-1-phenyl-2-butanone (**3b**), and 3.20 g of *t*-BuOK in 250 ml of liquid ammonia was fitted with a condenser cooled with solid CO_2 in 2-propanol and a drying tube, placed in a Rayonet photochemical reactor fitted with "350-nm" lamps and irradiated for 2 h with occasional interruptions to spray the exterior with 2-propanol and wipe away the frost. The solvent was allowed to evaporate, water and dilute HCl were added, the mixture was extracted with diethyl ether, and the extract was evaporated. The residue was crystallized from methanol: yield 1.15 g (33%); mp 131–131.5 °C; NMR (CCl_4) δ 1.13 (s, 9 H), 5.43 (s, 1 H), 7.10 (s, 10 H); IR (KBr pellet) 704, 741, 1060, 1370, 1401, 1456, 1479, 1502, 1590, 1700, and 2976 cm^{-1}; MS *m/e* 252 (M^+), 167 (likely Ph_2CH^+). Anal. Calcd for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.46; H, 8.05.

Kinetic Procedure. A single-neck 100-ml flask with a gas inlet side arm and short condenser was purged with N_2. A weighed portion of *t*-BuOK, slightly in excess of the ketone to be used, was placed in the flask and then 50 ml of Me_2SO was added through the condenser by means of a syringe. After being stirred for several minutes, the solution was alternately evacuated and flushed with N_2 for at least three cycles. The system was placed in a Rayonet Model RPR-100 photochemical reactor equipped with 16 "350-nm" fluorescent tubes rated at 24 W. (In expt 15–19, Table II, the flask was placed in a glass vessel within the reactor containing water preheated to 34 °C). The ketone and halobenzene were added in the dark, the solution was swirled for mixing, and an aliquot was removed to ascertain how much dark reaction had occurred. Another aliquot was removed and placed in an N_2-flushed, screw cap test tube wrapped with aluminum foil. (This portion was maintained at reaction temperature until the end of the period of irradiation, when it was quenched.) Irradiation was begun and aliquots were removed at recorded times by syringe, through the condenser with N_2 flowing slowly, and delivered into dilute HNO_3 in water for quenching. Halide ion in the quenched aliquots was determined by potentiometric titration with standard $AgNO_3$.

For expt 18 and 19, Table II, the reaction solution was prepared under N_2 in a flask in the dark, and 5-ml aliquots were transferred to screw cap test tubes flushed with argon. The tubes were placed in a "merry-go-round" within the reactor which rotated during irradiation, which was performed with only 4 of the usual 16 lamps in service. Tubes were removed for quenching at recorded times.

Registry No.—Dimethyl sulfoxide, 67-68-5.

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(1) (a) Research supported in part by the donors of the Petroleum Research Fund, administered by the American Chemical Society. (b) On sabbatical leave from Ripon College, 1975–1976.
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Nitrogen Photochemistry. A Time Dependent Photooxidation of Alcohols by Aromatic Nitro Compounds

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Received July 1, 1976

The photoreduction of nitrobenzene by alcohols,[2-8] amines,[9] hydrocarbons,[10] and ethers[9] has been documented, and the absorption band of nitrobenzene in the 330-nm region assigned to an n,π^* transition,[11,12] and the hydrogen abstraction process to a triplet of nitrobenzene.[3,14] Hurley and Testa[3] have shown the reduction of nitrobenzene to be quite inefficient at long irradiation times, i.e., the quantum yield for the disappearance of nitrobenzene in 2-propanol is 0.011. The hydrogen abstraction results in the formation of acetone, and the quantum yield of acetone generation is approximately twice that for the disappearance of nitrobenzene.[3,13]

Experimental Section

Chemicals and Equipment. 2-Propanol was purified by distillation from magnesium, 1-propanol was refluxed over $NaBH_4$ and redistilled from magnesium, and nitrobenzene and propanol were distilled immediately before making up samples. 1,3,5-Trinitrobenzene was recrystallized from diethyl ether.

Irradiation of 1,3,5-Trinitrobenzene in 1-Propanol for Isolation of Acetal. A solution containing 1.32 g of 1,3,5-trinitrobenzene in 250 mL of 1-propanol (0.025 M) was prepared and degassed at 5 × 10^{-4} Torr. The sample was irradiated for 12 h using 366-nm lamps in a Rayonet photochemical reactor. Approximately 200 mL of 1-propanol was removed from the sample by distillation and the acetal collected by GLC on a Wilkens Aerograph Autoprep Model A-700 equipped a 10 × 0.25 in. 20% Carbowax 20M on Chromosorb W column: NMR (CCl_4) δ 1.0–1.6 (m, 15 H) 3.75 (m, 4 H), 4.8 (t, 1 H).

Quantum Yields. The quantum yields were run in a modified Rayonet merry-go-round[14] using a Hanovia 450-W medium-pressure mercury arc lamp. The 366-nm lines were isolated with Corning 0-52-7-37 filter. The samples were degassed four times to 5 × 10^{-4} Torr in 13 × 100 mm Pyrex tubes, sealed, and irradiated. A modified potassium ferrioxalate actinometry procedure was used.[15] The light intensity was measured before and after the samples were irradiated. After irradiation, the samples were opened and an aliquot was added to a known solution of chlorobenzene as an internal standard. The samples were then analyzed on a Beckman GC-5 using a 20-ft Carbowax on Chromosorb W column at 85 °C (aldehyde and acetal) and 95 °C (acetone). The amountsnofieldehyde and acetal in the dark reaction solution were subtracted from the amounts found in the irradiated samples before the quantum yields were calculated.

Results

The quantum yields of product formation for the 1-propanol–trinitrobenzene, 2-propanol–nitrobenzene, and 1-propanol–nitrobenzene solutions were found to decrease with increasing amounts of radiation, cf. Table I. These quantum yields are based on the amount of carbonyl compound produced both in the free as well as the acetal/ketal form. Only a negligible amount of 2,3-dimethyl-2,3-butanediol was found at the longest irradiation time of the 2-propanol reaction solution. At long irradiation times, the results herein reported are comparable to those reported by Hurley and Testa.[3] That is, at 4.8 × 10^{-4} einsteins, the quantum yield of acetone formation is 0.022 (this work); and, at 5 × 10^{-4} einsteins, the quantum yield of nitrobenzene disappearance was reported to be 0.011.

To determine the effect of acid on the irradiation of nitrobenzene in 2-propanol, a reference irradiation in 50% aqueous 2-propanol was compared to that of an acidic 2-propanol solution of nitrobenzene. In the acid solution, the quantum yields did not change (0.080 ± 0.003) with the amount of exposure, contrary to all of the neutral solution results.

The unirradiated portion of each sample was analyzed simultaneously with the irradiated sample and any observed product from a dark reaction compensated for; the optical density of the nitroaromatic solutions were always greater than 2 and the conversion of nitroaromatics was small. The quantum yields reduced in size much faster than sample conversion.

Discussion

The quantum yield change phenomenon observed in these solutions occurs in all four neutral alcoholic and aqueous slutions examined, on two different alcohols and with two different nitroaromatics. The phenomenon does not occur in acid solution. There are two possible explanations for these observations. Impurities could be causing the change or a

Table I. Quantum Yields for the Production of Aldehydes or Ketones

Nitroaromatic (concn), alcohol	Total einsteins × 10^6	Φ
Trinitrobenzene[a] (0.026 M), 1-propanol	12.7	0.071
Trinitrobenzene[a] (0.026 M), 1propanol	25 4	0.041
Trinitrobenzene[a] (0.026 M), 1-propanol	76.2	0.022
Trinitrobenzene[a] (0.026 M), 1-propanol	177.8	0.015
Nitrobenzene (0.098 or 0.195 M), 2-propanol	15.6	0.27
Nitrobenzene (0.098 or 0.195 M), 2-propanol	29.0	0.20
Nitrobenzene (0.098 or 0.195 M), 2-propanol	88.6	0.088
Nitrobenzene (0.098 or 0.195 M), 2-propanol	192	0.052
Nitrobenzene (0.098 or 0.195 M), 2-propanol	338	0.037
Nitrobenzene (0 098 or 0.195 M), 2-propanol	860	0.026
Nitrobenzene (0.098 or 0.195 M), 2-propanol	1030	0.022
Nitrobenzene (0.098 or 0.195 M), 1-propanol	10.9	0.067
Nitrobenzene (0.098 or 0.195 M), 1-propanol	29.5	0.045
Nitrobenzene (0.098 or 0.195 M), 1-propanol	91.0	0.025
Nitrobenzene (0.098 or 0.195 M), 1-propanol	266.0	0.015
Nitrobenzene (0.098 or 0.195 M), 1-propanol	1010.0	0.010
Nitrobenzene (0.0098 M), 2-propanol–water	19.9	0.12
Nitrobenzene (0.0098 M), 2-propanol–water	87.0	0.036
Nitrobenzene (0.0098 M), 2-propanol–water	386.0	0.017
Nitrobenzene (0.0098 M), 2-propanol–12 M HCl	17.9	0.083
Nitrobenzene (0.0098 M), 2-propanol–12 M HCl	114.0	0.079
Nitrobenzene (0.0098 M), 2-propanol–12 M HCl	470.0	0.082

quencher(s) could be formed in the solution as a consequence of the initial photochemical process.

Although it is difficult to rigorously exclude all impurities from the system, impurities probably are not responsible for the observed results because a solvent impurity would not show a dependence on the amount of light absorbed; nitrobenzene and solvents purchased from several sources gave duplicate results, and these results agree with Hurley and Testa's published results at long irradiation times.[3] Thus, the quencher idea is most plausible.

If a quencher is being generated which is not photochemically active, its concentration should be proportional to the total amount of light, and plots of I^0/I vs. E should be linear. Actually, these plots are reasonably linear in the initial stages of the reaction but progressively decrease to zero slope. Thus, the newly formed quencher is also decomposed by light, and its concentration becomes constant after a period of time. Nitrobenzene, itself, is not a quencher since the quantum yields are not dependent on the initial nitrobenzene concentration.

A nitroxide radical(s) is a good candidate for the quencher formed since these are known to be formed under the reaction conditions[13,16,17] and di-*tert*-butyl nitroxide has been used as a triplet quencher.[18] Since nitroxides are destroyed by acid,[16] the 2-propanol–nitrobenzene irradiation was done in an aqueous, acidic solution and the results compared to those from the corresponding neutral, aqueous solution. In acid, the quantum yield remains constant with time, albeit at a lesser value than the initial quantum yield in neutral solution.

The quantum yield effect described herein means that nitrobenzene is more efficient at product formation than earlier recognized. Consequently it is necessary to reevaluate the conclusion of Hurley and Testa[3] that the low quantum yield of nitrobenzene disappearance is due to a short lifetime of triplet nitrobenzene, ca. 10^{-9} s. Their determination was done with the assumption that no complexes are formed between any of the species present. However, nitrobenzene is known to form charge transfer complxes with benzene[19] and piperylene[20] and, furthermore, the formation of such complexes can increase the rates of radiationless processes.

Acknowledgments. This investigation was supported in part by a Public Health Service Research Career Development Award (1-K4-GM-9888, V.I.S.), a Hill Foundation Research Professorship (G.F.V.), and research grants 1-RO-AI-08138 from the National Institutes of Health, U.S. Public Health Service (V.I.S.), and Research Corporation (G.F.V.).

Registry No.—1,3,5-Trinitrobenzene, 99-35-4; nitrobenzene, 98-95-3; 1-propanol, 71-23-8; 2-propanol, 67-63-0; propanol, 123-38-6; acetone, 67-64-1.

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Ylide Autoxidation during the Stevens Rearrangement

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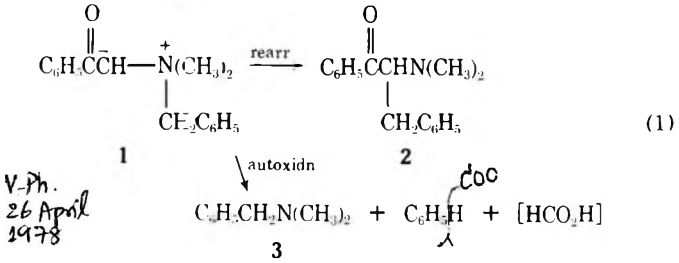
Received June 22, 1976

The autoxidation of enolate anions has been studied in detail by Doering and Haines[1] and more recently reinvestigated by Sawaki and Ogata.[2] Although the mechanistic question of a 1,2-dioxetane or an α-keto hydroperoxide intermediate remains unresolved, the overall process of oxidation followed by cleavage is well established.

Carbonyl stabilized ylides provide an example of a special enolate anion in which the onium atom can also participate in the anion stabilization process. Because of our interest in ylide rearrangements[4] it was of concern to know if a similar autoxidation process might occur with these anions. In the following we report our observations that such autoxidation of an ylide does occur competitive with the Stevens rearrangement process at lower temperatures and in those cases when oxygen is present.

Results and Discussion

Ylide **1** smoothly rearranges in chloroform to **2** with a specific rate constant of 5.9×10^{-4} min^{-1} at 0 °C as determined by following the reaction by NMR. The spectral data along with subsequent workup of the reaction mixture showed that dimethylbenzylamine (**3**) was also formed. The ratio of Stevens rearrangement product (**2**) to dimethylbenzylamine (**3**) varied markedly, dependent upon the amount of oxygen present in the reaction mixture (Table I). In addition, the major nonbasic product recovered was benzoic acid in a molar amount similar to the dimethylbenzylamine.



(1)

The presence of both dimethylbenzylamine and benzoic acid was of particular interest because of their relationship

Table I. The Effect of Oxygen on Product Distribution[a]

Atmosphere	Rel % products: Rearr (2)	Rel % products: Autoxidn (3)
Vacuum[b]	100	0
N_2[c]	76	24
Air[c]	65	35
O_2[c]	37	63
O_2[d]	22	78

[a] Ylide in $CDCl_3$ (0.25 M) at 0 °C. [b] Evacuated and freeze–thaw degassed. [c] Atmosphere over reaction solution. [d] Sample stirred in oxygen atmosphere.

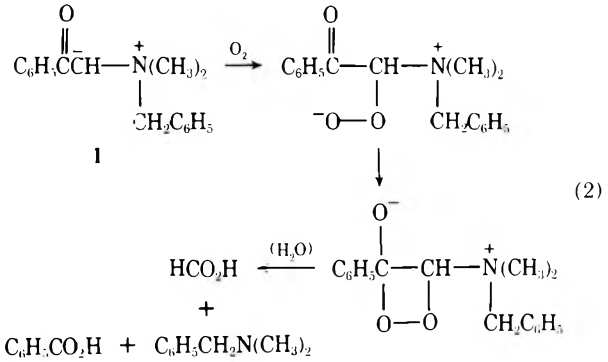
Table II. The Effect of Temperature on Product Distribution[a]

Temp, °C	Rel % products	
	Rearr (2)	Autoxidn (3)
0	65	35
12	75	25
24	86	14
29	88	12
34	91	9

[a] Ylide in $CDCl_3$ (0.24 M) with air atmosphere.

to other potential reaction pathways for the nitrogen ylide. Thus a carbenoid decomposition of the ylide to give tribenzoylcyclopropane and benzyldimethylamine could have been indicated. This process has been observed for phenacyl sulfur[5a] and nitrogen[5b] ylides. However, in our work no tribenzoylcyclopropane (or precursor dibenzoylethylene) was detected. Benzoic acid might have originated through oxidation of the benzyl radical[6] escaping from the proposed radical pair cage of the Stevens rearrangement.[7] Yet no indication of dimethylphenacylamine, the other component of the cage pair, was found.

The phenacyl stabilized ylide is a special case of an enolate anion. Doering and Haines[1] have shown that enolate anions autoxidize and cleave. In the case of phenones, benzoic acid is one of the fragmentation products. In our work, equal amounts of benzoic acid and benzyldimethylamine would be expected to form as is experimentally observed (eq 2). We have



(2)

also observed the formation of phenyl substituted dimethylbenzylamines when the starting ylides were *p*-methoxybenzyl and *p*-chlorobenzyl phenacylammonium.

It is of interest that dimethylbenzylamine was not reported in the many previous studies of the Stevens rearrangement.[7,8] Further results (Table II) demonstrate that there is a marked temperature dependence on the rates of the competitive Stevens rearrangement and autoxidation–cleavage reactions. The latter process is only important at low temperatures. The Stevens rearrangement has normally been studied at elevated temperatures precluding the observation of significant autoxidation product.

Experimental Section

Benzyldimethylammonium phenacyl ylide (1) was prepared by the method of Ollis et al.:[8c] mp 72–73 °C; NMR ($CDCl_3$) δ 3.3 (s, 6), 5.9 (s, 2), 7.3–8.0 (m, 10). (The ylide carbanion proton is not observed.)

Kinetics of the rearrangement process were obtained by mixing the precooled ylide and solvent in a cold NMR tube, then following the disappearance of the ylide $-N^+(CH_3)_2$ peak and appearance of the product $N(CH_3)_2$ peak. The temperature of the reaction was controlled by an appropriate constant temperature bath or by the variable temperature unit of the NMR spectrometer (Varian A-60).

Product analysis was based upon the NMR spectrum of the total reaction, or in some cases by running an identical reaction on a larger scale and isolating products. Final analysis was by gas chromatography and/or NMR spectra.

The effect of oxygen was studied by changing the gas over the sample in the NMR tube or within the flask in larger scale reactions. In one case, the NMR tube was evacuated, sealed, and degassed.

Acknowledgment. Support from the donors of the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.

Registry No.—**1**, 25241-18-3; **2**, 30669-80-8; **3**, 103-83-3.

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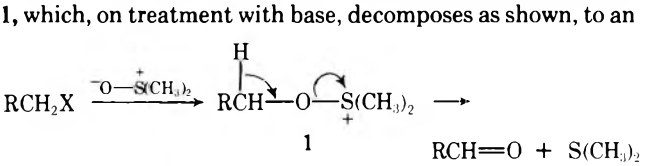
A One-Step Conversion of RCH_2CO_2H to RCH=O

Leon Mandell,* Richard F. Daley, and R. A. Day, Jr.

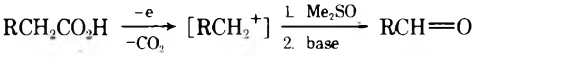
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Received July 2, 1976

The electrolytic decarboxylation of carboxyl functions to a variety of products has been the subject of much study in recent years.[1] Typically the products are those formed via radical intermediates; however, in some cases the oxidation of the radical to form carbonium ion proceeds more rapidly than the radical reactions.[2,3] Our interest in exploring this area was due to the possibility of utilizing carbonium ions so generated for the production of Moffatt oxidation intermediates. The Moffatt oxidation usually involves[4] solvolysis of alkyl halides or tosylates in dimethyl sulfoxide to form the product **1**, which, on treatment with base, decomposes as shown, to an



aldehyde and dimethyl sulfide. We have now demonstrated that it is possible to combine the two processes described above by carrying out electrolytic decarboxylation in dimethyl



sulfoxide as the solvent to produce directly the Moffatt intermediate. Workup with base according to the usual Moffatt procedure then affords the desired aldehyde.

This reaction was run on a number of phenylacetic acids. The results of this survey are summarized in Table I. It is apparent from the failure of 4-nitrophenylacetic acid to undergo this transformation that the reaction indeed does involve a carbonium ion and is not a free-radical process.

Experimental Section

Electrolysis Apparatus. The electrolytic vessel was a 100-ml three-neck round-bottom flask fitted with a Claisen adapter con-

Table I. Oxidative Decarboxylation of Phenylacetic Acids

R = [a]	Aldehyde, %[b]	Kolbe dimer, %[c]	Other products, %[d]
4-Methoxy	72		4-Methoxybenzoic acid, 14%
3-Methoxy	78		3-Methoxybenzoic acid, 12%
4-Chloro	62	12	4-Chlorobenzoic acid, 15%
Hydrogen	41	52	
4-Nitro	0	82	

[a] Registry no. are, respectively, 104-01-8, 1798-09-0, 1878-66-6, 103-82-2, 104-03-0. [b] Registry no. are, respectively, 123-11-5, 591-31-1, 104-88-1, 100-52-7. [c] Registry no. are, respectively, 5216-35-3, 103-29-7, 736-30-1. [d] Registry no. are, respectively, 100-09-4, 586-38-9, 74-11-3.

taining a gas lead in pipe and condenser, and, in the outer joints, a pair of smooth platinum electrodes (1 cm^2). The electrodes were placed parallel to each other 3 cm apart.

4-Methoxybenzaldehyde. To a solution of 3.32 g (0.02 mol) of 4-methoxyphenylacetic acid in 70 ml of dry Me_2SO was added 0.48 g (0.01 mol) of 50% sodium hydride suspended in mineral oil. This solution was placed in the above cell. The solution was degassed by bubbling nitrogen through the stirred solution for 30 min. Fifty-five volts at 0.25 A was applied to the solution for 4 h. Sodium bicarbonate (5 g, 0.065 mol) was added and the mixture heated to 150 °C for 4 min and cooled rapidly by quenching in an ice bath. The mixture was poured into 350 ml of saturated sodium chloride solution. This was extracted with 4 × 150 ml of ether. Evaporation of the solvent left an oily residue which, on distillation, afforded 1.96 g (74%) of 4-methoxybenzaldehyde. The physical and spectral properties were identical with those of an authentic sample.

The aqueous layer was acidified and extracted with 3 × 75 ml of ether. On evaporation of the solvent a crystalline solid remained which was recrystallized to afford 0.44 g (14%) of 4-methoxybenzoic acid.

The reaction was repeated with the following phenylacetic acids: 3-methoxy, 4-chloro, hydrogen, and 4-nitro. The results are given in Table I. All products were identified by comparison with authentic samples.

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Preparation of Alkyl Phenyl Sulfides by Electrophilically Catalyzed Displacement of Certain Nucleophiles by Thiophenoxy Group[1]

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Received November 3, 1976

Water and alcohols are commonly considered to be solvents of high nucleophilicity[2] and upon their reaction with a carbenium ion afford the corresponding alcohol and ether. In fact, Winstein et al.[3] have employed water as an effective agent for intercepting carbocationic species in order to elucidate relevant reaction mechanisms. More recently certain charged nucleophiles, such as azide ion, have been used for the same purpose.[4] Comparing Ritchie's N_+ values for various *charged* nucleophiles, it appears that thiophenoxide anion is by far a better trapping agent than azide by over two orders of magnitude in methanol and even larger in Me_2SO.[4] N_+ values for a given nucleophile show a marked dependence upon the medium, the obvious trend being the greater the basicity of the medium the larger the N_+ value. In a protic medium of high acidity thiophenoxide can no longer exist, of course, as a charged species but rather as its protonated form, namely thiophenol. The purpose of this note is to show that thiophenol itself exhibits a marked reactivity toward carbenium ions, being capable of displacing rather readily various nucleophiles at a carbenium ion center (eq 1).

$$RZ + PhSH \xrightarrow{\text{cat.}} RSPh + HZ \quad (1)$$
$$Z = OH, OR, Cl, N_3$$

The ready conversion of triphenylcarbinol and *tert*-butyl alcohol to the corresponding alkyl sulfides by their acid-catalyzed reaction with thiols[5] has been known for a long time. It is quite probable that this reaction owes its feasibility to the ready ionization of these alcohols in acid media, and to the pronounced nucleophilicity of thiols. Employing a modification of this method we found that certain alkyl phenyl sulfides can be prepared very conveniently and in high yields. The results are summarized in Table I. According to this method an alcohol is transformed to the corresponding alkyl phenyl sulfide by boiling an equimolar mixture of the alcohol and thiophenol in benzene or methylcyclohexane, in the presence of perchloric acid catalyst. The results indicate that ease of reaction and product yield are highly dependent on the structure of the alcohol. Aryl methanols and tertiary alcohols, which are expected to have high pK_{R+} values, react readily with thiophenol and the yields of the sulfides are usually good to excellent. Primary alcohols require exceedingly long reaction times and even so the corresponding sulfides are produced in very poor yields.

Perhaps more novel could be the ready displacement of alcohol in the acid-catalyzed reaction between thiophenol and certain ethers. Upon dissolving an equimolar mixture of 2-phenylisopropyl methyl ether and thiophenol in trifluoroacetic acid (TFA) an exothermic reaction takes place and the ether is transformed instantly into the relevant phenyl sulfide (eq 2).

$$Ph(CH_3)_2COCH_3 + PhSH \xrightarrow{\text{TFA}} Ph(CH_3)_2CSPh + CH_3OH \quad (2)$$

Results with various ethers from reactions such as 2 are summarized in Table II. Two main factors seem to emerge from the examination of the data. (a) The basicity of the ether; comparing cases 2 and 3 it can be seen that methyl ether is less reactive than the ethyl analogue, and this might well be due to lower basicity of the methyl ether[6] (eq 3a). (b) The stability

$$ArCH_2{-}OR + H^+ \rightleftharpoons ArCH_2{-}O^+(H)H \quad (a)$$

$$ArCH_2{-}O^+(H)H \rightleftharpoons ArCH_2^+ + ROH \quad (b) \quad (3)$$

of the carbenium ion produced in step b obviously is the second important factor. *o*-Chlorobenzyl methyl ether appears to be inert under the reaction conditions employed in this investigation, whereas the *p*-chlorobenzyl ether reacted incompletely. This can be understood by comparing, for example, the ionization potentials of benzyl and *p*-chlorobenzyl radicals.[8] *p*-Chlorobenzyl cation appears to be less stable by

Table I

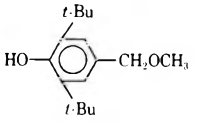
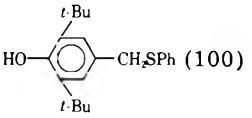
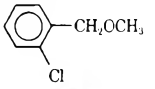
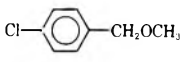
$$ROH + PhSH \xrightarrow[-H_2O]{H^+ClO_4^-} RSPh$$

Registry no.	Alcohol	Reaction time	Sulfide (yield, %)	Registry no.
100-51-6	$PhCH_2OH$[a]	16 min	$PhCH_2SPh$ (25)	831-91-4
105-13-5	p-$CH_3OC_6H_4CH_2OH$[b]	15 min	p-$CH_3OC_6H_4CH_2SPh$ (90)	5023-67-6
98-85-1	$Ph(CH_3)CHOH$[b]	15 min	$Ph(CH_3)CHSPh$ (100)	21213-26-3
91-01-0	Ph_2CHOH[b]	11 min	Ph_2CHSPh (100)	21122-20-3
75-84-3	$(CH_3)_2(CH_3CH_2)COH$[b]	30 min	$(CH_3)_2(CH_3CH_2)CSPh$ (53)	41469-79-8
123-51-3	$(CH_3)_2CHCH_2CH_2OH$[c]	84 h	$(CH_3)_2CHCH_2CH_2SPh$ (13)	13910-11-7

[a] In boiling methylcyclohexane. [b] In boiling benzene. [c] In boiling toluene. Standard conditions: 0.1 mol alcohol; 0.1 mol PhSH; 1.0 mL 70% $H^+ClO_4^-$; solvent 100 mL; Dean-Stark water separator.

Table II

$$R\text{-}OR' + PhSH \xrightarrow{TFA} R\text{-}SPh + R\text{—}OH$$

Registry no.	Ether	Remarks	Sulfide (conversion,[a] %)	Registry no.
935-67-1	1 $Ph(CH_3)_2COCH_3$	Rapid, RT[b]	$Ph(CH_3)_2CSPh$ (100)	4148-93-0
538-86-3	2 $PhCH_2OCH_3$	24 h, 53 °C, incomplete reaction	$PhCH_2SPh$ (75)	
539-30-0	3 $PhCH_2OCH_2CH_3$	24 h, 53 °C, complete reaction	$PhCH_2SPh$ (100)	
87-97-8	4 	Rapid, RT	 (100)	17258-84-3
5670-78-0	5 $Ph_2CHOCH_2CH_3$	Very rapid, RT	Ph_2CHSPh (100)	
7495-83-2	6 $Ph_2CHO(CH_2)_3CH_3$	Very rapid, RT	Ph_2CHSPh (100)	
59579-08-7	7 	No reaction, 53 °C, 48 h		
1195-44-8	8 	61 h, 53 °C, incomplete reaction	p-$ClC_6H_4CH_2SPh$ (70)	7693-30-3
10574-17-1	9 $PhOCH(CH_2CH_3)CH_3$	No reaction, 48 h, 53 °C		
103-50-4	10 $PhCH_2OCH_2Ph$	42 h, 53 °C, complete reaction	$PhCH_2SPh$ (100)	

[a] Based on analysis by NMR. [b] Standard conditions: 10 mmol of ether, 15 mmol of thiophenol, 2 mL of TFA.

4 kcal/mol. An even larger[9] destabilizing effect could be expected for the o-chloro substituent.

The transformation depicted in eq 4 has been carried out successfully.

$$ROR' + HN_3 \xrightarrow{TFA} RN_3 + R'OH$$

$$RN_3 + PhSH \xrightarrow{TFA} RSPh + HN_3 \quad (4)$$

R = 2-phenylisopropyl, benzhydryl, 3,5-di-*tert*-butyl-4-hydroxybenzyl

The ease of reaction of the azides studied seems to parallel that of the corresponding ethers. For example, 2-phenylisopropyl azide reacts exothermically with thiophenol in the presence of TFA and it is converted to the relevant sulfide rapidly. It is quite possible that the displacement of the azide group follows an S_N1 pathway, through the intermediacy of a protonated azide species (eq 5).

$$RN_3 \xrightarrow{TFA} RN_3^+H \rightarrow R^+ + HN_3 \xrightarrow{PhSH} RSPh \quad (5)$$

Certain organic halides were found to react with thiophenol in $POCl_3$ solvent and in the presence of catalytic amounts of ferric chloride (eq 6).

$$RCl + PhSH \xrightarrow[POCl_3]{FeCl_3} RSPh + HCl \quad (6)$$

Particularly clean reaction occurs with *tert*-butyl chloride and the yield of the *tert*-butyl phenyl sulfide is quantitative. Less reactive appears to be benzyl chloride; under the same conditions about 30% remained unreacted. Employing ferric chloride and *tert*-butyl chloride in equimolar quantities the reaction with thiophenol is complete within minutes at room temperature. This most probably means that under these conditions *tert*-butyl chloride ionizes to the relevant carbenium ion to a substantial extent[11] (eq 7).

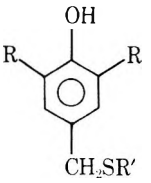
$$t\text{-}BuCl + FeCl_3 \xrightarrow{POCl_3} t\text{-}Bu^+FeCl_4^-$$

$$\xrightarrow[\text{fast}]{PhSH} t\text{-}BuSPh + H^+FeCl_4^- \quad (7)$$

The chlorides *n*-butyl, *sec*-butyl, benzhydryl, and *p*-chlorobenzyl did not react with thiophenol in $POCl_3$ and in the presence of catalytic amount of ferric chloride. Antimony pentachloride in $POCl_3$ did not catalyze the reaction of *sec*-butyl chloride with thiophenol.

Benzhydryl benzoate (BB) undergoes ready solvolysis by thiophenol in TFA and affords the corresponding sulfide quantitatively. However, when thiophenol is allowed to compete against ethanol for a limited amount of BB in TFA the sulfide, which is the sole reaction product, is produced at a very slow rate, incomplete reaction in 12 h at 53 °C vs. a few seconds at room temperature, in the presence and in absence of ethanol, respectively. This finding probably indicates that esters could be more susceptible to acid catalysis in their solvolysis with thiols rather than with alcohols. Specific interaction of the acid catalyst with alcohol, manifested, for example, as a leveling effect, could be responsible for this phenomenon.

It is felt that the chemistry described in this note could be of a wider synthetic utility. The ready availability of methyl ethers by methoxymethylation[13] of hindered phenols in conjunction with their ready reaction with thiophenol, and most probably with other thiols, could make the sulfides of the general structure A readily available.



A

Experimental Section

p-Methoxybenzyl alcohol was prepared by sodium borohydride reduction of anisaldehyde (Fluka). The other alcohols used in this work were products of Merck. Methyl and ethyl benzyl ethers as well as chlorobenzyl methyl ethers were prepared by the classic Williamson synthesis from the corresponding benzyl chlorides. Ethyl and butyl benzhydryl ethers were prepared according to a procedure of "Organic Syntheses".[14] Dibenzyl ether was purchased from Fluka. 3,5-Di-*tert*-butyl-4-hydroxybenzyl methyl ether[13] and 2-phenylisopropyl methyl ether[15] were prepared according to the literature. *sec*-Butyl phenyl ether and benzhydryl benzoate were prepared as described in this section.

The following preparation serves as an example for the transformation of an alcohol to the corresponding phenyl sulfide.

1-Phenylethyl Phenyl Sulfide. The reaction system was a 500-mL Erlenmeyer flask with ground joint, equipped with a magnetic stirring bar, a Dean-Stark water separator, and a reflux condensor. A stirred mixture of 12.2 g (0.1 mol) of 1-phenylethanol, 11 mL of thiophenol, 100 mL of dry benzene, and 1.0 mL of 70% perchloric acid was heated rapidly to reflux. In 5.5-min time from the beginning of reflux 1.0 mL of water had been collected. At 6.0 min the solution turned pale yellow. At 8.5 min, 1.5 mL of water had been separated; at this stage the solution was bright yellow. At 10.5 min the solution turned brown-red. Sodium hydroxide solution (10%, 50 mL) was added to the reaction mixture, and after stirring for a few minutes the benzene layer was separated, washed with water, dried over anhydrous magnesium sulfate, and evaporated to smallest volume in the rotary evaporator. The free of benzene liquid portion weighed 21.5 g and was found to be 1-phenylethyl phenyl sulfide by NMR analysis in a better than 95% purity, yield quantitative.

***sec*-Butyl Phenyl Ether.** A mixture of 30 g of anhydrous potassium carbonate, 23.5 g (0.25 mol) of phenol, and 45 mL of *sec*-butyl bromide in 100 mL of diethylene glycol was stirred and heated for about 2 h, so that the excess of bromide was refluxing gently. During this period of time the following changes were observed. Firstly, K_2CO_3 dissolved, then a white precipitate formed, and finally the mixture started foaming. At this stage the reaction mixture was poured into 500 mL of water. The upper layer was separated, diluted with benzene (150 mL), washed with sodium hydroxide solution and then with water, and dried over $MgSO_4$. The product, after removal of the solvent, was subjected to vacuum distillation. The fraction boiling (3.5 mm) at 59–60 °C weighed 26.7 g (71%), based on phenol used, and it was *sec*-butyl phenyl ether (NMR).

3,5-Di-*tert*-butyl-4-hydroxybenzyl Phenyl Sulfide. 3,5-Di-*tert*-butyl-4-hydroxybenzyl methyl ether (1.25 g, 5 mmol) was dissolved in 2 mL of thiophenol with development of a yellow coloration. Addition of 0.25 mL of 70% perchloric acid caused a mild exotherm and the solution was decolorized instantly. The resulting mixture was shaken for a few seconds and then allowed to stand at room temperature for 15 h. Excess thiophenol was removed from the product by steam distillation, the nonvolatile product was taken up in ether, and the ether solution was dried over anhydrous $MgSO_4$ and evaporated to dryness. The residue, a viscous liquid, solidified on scratching the walls of the evaporating dish. It weighed 1.40 g (85%) and melted at 61–63 °C (lit.[17] mp 63–65 °C) after one recrystallization from hexane.

2-Phenylisopropyl Azide. To a solution of hydrazoic acid (ca. 0.1 mol) in 40 mL of chloroform,[16] over anhydrous $MgSO_4$, was added 1.90 g (12.5 mmol) of 2-phenylisopropyl methyl ether, followed by 2.0 mL of TFA. The resulting mixture was allowed to stand at room temperature for 24 h. Chloroform, TFA, and reaction by-products were removed in the rotary evaporator, without any heating. The residue, a pale yellow oil, weighed 1.71 g (85%). The NMR spectrum of this product showed absence of methoxy protons as well as olefinic ones; IR strong band near 2100 cm^{-1} (azide).

Reaction of 2-Phenylisopropyl Azide with Thiophenol. 2-Phenylisopropyl azide (3.22 g, 20 mmol) was mixed with 3.0 mL of thiophenol and 5.0 mL of TFA. An exothermic reaction took place, and the mixture started foaming (gas evolution), and became cloudy. In about 10-min time two liquid phases had been separated completely. The mixture was allowed to stand at room temperature overnight. TFA was removed by evaporation under reduced pressure, benzene added, and the benzene solution was washed with sodium hydroxide solution and with water and dried over anhydrous $MgSO_4$. Evaporation of benzene left 3.45 g (76%) of 2-phenylisopropyl phenyl sulfide (NMR).

Reaction of *tert*-Butyl Chloride with Thiophenol in the Presence of Ferric Chloride in $POCl_3$. A mixture of *tert*-butyl chloride (12 mL, ca. 0.1 mol), thiophenol (10 mL), anhydrous ferric chloride (1.30 g, 8 mmol), and phosphorus oxychloride (50 mL) was stirred overnight at room temperature. $POCl_3$ was removed by evaporation in the rotary evaporator, the residue was taken up in 100 mL of benzene, and the benzene solution was washed successively with water, sodium hydroxide solution, and water and dried over anhydrous $MgSO_4$. Removal of benzene in the rotary left 16.35 g (98%) of *tert*-butyl phenyl sulfide (NMR). Employing glacial acetic acid as the reaction medium instead of $POCl_3$, significantly lower yields of *tert*-butyl phenyl sulfide were obtained, namely, 48 and 53% for duplicate runs.

Benzhydryl Benzoate. This ester was prepared in 50-mmol run by azeotropically distilling the water from a benzene solution of equimolar amounts of benzhydrol and benzoic acid, containing 1 drop of concentrated sulfuric acid. The end of the reaction can be noticed from the appearance of a yellow-orange coloration, yield 65%, mp 90–92 °C from hexane (lit.[18] mp 88–89 °C).

Acknowledgment. We thank Miss M. Avgerinou and Mrs. M. Voyadji for laboratory assistance.

Registry No.—Thiophenol, 108-98-5; phenol, 108-95-2; *sec*-butyl bromide, 78-76-2; hydrazoic acid, 7782-79-8; *tert*-butyl chloride, 507-20-0; *tert*-butyl phenyl sulfide, 2396-68-1; benzhydryl benzoate, 7515-28-8; 2-phenylisopropyl azide, 32366-26-0; benzoic acid, 65-85-0.

References and Notes

(1) This is not a typical nucleophilic displacement. The attacking species is thiophenol rather than thiophenoxide ion.
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Salicylidene–Thiolactone Rearrangement. A Direct Synthesis of 4*H*-2-Arylthieno[3,2-*c*][1]benzopyran-4-ones

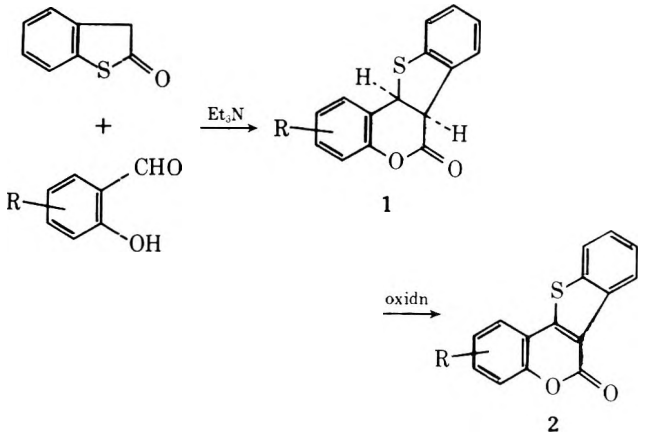
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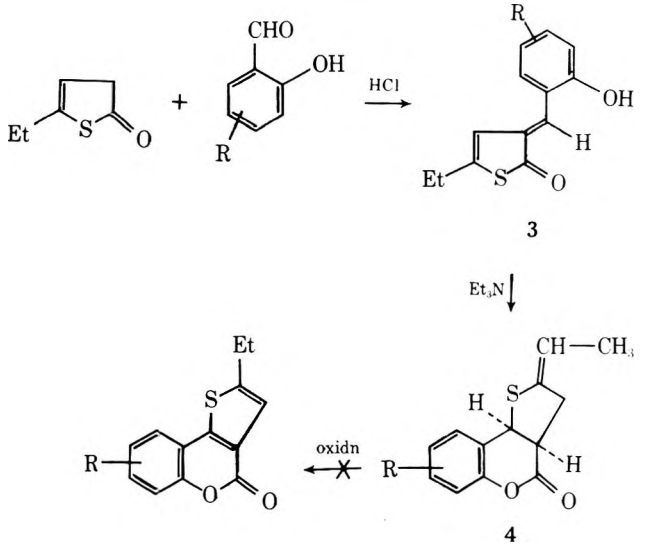
Received November 2, 1976

Previous publications from these laboratories have reported two related molecular transformations: the benzylidene–thiolactone rearrangement[1] and the salicylidene–thiolactone rearrangement.[2,3] In one of these, condensation of salicylaldehydes with thianaphthen-2-ones led to dihydrothienobenzopyranones (**1**) which upon oxidation gave the fully aromatized forms (**2**)[2] (see Scheme I). The salicylidene intermediates (**3**) were actually isolated in the condensation of 5-ethyl-4-thiolen-2-one and were rearranged to dihydrothienobenzopyranones (**4**).[3] Oxidations of the latter were unsuccessful and this resistance has been attributed to the exocyclic unsaturation in **4** (see Scheme II).

Scheme I



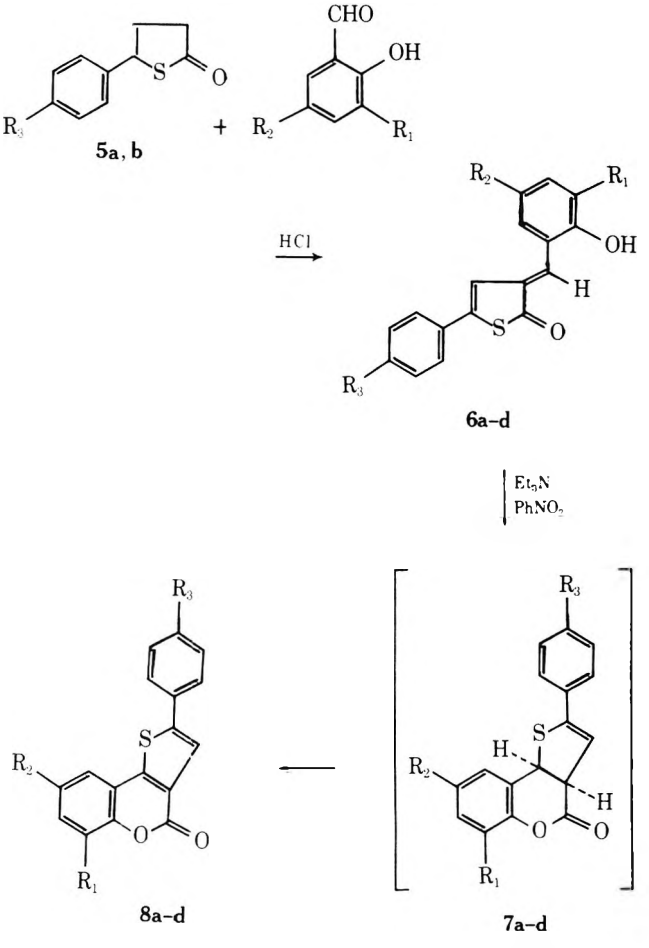
Scheme II



Several new thienobenzopyrans which bear unsaturation at the ring fusion locus have demonstrated potency as tranquilizers, analgesics, and antipyretics.[4–6] Although our earlier studies with 5-ethyl-4-thiolen-2-one did not lead to such oxidized products, we wish to report a new method which applies the salicylidene–thiolactone rearrangement to the direct preparation of such fully aromatized thienobenzopyranones. In this procedure, attachment of an aryl moiety at C-5 of the thiolenone prevents exocyclic unsaturation in the rearranged intermediate and greatly facilitates dehydrogenative oxidation.

These 5-aryl-4-thiolen-2-ones (**5a, 5b**) were prepared by sulfuration and cyclization of β-aroylpropionic acid according to a method developed by Kosak.[7] Although highly labile to oxidative formation, especially in basic media, of indigoid dimers,[7] these thiolactones could be condensed with salicylaldehydes under acidic conditions to yield stable, crystalline salicylidene derivatives (see Scheme III). These compounds (**6a–d**) were orange to red solids which gave positive $FeCl_3$ tests and which displayed carbonyl absorptions at 1653 ± 10 cm^{-1}. Only one vinylic hydrogen could be detected in the ^1H NMR spectrum and that resonance invariably fell within the aromatic complex. It thus appears that these salicylidenes possess the more sterically favored trans configuration (vinyl proton cis to carbonyl). Earlier reports have indicated a greater anisotropic deshielding for trans vinyls in closely related systems.[8–10]

Scheme III



While stable to nonbasic refluxing solvents at temperatures up to 80 °C, these salicylidenes underwent facile rearrangement—apparently after initial isomerization to a cis configuration—with amine bases at temperatures as low as 5–10 °C. Rearrangements carried out with triethylamine in chloroform, even under nitrogen atmosphere, invariably gave difficultly

Table I. Thiolenone-Salicylidenes and the Thieno[3,2-c][1]benzopyran-4-ones Produced by Their Rearrangement

				6			8		
Compd	R_1	R_2	R_3	% yield	Mp, °C	Mol formula[a]	% yield	Mp, °C	Mol formula[b]
a	H	H	H	89	172–173	$C_{17}H_{12}O_2S$	60	155–157	$C_{17}H_{10}O_2S$
b	H	Cl	H	53	204–206	$C_{17}H_{11}ClO_2S$	74	215–217	$C_{17}H_9ClO_2S$
c	OCH_3	H	H	83	160–162	$C_{18}H_{14}O_3S$	44	204–206	$C_{18}H_{12}O_3S$
d	H	H	CH_3	28	184–186	$C_{18}H_{14}O_2S$	43	202–204	$C_{18}H_{12}O_2S$

[a] All compounds were analyzed for C and H and had values within ±0.4% of theoretical for these elements. [b] All compounds were analyzed for C, H, and S and had values within ±0.4% of theoretical for these elements.

separable mixtures whose infrared spectra implicated the presence of a nonconjugated lactone, presumably **7a–d** (C=O approximately 1745 cm^{-1}) and a conjugated one, **8a–d** (C=O approximately 1725 cm^{-1}). Low yields of the dehydrogenated compounds could, in fact, be isolated but **7a–d** could not be obtained in pure form.

If conditions were altered to provide a mildly oxidizing solvent (nitrobenzene) excellent yields of the rearranged and dehydrogenated products could be directly obtained (see Table I). These products were characterized as the 4*H*-2-arylthieno[3,2-c][1]benzopyran-4-ones (**8a–d**) by the absence of the usual ring-fusion methinyl doublets in the ^1H NMR, by the conjugated lactone carbonyls at 1727 ± 3 cm^{-1}, by suitable elemental analyses, and by unique mass spectral fragmentation patterns.

The electron impact scission pathways established for 2-arylthiophenes[11] and for coumarins[12] were evident in the spectra of these 2-arylthienobenzopyranones. The molecular ion constituted the base peak in each case with weak (approximately 10% relative intensity) peaks appearing at half mass ($M^+/2e$). The $ArC{\equiv}S^+$ peak reported for thiophene models was one of the few strong fragment ions (*m/e* 121 in **8a–c** and *m/e* 135 in **8d**). The typical coumarin-like successive scission from the parent ion of CO and CHO was found in **8a** and **8d**.[12] In the methoxy analogue (**8c**), these two carbon monoxide cleavages followed an initial demethylation ($M^+ - CH_3$ or *m/e* 293, then *m/e* 265 and 237). However, this pattern, too, is in exact accord with that reported by Barnes and Occolowitz for 7-methoxycoumarin in which a demethylation precedes two CO losses.[13] In the chlorinated thienobenzopyranone (**8b**) the dual CO fragmentations compete with the halogen scission. Thus the molecular ion decomposes ($M^+ \rightarrow 284 \rightarrow 249 \rightarrow 221$ amu) for loss of CO, Cl, and CO and decomposes ($M^+ \rightarrow 277 \rightarrow 249 \rightarrow 221$ amu) for loss of Cl, CO, and CO.

Experimental Section

All of the melting points are uncorrected. ^1H NMR spectra were recorded on a Hitachi R20A spectrometer. IR spectra were obtained on a Perkin-Elmer Model 257. Mass spectra were provided, in part, by Dr. James Sturm of the Lehigh University Mass Spectrometry Laboratory on a Hitachi RMU-6E double focusing mass spectrometer and, in part, by Dr. Barbara L. Jelus of the University of Delaware Mass Spectrometry Laboratory on a CEC 21-110B. In both facilities the ionizing voltage was 70 eV and the temperature of the direct solids inlet was 60–80 °C. Microanalyses were provided by Robertson Microanalytical Laboratory, Florham Park, N.J.

Preparation of 5-Aryl-4-thiolen-2-ones (5a,b). 5-Phenyl-4-thiolen-2-one (**5a**) was prepared from β-benzoylpropionic acid and P_2S_5 in anhydrous pyridine–chloroform according to Kosak's method.[7] A yield of 12% of light green crystals was isolated (from 1:1 ethyl ether–hexane) and these darkened rapidly in air as noted. A melting point of 85–86 °C (lit. mp 81–82 °C)[7] could be obtained by sublimation, leaving a purple residue behind. Elemental analyses were not in accepted accord with the theoretical values but spectral data supported the structure: IR (KBr) 1725 cm^{-1}; NMR ($CDCl_3$) δ 3.39 (d, J = 3 Hz, C_3H_2), 5.75 (t, J = 3 Hz, C_4H), and 7.30–7.90 (m, 5 H, ArH); mass spectrum *m/e* 176 (M^+), 148 ($M^+ - CO$), and 115 ($M^+ - HCSO$). Anal. Calcd for $C_{10}H_8OS$: S, 18.18. Found: 19.08.

5-*p*-Tolyl-4-thiolen-2-one (**5b**) was synthesized in 23% yield from β-toloylpropionic acid and P_2S_5 exactly as described for the phenyl analogue. This compound too was oxidatively labile and the initially obtained pale green solid (from 1:1 ether–hexane) became deep purple on exposure to air. Sublimation in vacuo gave white crystals, mp 95–97 °C: IR (KBr) 1730 cm^{-1} (CO); NMR ($CDCl_3$) δ 2.35 (s, 3 H, $ArCH_3$), 3.65 (d, J = 3 Hz, C_3H_2), 6.06 (t, J = 3 Hz, C_4H), and 7.07–7.50 (m, 4 H, ArH); mass spectrum *m/e* 190 (M^+), 162 ($M^+ - CO$), and 129 ($M^+ - HCSO$) Anal. Calcd for $C_{11}H_{10}OS$: C, 69.44; H, 5.30; S, 16.85. Found: C, 67.60; H, 5.45; S, 17.80.

Both compounds were employed immediately after synthesis in the preparation of the salicylidene derivatives, which were stable, isolable compounds.

Preparation of 3-(2′-Hydroxyarylidene)-5-aryl-4-thiolen-2-ones (6a–d). A well-stirred solution of equimolar amounts (5.75 mmol) of **5a** or **5b** and the appropriate salicylaldehyde in 35 mL of absolute ethanol was chilled in an ice–water bath. Anhydrous hydrogen chloride gas was introduced at a rapid rate through a bubbler and precipitation of a solid product commenced almost immediately. After 4 min the gas flow was terminated and the suspension stirred and chilled for an additional 3 h. It was then filtered, and the solid washed with 2 mL of cold ethanol and recrystallized from 1:1 ethanol–benzene. Yields and physical properties of the products, which were orange to red solids, are reported in Table I.

Preparation of 4*H*-2-Arylthieno[3,2-*c*][1]benzopyran-4-ones (8a–d). A suspension of 1.75 mmol of the appropriate salicylidene derivative **6a–d** in 20 mL of nitrobenzene was heated with stirring to 85 °C and treated to the dropwise addition of 10 drops of triethylamine. The temperature of the mixture was then raised to 125 °C, maintained there for 0.5 h, and cooled slowly to ambient temperatures. The nitrobenzene was removed in vacuo and the resulting crude crystals recrystallized twice from 1:1 benzene–cyclohexane. Yields and physical properties are given in Table I.

Registry No.—**5a,** 939-09-3; **5b,** 61477-86-9; **6a,** 61477-87-0; **6b,** 61477-88-1; **6c,** 61477-89-2; **6d,** 61477-90-5; **8a,** 61491-10-9; **8b,** 61477-91-6; **8c,** 61477-92-7; **8d,** 61477-93-8; β-benzoylpropionic acid, 2051-95-8; β-toloylpropionic acid, 4619-20-9; salicylaldehyde, 90-02-8; 5-chlorosalicylaldehyde, 635-93-8; 5-methoxysalicylaldehyde, 148-53-8.

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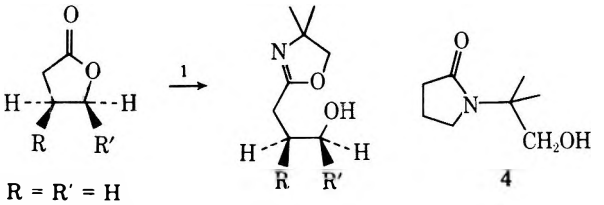
Preparation of 2-Oxazolines from Lactones

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Received October 5, 1976

A recent report[1] described the preparation of functionalized 2-substituted 2-oxazolines (**3**) from lactones and 2-amino-2-methyl-1-propanol (**1**). The apparent synthetic potential[2] of this reaction prompts us to describe two observations. We have been able to improve yields of oxazolines from lactones derived from secondary alcohols, and we have found an unexpected side product that may complicate certain applications of this reaction.



2a, R = R′ = H
b, R = R′ = CH_3
c, R = H; R′ = CH_3

3a, R = R′ = H
b, R = R′ = CH_3
c, R = H; R′ = CH_3

4

We were specifically interested in the preparation of 2-(3-hydroxy-2-methyl-1-butyl)-4,4-dimethyl-2-oxazoline (**3b**) from *cis*-4,5-dimethyltetrahydrofuran-2-one (**2b**). Heating **2b** with **1** in refluxing xylene under a water separator, conditions that we and others[1] had found useful for conversion of **2a** to **3a**, led to no observable reaction. As an alternative means of removing the water formed in the reaction, we refluxed the lactone **2b** with 3 equiv of **1** (no other solvent) under a Soxhlet apparatus charged with 4A molecular sieve. This was very successful, leading to nearly complete conversion of **2b** to **3b** in about 6 days, as judged by gas chromatographic analysis. The same technique appears to be advantageous for other lactones derived from secondary alcohols; γ-valerolactone (**2c**) reacted to at least 85% conversion under these conditions, compared with about 50% conversion[1] in xylene, and more important, pure product was isolated in 41% yield as opposed to 11%.[1]

On the other hand, this technique, with its somewhat higher temperature[3] and more polar solvent character, complicated the synthesis of **3a** from butyrolactone (**2a**). While **3a** forms very quickly by either method, a solid isomeric side product (**4**) forms a much larger fraction of the product when xylene is not present, and is formed almost exclusively if the starting materials are refluxed together with no effort to remove water. Thus, after 5 days, **4** is 5% of the product in xylene, about 45% with the molecular sieve technique, and about 75% if the reagents are simply refluxed. In the last case, workup of the mixture yields only **4**.[4]

This new product, whose IR and NMR spectra (see Experimental Section) are very similar to those of **3a**, has been assigned the lactam structure shown. Several lines of evidence lead to this conclusion. Thus, when an NMR sample of **4** is treated with $Eu(fod)_3$, complexation appears to occur at the hydroxyl group, and the two-proton singlet arising from the hydroxymethylene protons (δ 3.72) is shifted more than any other signal from protons bound to carbon.[5] The nearby triplet (δ 3.50) corresponding to the ring methylene α to the nitrogen atom is shifted much less. When **3a** is treated similarly, the hydroxymethylene signal, now a triplet (δ 3.67), is again shifted most, while the nearby two-proton singlet (oxazoline ring methylene, δ 3.94) remains nearly stationary. Unlike the IR and NMR spectra, the mass spectra[6] of the two compounds are quite distinct. That from **4** is dominated by a peak at *m/e* 126, corresponding to loss of 31 mass units, presumably as CH_2OH. The base peak in the spectrum of **3a** is at *m/e* 113, indicating preferred loss of a larger fragment of the side chain (C_2H_4O). Not surprisingly, neither compound shows a significant molecular ion.

Finally, the assignment of structure to **4** was strengthened by an alternate synthesis. Alkylation of **1** with ethyl 4-bromobutanoate led to the amino ester $HOCH_2C(CH_3)_2NH(CH_2)_3CO_2C_2H_5$ (**5**), which, when heated, underwent cyclization with loss of ethanol to form a solid identical with the product from the lactone reaction.

In summary, then, it appears that the use of molecular sieve rather than azeotropic distillation with xylene is advantageous for lactones derived from secondary alcohols, both in terms of conversion to the oxazoline and ease of isolation of reasonable quantities of product. For lactones derived from primary alcohols, however, the xylene route may be preferable to avoid the lactam-forming side reaction. In any case, oxazolines like these are anticipated to have synthetic application in a number of situations, some of which are under investigation in this laboratory.

Experimental Section

The IR spectra in this study were obtained from neat liquids or KBr pellets on a Perkin-Elmer Model 337 grating spectrometer, and the NMR spectra, with deuteriochloroform as solvent and tetramethylsilane as internal reference, on a Perkin-Elmer R12B, 60 MHz, instrument. Gas chromatograms were run on a Varian-Aerograph 90-P3 instrument using a 6 ft × 0.25 in. aluminum column packed with 10% Carbowax 20M on 60/80 mesh Chromosorb W. Reactant conversions were determined by area measurements on the chromatograms and corrected for results on mixtures of known composition. Microanalyses were done by Galbraith Laboratories, Knoxville, Tenn. The mass spectra were run on a Hewlett-Packard 5930A quadrupole spectrometer operating at 70 eV.

The following procedure is typical of the oxazoline-forming reactions run using molecular sieve.

2-(3-Hydroxy-2-methyl-1-butyl)-4,4-dimethyl-2-oxazoline (3b). A mixture of 3.0 g (0.026 mol) of *cis*-4,5-dimethyltetrahydrofuran-2-one[7] and 11.72 g (0.131 mol) of 2-amino-2-methyl-1-propanol (**1**) was introduced to a 25-mL round-bottom flask fitted with a small Soxhlet extractor with reflux condenser. The extraction thimble was filled with 4A molecular sieve (Baker), previously dried and activated at 325 °C. The quantity used was seven to ten times the weight of the water expected from the reaction; if necessary, the material was replaced after partial reaction. The mixture was heated to reflux and its composition monitored by GC. After 48 h the lactone was 60% converted to product; after 72 h, conversion was 80%, and after 6 days, 88%. At this time the mixture was cooled, diluted with 10 mL of H_2O, and extracted with five 10-mL portions of benzene. The extract was dried and distilled, yielding 1.50 g (31%) of product (**3b**), bp 130–140 °C (25 mm). A sample was purified for analysis by preparative GC. Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34. Found: C, 64.89; H, 10.33. Spectral data: IR 1655 cm^{-1}; NMR δ 4.4 (broad s, 1 H), 3.93 (s, 2 H), 3.80 (m, 1 H), 2.3 (m, 2 H), 2.0 (m, 1 H), 1.37 (s, 6 H), 1.15 (d, 3 H), 0.95 (d, 3 H).

A similar but larger scale reaction using γ-valerolactone as the starting material showed 85% conversion to the oxazoline after 5 days, and a 41% yield of 95% pure product (**3c**) was isolated by simple vacuum distillation. Its properties matched those reported for this compound in ref 1.

Reaction of γ-Butyrolactone with 1. A. In Xylene. A procedure like that of McManus et al.[1] was used to prepare the oxazoline **3a**; a small amount of lactam **4** could be seen in the gas chromatogram of the crude product, but it did not appear in the distilled sample. This was a very hygroscopic compound, and best analytical data[8] correspond to 0.3 mol of H_2O per mole of $C_8H_{15}NO_2$. Anal. Calcd for $[C_8H_{15}NO_2 + 0.3(H_2O)]$: C, 59.09; H, 9.67; N, 8.61. Found: C, 58.90; H, 9.94; N, 8.88. Spectral data:[9] IR 1660 cm^{-1}; NMR δ 4.3 (broad s, 1 H), 3.94 (s, 2 H), 3.69 (t, 2 H), 2.39 (t, 2 H), 1.90 (m, 2 H), 1.27 (s, 6 H).

B. Neat. A mixture of 30.96 g (0.36 mol) of **2a** and 31.90 g (0.36 mol) of **1** was refluxed for approximately 48 h, then distilled. A 55.0-g (75%) sample of the amide **4** was obtained, bp 109 °C (0.25 mm). The com-

pound crystallized on standing, and a sample recrystallized from pentane/dichloromethane melted at 51 °C. Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.02; H, 9.46; N, 8.74. Spectral data: IR 1655 cm^{-1}; NMR δ 4.5 (broad s, 1 H), 3.72 (s, 2 H), 3.50 (t, 2 H), 2.4 (t, 2 H), 2.0 (m, 2 H), 1.28 (s, 6 H).

Synthesis of 4 from Ethyl 4-Bromobutanoate. Ethyl 4-bromobutanoate (5.0 g, 0.025 mol) and 1 (5.94 g, 0.067 mol) were dissolved in 50 mL of 95% ethanol and the mixture refluxed for 20 h, or until starting ester had completely reacted (as determined by GC). The mixture was cooled, acidified with dilute HCl, and extracted with ether to remove neutral compounds. The aqueous layer was made basic with NaOH and extracted with ether. The extract was dried (K_2CO_3) and distilled, yielding pure **5** as a liquid, bp 95 °C (22 mm). The product crystallized on standing.

A sample was purified for analysis by recrystallization from pentane and dichloromethane, mp 25–26 °C. Anal. Calcd for $C_{10}H_{21}NO_3$: C, 59.08; H, 10.41. Found: C, 58.95; H, 10.78. Spectral data: IR 1730 cm^{-1}; NMR δ 4.15 (q, 2 H), 3.28 (s, 2 H), 2.7–1.7 (overlapping multiplets, 8 H), 1.27 (t, 3 H), 1.05 (s, 6 H).

The remaining sample of **5** was heated in a 150 °C oil bath under a reflux condenser for 20 h and then distilled. After an ethanol forerun, the entire sample was collected at 110 °C (0.25 mm). This product crystallized on cooling, and was identical with **4** prepared from butyrolactone as described above.

Acknowledgment. The authors wish to thank Lawrence University and the Research Corporation for support of this work.

Registry No.—**1**, 124-68-5; **3a**, 51849-54-8; **3b**, 61484-26-2; **4**, 61484-27-3; **5**, 61484-28-4; *cis*-4,5-dimethyltetrahydrofuran-2-one, 10150-95-5; γ-butyrolactone, 96-48-0; ethyl 4-bromobutanoate, 2969-81-5.

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(2) See, for example, A. I. Meyers and E. D. Mihelich, *J. Org. Chem.*, **40**, 1186 (1975).
(3) The amine **1** has a boiling point of 165 °C.
(4) The oxazoline **3a** is also converted cleanly to **4** simply by extended heating in the presence of **1** and water.
(5) Interestingly, the triplet corresponding to the ring methylene of **4** adjacent to the carbonyl group shifts nearly as much as the hydroxymethylene signal does.
(6) Mass spectra were kindly supplied by Dr. M. L. Deuelinger of the Chemistry Department, Indiana State University.
(7) This lactone was prepared in 33% yield from diethyl malonate and *trans*-2,3-dimethyloxirane. For a similar preparation of the compound, see P. L. Pacini and R. G. Ghirardelli, *J. Org. Chem.*, **31**, 4133 (1966).
(8) Published analytical results for this compound in ref 1 are inconsistent,[10] at least partially because of the hygroscopic nature of the material, but there is no doubt that the compound we isolated is the same reported there.
(9) These data match those given in ref 1 quite well, and are included here only to emphasize the similarity between the spectra of **3a** and **4**.
(10) Personal communication from S. P. McManus.

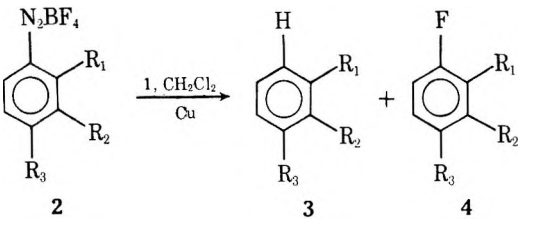
Crown Ether–Copper-Catalyzed Decomposition of Arenediazonium Fluoroborates

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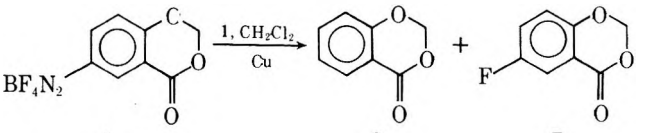
Received August 27, 1976

We wish to report what appears to be the first example of arenediazonium tetrafluoroborate salt decomposition catalyzed by a macrocyclic polyether.[1] The arenediazonium salts shown in Table I were readily decomposed in methylene chloride under a nitrogen atmosphere in the presence of catalytic amounts (10 mol %) of dicyclohexyl-18-crown-6 (**1**) and powdered copper to afford varying proportions of reduction and Schiemann products. No reaction occurred under these conditions in the absence of the crown ether or if powdered glass was substituted for copper.



2 **3** **4**

2a, $R_1 = R_3 = F$; $R_2 = H$
b, $R_1 = R_2 = H$; $R_3 = NO_2$
c, $R_1 = H$; $R_2 = NO_2$; $R_3 = Cl$
d, $R_1 = R_2 = R_3 = H$
e, $R_1 = R_2 = H$; $R_3 = CH_3$

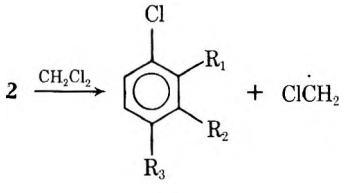


5 **6** **7**

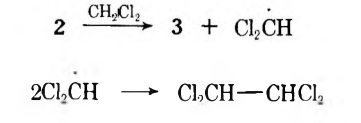
In addition, no reaction was observed when 15-crown-5 was substituted for **1**. Decomposition was facilitated by the presence of electron-withdrawing groups in the aromatic nucleus. Evolution of nitrogen was complete for **2a, 2b,** and **2c** within a few minutes with gentle warming, while the remaining salts required longer periods of reflux (see Table I).

The initial report of an interaction between a polyether and a diazonium salt appears to be that of Martin and Bloch[2] who utilized **1** to aid in the decomposition of potassium diazocyclopentadiene-2-carboxylate. More recently, Gokel and Cram[3] showed that arenediazonium salts were solubilized in nonpolar media by 18-crown-6 and binaphtho-20-crown-6 while binaphtho-17-crown-5 was ineffective. We have found that while use of **1** in the presence of copper leads to spontaneous decomposition of fluoroborate salt **2b,** treatment with 15-crown-5 (**8**) results in no detectable reaction. As suggested by earlier workers,[3] complexation of the diazonium species appears to involve insertion into the cavity of the crown ether as is known for complexation of metal ions.[4] Complexation very likely affords a critical amount of solubilized diazonium salt which is necessary for further reaction.[5,6] In the present case, the cavity of **1** is able to accommodate the diazonium species, while that of **8** is apparently too small.

Reaction in the case of salts **2a, 2b,** and **2c** led cleanly to the reduction product. The present method thus constitutes for these salts an extremely mild, nonaqueous way of replacing the diazonium group by hydrogen, a transformation which has attracted much attention.[7–15] The remaining salts afforded mixtures of reduction and Schiemann products as shown in Table I. We were also able to detect (VPC/mass spectrum) in each case the presence of minor amounts of chloroaromatic derivative (**9**)[16] and 1,1,2,2-tetrachloroethane (**10**), apparently from dimerization of the dichloromethyl radical. It is also



9



10

Table I. Products from the Crown Ether–Copper-Catalyzed Decomposition of Arenediazonium Fluoroborates

Reactant[a,b]	Registry no.	Reaction conditions	Products[d] (yields)[e]	Registry no.
2a	326-87-4	10 mol % 1,[g] CH_2Cl_2, 30 min, 40 °C	3a (95%); 4a (0)	372-18-9 (3a)
2b[c]	456-27-9	10 mol % 1,[g] CH_2Cl_2, 30 min, 40 °C	3b (91%); 4b (0)	58777-17-6 (3b)
2c	41136-80-5	10 mol % 1,[g] CH_2Cl_2, 30 min, 40 °C	3c (93%); 4c (0)	88-73-3 (3c)
2d	58801-43-7	10 mol % 1,[g] CH_2Cl_2, 3 h, 40 °C	3d (17%); 4d (60%)	71-43-2 (3d) 462-06-6 (4d)
2e	459-44-9	10 mol % 1,[g] CH_2Cl_2, 3 h, 40 °C	3e (56%); 4e (29%)	108-88-3 (3e) 352-32-9 (4e)
5	61702-20-3	10 mol % 1,[g] CH_2Cl_2, 3 h, 40 °C	6 (83%); 7 (6%)[f]	6009-10-5 (6) 61702-21-4 (7)

[a] All diazonium salts were prepared by standard techniques see ref 7. [b] Identity confirmed by comparison of physical properties with literature values and by IR, ^1H NMR, and elemental analyses. [c] The authors thank Dr. D. Mulvey for a sample of this compound. [d] Identity determined by isolation and VPC/mass spectrum. [e] Yields determined by VPC vs. standard. [f] Decomposition occurred upon attempted distillation. [g] Registry no., 16069-36-6.

interesting to note the lack of biaryl coupling products, despite the assumed presence of aryl radicals.

We are currently exploring the synthetic utility of these crown ether catalyzed decompositions in the generation of coupling and Sandmeyer type products. We anticipate that crown ethers may also facilitate other gas evolving decompositions, such as those involving diazomethane, α-diazo ketones, and *p*-toluenesulfonylhydrazones.

Experimental Section

General. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Analysis of the products of decomposition of the diazonium salts was carried out on a Hewlett-Packard 6830 gas chromatograph with use of an SP-2401 column.

Preparation of Diazonium Salts. All salts were prepared by standard techniques (ref 7). The only compound which was prepared for the first time was **5**, which had a decomposition point of 145–150 °C.

Arenediazonium Fluoroborate Decomposition. All salts were decomposed in identical fashion with the only variable being the heating period as shown in Table I. A representative procedure is given below for the decomposition of **2a**.

Decomposition of 2,4-Difluorobenzenediazonum Tetrafluoroborate (2a). A 100-mL round-bottom flask was charged with 1.33 g (5.9 mmol) of **2a**, 11 mL of methylene chloride, and 0.19 g (0.5 mmol) of dicyclohexyl-18-crown-6 (**1**) under a nitrogen atmosphere. With continuous nitrogen flow, 0.1 g of copper powder was added in one portion and the reaction mixture was heated at 40 °C for 15 min with magnetic stirring. The cooled reaction mixture was then filtered and analyzed by VPC to indicate that 1,3-difluorobenzene (**3a**) was the sole product in 95% yield vs. internal standard. A portion of the reaction mixture was distilled to give a pure sample of **3a**, which had boiling point, IR, and NMR identical with published values. Another portion of the reaction mixture was subjected to VPC/mass spectrum analysis, indicating a single peak at *m/e* 113, correct for **3a**.

Registry No.—Copper, 7440-50-8.

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Reduction of Aryldiazonium Compounds in Nonpolar Media

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Received November 8, 1976

While studying diazonium ion reactivity in nonpolar media, we required a convenient method for protodediazoniation (reduction) of these substances. In particular, the method had to afford high yields of reduction product at low temperatures in a short period of time and be applicable in such nonpolar media as chloroform and methylene chloride. Numerous methods are available for reduction of aryldiazonium salts (particularly chlorides) in aqueous media,[1] but these are commonly ineffective for reduction of BF_4^- and PF_6^- salts which are more stable than chlorides but much less soluble in water. Reducing systems which have been reported for the reduction of BF_4^- or PF_6^- salts include zinc in ethanol,[2] tributyltin hydride in tetrahydrofuran or diethyl ether and triethylsilane in acetonitrile,[3] rhodium complexes in dimethylformamide,[4] tetramethylurea,[5] sodium borohydride in methanol or dimethylformamide,[6] 1,4-dioxane in the presence of Cu_2O,[7] and 1,4-dioxane, tetrahydrofuran, 1,3-dioxolane, and 1,2-dimethoxyethane in aqueous sodium acetate.[8] Moreover, the potential of hypophosphorous acid for our requirements could be inferred from Lamm's observation[9] that 2-bromo-4,6-dichloro-, 2,4,5-trichloro-, and 2,4-dichloro-6-nitrobenzenediazonium tetrafluoroborates were reduced by 10 equiv of hypophosphorous acid in 5 M HCl in 83, 77, and 64% yields, respectively.

We wish to report that hypophosphorous acid[10] in chlorocarbon solution in the presence of trace cuprous oxide fulfills the conditions set forth above. Thus, excellent yields of reduction products were obtained in eight of the nine cases examined (see Table I). The single exception is *p*-methoxybenzenediazonium tetrafluoroborate, which undergoes reduction in only 67% yield. Apparently, electron-attracting substituents favor the reduction and mildly electron-releasing

Table I. Reduction of Diazonium Ions in Chloroform

$$Ar—N{\equiv}N^+BF_4^- \xrightarrow[Cu_2O]{H_3PO_2} ArH$$
$$CHCl_3$$

Diazonium tetrafluoroborate	Registry no.	Product[a]	% yield[b]	Registry no.
p-Bromobenzene-	673-40-5	Bromobenzene	99	108-86-1
o-Bromobenzene-	10448-07-4	Bromobenzene	99	
p-Chlorobenzene-	673-41-6	Chlorobenzene	97 (90)[c]	108-90-7
o-Chlorobenzene-	1956-97-4	Chlorobenzene	97	
2,4-Dichlorobenzene-	21872-70-3	*m*-Dichlorobenzene	97	541-73-1
p-Methylbenzene-	459-44-3	Toluene	99	108-88-3
3,4-Dimethylbenzene-	2192-34-9	*o*-Xylene	92	95-47-6
p-Methoxybenzene-	459-64-3	Anisole	67[e]/88[d]	100-66-3
p-Nitrobenzene-	456-27-9	Nitrobenzene	99	98-95-3

[a] The identities of products were confirmed by spectral analysis of samples obtained by preparative GLC. [b] Yields were determined by GLC using a 5 ft × 0.25 in. 10% SE-30 on Chromosorb P column utilizing an internal standard and are corrected for detector response. All yields represent at least four replicate experiments and are reproducible to ±2%. [c] Isolated yield. Reaction carried out on a 44-mmol scale using 7 equiv of H_3PO_2. [d] 0.075 equiv of 18-crown-6 added. [e] Extension of the reaction time to 3 h and addition of 14 equiv of H_3PO_2 did not alter the yield.

substituents do not appreciably hinder the reduction. The difficulty encountered in the latter case may be overcome by addition of a small amount of 18-crown-6 polyether.[11] When 0.075 equiv (7.5 mol %) of 18-crown-6 was added to the reducing mixture containing *p*-methoxybenzenediazonium tetrafluoroborate, the yield of reduction product was increased to 88%. It should be noted that neither in the presence or absence of crown were chlorinated or fluorinated by-products isolated.

We presume that the reduction involves aryl radical formation and hydrogen atom capture as proposed by Kornblum and co-workers some years ago.[9b] The crown effect is somewhat more difficult to explain. There are three obvious explanations we have considered. The first is that crown is enhancing the solubility of the diazonium salt, a now well-established phenomenon.[12] The second possibility is that the crown complexed diazonio function is more prone to reduction than the noncomplexed function, an unlikely prospect in light of the recent results reported for the Schiemann reaction.[13] The third possibility is that the crown and copper ion interact to enhance the reduction process. No increase in yield was observed, however, when 15-crown-5 was substituted for 18-crown-6. The smaller crown is of the appropriate size to

$$Ar—\overset{+}{N}{\equiv}N\ BF_4^- + \text{crown} \rightleftharpoons Ar—\overset{+}{N}{\equiv}N\ BF_4^-$$

complex cuprous or cupric but not diazonium ion. The latter possibility therefore seems unlikely. We are currently considering the two aforementioned and other possibilities, although this in no way affects the efficacy of the method herein reported.

Experimental Section

The diazonium tetrafluoroborates were prepared by standard methods[14] from commercially available anilines. Hypophosphorous acid (50% aqueous, Fisher) was used as obtained. The chloroform used was ACS reagent grade, although substitution of carefully dried, alcohol-free reagent gave identical results.

Reduction Procedure.[15] To a stirred suspension of the diazonium tetrafluoroborate (1.5 mmol) in chloroform (10 mL) cooled in an ice water bath was added 0.80 mL (7.5 mmol) of H_3PO_2 and a few milligrams (trace) of Cu_2O. The mixture was stirred for 5 min, after which time Na_2CO_3 was added continuously until the pH was 8. The mixture was then washed with water and the aqueous layer backwashed with chloroform; the combined organic layers were filtered (if necessary), dried over sodium sulfate, and subjected to GLC analysis.

Acknowledgment. We warmly thank the Research Corporation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for grants which supported this work.

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Metal Ion Promoted Lactonizations

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Received September 28, 1976

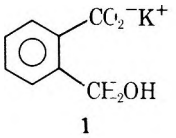
The acid-catalyzed lactonization of hydroxy acids of fixed conformation has been a topic of considerable interest.[1] Alkyl substituents on the aromatic nucleus enhance lactonization rates of derivatives of 1.[1d] The terms "stereopopulation control" [1b] and "trialkyl lock" [1e] have been applied to methylated

Table I. Lactonization Rates at 25 °C

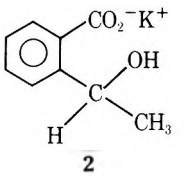
Compd	Conditions[a]	$10^3 k$, s^{-1}
3	A	6.52 (0.26)[b]
	B	4.57 (0.66)[c]
	C	0.601 (0.117)[d]
4	A	4.37 (0.63)[b]
	B	5.51 (2.43)[c]
	C	0.618 (0.284)[d]

[a] A = 0.01 M $Cu(OAc)_2$ (pH 5.92); B = 0.01 M $CuSO_4$, 0.05 M HOAc, 0.05 M NaOAc; C = 0.02 M $ZnSO_4$ (pH 6.27). [b] Calculated rate at pH 5.92. See ref 2a. [c] Rate in 0.05 M HOAc, 0.05 M NaOAc. [d] Calculated rate at pH 6.27. See ref 2a.

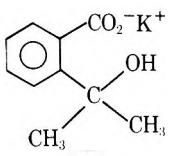
derivatives of **5** to explain rate enhancements in lactonization. Recently increased lactonization rates of methylated derivatives of **5** have been attributed to relief of steric strain.[1f,g] The formation of lactones from the hydroxy acids corresponding to **1**, **3**, **4**, and **5** is catalyzed not only by hydronium ion, but



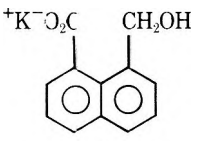
1



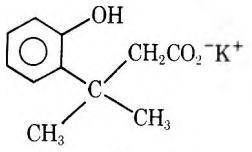
2



3



4



5

also by general acids and bases in carboxylic acid–carboxylate buffers.[1b,2]

We now report that the potassium salts **3** and **4** lactonize rapidly under the influence of dilute copper(II) salts. Table I presents lactonization rate data. That the reactions are truly due to metal ion and not acid catalysis is shown by comparison of reaction rates in aqueous media of comparable pH. Figures 1 and 2 show the effect of copper concentration on lactonization rates of **3** and **4**. The varying rates in both buffered and unbuffered media also support the conclusion of a metal ion promoted reaction. Temperature effect studies give an enthalpy of activation of 18.6 kcal/mol and an activation entropy of −6.4 eu for formation of 3,3-dimethylphthalide from **3** in 0.01 M cupric acetate. These values differ significantly from the buffer-catalyzed reaction, characterized by large negative entropies of activation.[2a] Zinc salts also promote these lactonizations, but to a lesser extent than copper.

Potassium salt **1**, when dissolved in copper(II) solutions, gives a complex differing spectrally from either **1** or the corresponding lactone, phthalide. Only upon addition of mineral acid does this complex slowly revert to phthalide. Incorporation of a single methyl group (potassium salt **2**) leads to the observation of a copper-promoted cyclization. Larger copper-promoted rates are seen for the dimethyl-substituted hydroxy acid salt **3**. These observations suggest a hydroxyl group conformation favoring lactonization for the occurrence of copper catalysis.

Where do these observations fit in the context of metal ion catalyzed hydrolyses? Previously copper and other transition metals have been shown to catalyze hydrolysis of specific amino esters in which the ester is coordinated to the metal ion by way of both the amino group and the ester carbonyl.[3] The carbonyl is "metal activated" toward nucleophilic attack. Coordination with the amino group is necessary for the

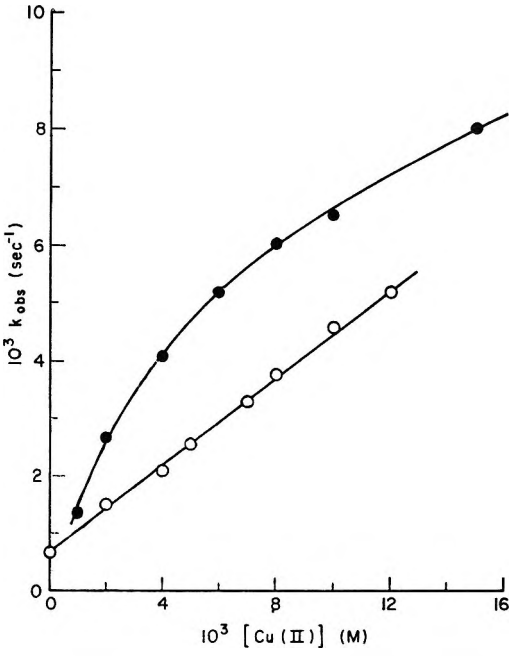


Figure 1. Rates of lactonization of **3** in copper(II) solutions at 25 °C: ●, $Cu(OAc)_2$; ○, $CuSO_4$, 0.05 M HOAc, 0.05 M NaOAc.

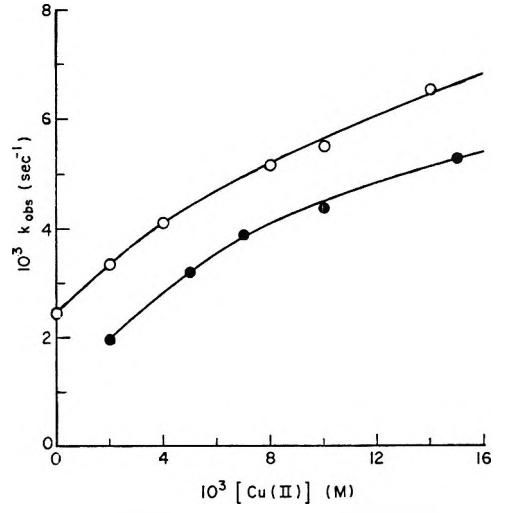
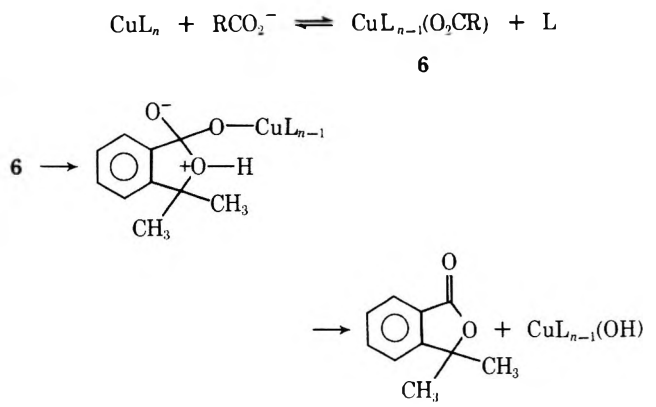


Figure 2. Rates of lactonization of **4** in copper(II) solutions at 25 °C: ●, $Cu(OAc)_2$; ○, $CuSO_4$, 0.05 M HOAc, 0.05 M NaOAc.

metal-catalyzed hydrolysis reaction. Hydrolysis of "normal" esters such as ethyl acetate are not metal catalyzed. The metal-promoted cyclizations of **3** and **4** are unusual in that there can be no coordination with nitrogen. The intimate details of the lactonization mechanism therefore cannot be the precise microscopic reverse of the metal-catalyzed hydrolysis of amino esters which involves nitrogen complexed intermediates.

A mechanism consistent with the nonlinear plot of rate as a function of cupric acetate concentration involves reversible displacement of acetate ligand by carboxylate salt. This copper complexed substrate, **6**, is activated toward intramolecular nucleophilic attack by a properly oriented hydroxyl group.[4] Either cyclization or collapse of the tetrahedral intermediate may be rate determining. The nonlinear plot in Figure 1 in cupric acetate solutions is a result of an acetate ion rate suppression as can be shown by addition of excess acetate at constant copper concentration. Also of interest is the rate behavior in buffered solution. In acetic acid–acetate buffers a linear plot of rate vs. copper(II) concentration is observed.



However, rates are slower than in unbuffered solutions of comparable copper concentration even though the buffer components are known to catalyze cyclization of the hydroxy acid. Additionally, the pH of the unbuffered solutions (5.8–6.3) is greater than that of the buffered solutions (4.74) and hence cannot account for the increased reactivity in unbuffered media. The rate suppression in buffered media follows from the increased amount of free uncomplexed hydroxy acid and hydroxy acid salt in the buffered medium. In the absence of buffer, more substrate is complexed with copper and hence faster rates are observed.

In contrast, lactonization rates of **4** are faster in buffered media (Figure 2) and rate plots give nonlinear behavior as a function of copper concentration. This is attributed to the presence of significant buffer catalysis in the buffered medium. Such buffer catalysis apparently contributes less to the overall lactonization rate of **3** than for **4**. In general, the effect of carrying out studies in buffered media is to partially obscure the metal ion promoted reaction. Studies show less spectacular catalysis in lactonization of **2** and **5** which are less well aligned for cyclization.

The mechanism suggested is similar to the microscopic reverse of the process proposed by Buckingham for the recently observed metal-catalyzed hydrolysis of propionic anhydride.[5] Our results suggest that copper and zinc ions can promote analogous esterifications when aqueous equilibria strongly favor the synthesis side of the reaction.

Experimental Section

Preparation of Hydroxy Acid Salts. General Procedure. A given amount of the appropriate lactone was saponified by refluxing with 1.05 equiv of potassium hydroxide in methanol. The solvent was removed in vacuo and the dry salt was used for rate measurements.

Preparation of Lactones. The lactones employed were all prepared using literature procedures. Phthalide was prepared by zinc reduction of phthalimide.[6] 3-Methylphthalide was prepared by sodium borohydride reduction of *o*-acetylbenzoic acid. 3,3-Dimethylphthalide was prepared by reaction of methylmagnesium iodide with diethyl phthalate.[7] 1,8-Naphthalide was prepared by cleavage of acenaphthenequinone with potassium hydroxide followed by reduction of the 1,8-naphthaldehydic acid with formaldehyde.[8] 4,4-Dimethylhydrocoumarin was prepared by acid-catalyzed reaction of phenol and methyl 3-methyl-2-butenoate.[9]

Kinetic Procedure. A solution of appropriate concentration of a given hydroxy acid salt in methanol was prepared. Injection of a 0.01-mL aliquot of this solution into a temperature equilibrated cuvette in a constant temperature compartment of a Cary 15 or Gilford 240 spectrophotometer initiated the kinetic run. Changes in absorbances at a given wavelength were monitored as a function of time. Substrate concentrations were typically 10^{-4}–10^{-5} M. Rate constants were calculated by the usual least-squares procedure. For the copper-promoted reactions, rates were monitored at 280–285 nm. At higher copper concentrations, this region becomes obscured by absorbance due to copper. At the copper concentrations employed, rates could be conveniently monitored at these wavelengths. For compounds **4** and **5**, decreases in absorbances were observed as a function of time (disappearance of the copper complex) while **2** and **3** led to absorbance increases. Upon completion of a kinetic run, the spectrum was identical with that of corresponding lactone solutions prepared independently.

Other copper(II) salts also promoted lactonization. However, precipitation of copper(II) hydroxides interferes with spectral measurements and rate determinations. In cupric acetate media or copper(II) sulfate in acetate buffered media, precipitation of copper(II) hydroxides did not present a problem. The following wavelengths were used for monitoring lactonization rates for copper-promoted reactions: **2**, 280 nm; **3**, 283 nm; **4**, 285 nm; **5**, 282 nm. Zinc sulfate promoted reactions of **4** were monitored at 240 nm.

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.—**3**, 61490-94-6; **4**, 61490-95-7.

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Interconversions in Pentamethylbicyclo[3.2.0]- and Bicyclo[2.2.1]heptadienyl Cations

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Received October 14, 1976

Recently several communications have dealt with the properties and rearrangements of polymethylbicyclo-[3.2.1]octadienyl[1] and -[2.1.1]hexenyl[2] cations. In view of the intriguing interconversions within these ions we were interested to learn about the behavior of carbonium ions, which are intermediate between these types as far as the number of skeleton carbon atoms is concerned—seven instead of eight and six, respectively—viz., the polymethylbicyclo[3.2.0]- and -[2.2.1]heptadienyl cations. In the present publication the results of a study of the pentamethyl derivatives are reported.

Reduction of ketone **1**[3] with $LiAlH_4$ gave in good yield (77%) the crystalline secondary alcohol **2**. Upon ionization of **2** in

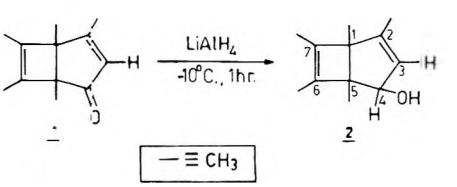
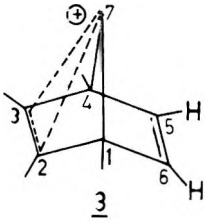
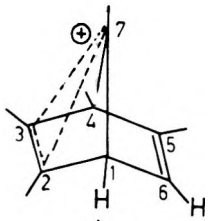
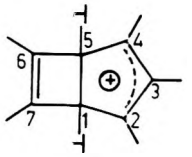
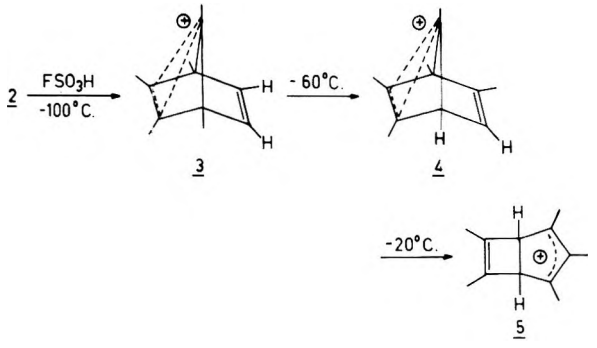


Table I. ^{1}H NMR[a] and ^{13}C NMR[b] Chemical Shifts[a]

		C-1,4	C-2,3	C-5,6	C-7
 3	^{1}H NMR	1.70	2.17	5.92	1.33
	^{13}C NMR, CH_3	9.9	10.9		1.6
	^{13}C NMR, ring C	68.8	133.0	129.8	75.4
 4	^{1}H NMR	4.34 (H), 1.64 (CH_3)	2.17/2.26	5.70 (H), 1.87 (CH_3)	1.44
	^{13}C NMR, CH_3	8.6	11.2/12.3	14.6	4.7
	^{13}C NMR, ring C	75.0/71.1	140.5/135.0	130.8/118.7	63.2
 5		C-1,5	C-2,4	C-6,7	C-3
	^{1}H NMR	4.65	2.90	1.90	2.15
	^{13}C NMR, CH_3		11.8	23.6	10.4
	^{13}C NMR, ring C	68.5	234.5	139.5	155.8

[a] Measured relative to internal CH_2Cl_2 (δ 5.30). [b] Measured relative to internal CD_2Cl_2 (δ 53.16).

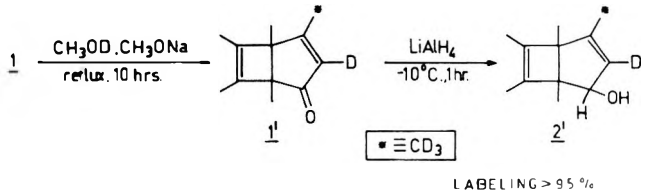
FSO_3H/SO_2ClF at −100 °C, a carbonium ion was generated to which we assign structure **3**. Warming up this solution to −60 °C caused an irreversible rearrangement of ion **3** into ion **4**, which has an additional stabilization because of a higher alkyl-substituted double bond. The thermodynamically most stable ion **5**, in which the double bond is completely alkyl



substituted, was finally formed when the solution of **4** was warmed to −20 °C.

The assignments of structures **3**, **4**, and **5** are based on NMR spectroscopic evidence, as summarized in Table I.

The two hydrogen atoms appeared to be good labels to test the mechanism for the interconversions of these carbonium ions. Additional affirmation was obtained by the use of the labeled alcohol **2'**, which was prepared from compound **1** by the sequence **1** → **1'** → **2'**. The interconversions are in accord

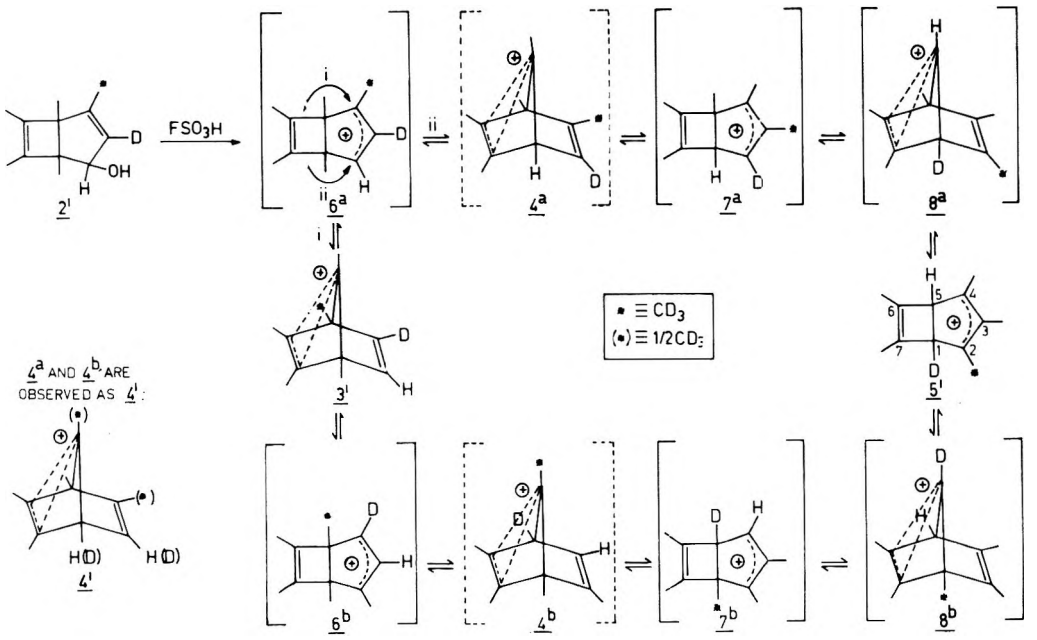


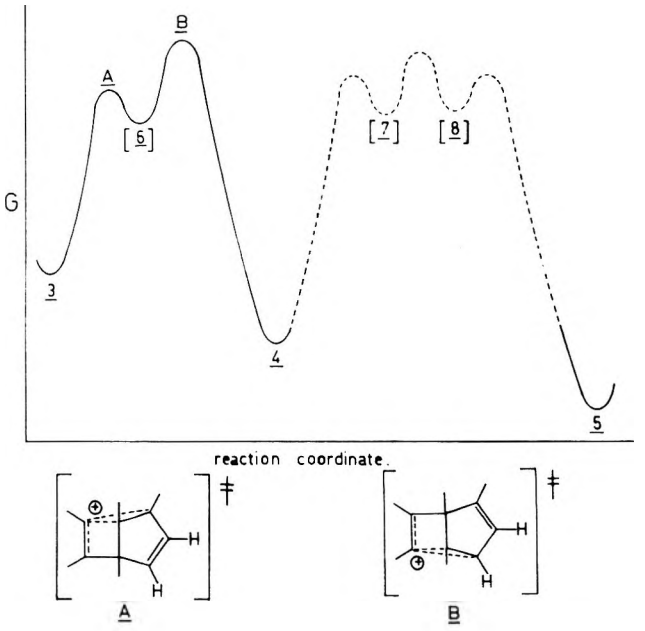
with a mechanism involving a stepwise circumambulatory motion of five carbon atoms (C-1,4,5,6,7 in **3**) with respect to the remaining two carbon atoms (C-2,3 in **3**) analogues to the one Winstein observed in 7-norbornadienyl cations.[5] The ions **3'**, **4'**, and **5'**[6] showed the correct areas for the ^{1}H NMR signals, which confirms the proposed mechanistic sequence. Remarkably, none of the intermediate carbonium ions which have a hydrogen at a positively charged carbon atom is observed (**6**, **7**, **8**, and their deuterated analogues). An explanation for the kinetic formation of ion **3** in preference to ion **4** is the stabilizing effect of three methyl groups on the positive charge in the transition state A, that belongs to the conversion **6** → **3** (path i) as compared to that of two methyl groups in the transition state B for the conversion **6** → **4** (path ii). The effect of the number of methyl groups on the stability of protonated cyclopropane rings has recently been summarized by Brouwer and Hogeveen.[7] The difference in thermodynamic stability between ions **3** and **4** is due to the different number of alkyl substituents at the C=C bond whereas the difference between ions **4** and **5** not only resides in that factor, but also in the different geometry and, as a consequence, the different strain of the [2.2.1] vs. the [3.2.0] carbon skeleton.[8] The results are finally drawn schematically in the free-enthalpy diagram.

Experimental Section

General. The IR spectra were taken on a Perkin-Elmer 257 spectrophotometer. Mass spectra were obtained on a AEI MS-902 by Mr. A. Kiewiet. Proton magnetic resonance spectra were recorded using Varian A-60D or JEOL C-60HL spectrometers equipped with variable temperature probes and tetramethylsilane (δ 0.00) as internal standard (unless otherwise stated). Natural abundance carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were obtained with a Varian XL-100 spectrometer operating at 25.2 MHz. Spectra were recorded with the use of Fourier transform and were proton-noise decoupled. We thank Drs. W. Mellink for assistance in recording the ^{13}C spectra.

Generation of Carbonium Ions in Strong Acid Media. No attempt will be made to detail all the procedures used. One of the most satisfactory techniques is described below.





In a typical experiment 80 mg of FSO_3H was brought into a dry, clean ^1H NMR tube at −115 °C followed by condensation of SO_2ClF (about 0.35 mL). With the aid of a cooled glass rod 30 mg of precursor was introduced and the obtained mixture homogenized. Appropriately larger amounts were used for the ^{13}C NMR than for the ^1H NMR spectra.

1,2,5,6,7-Pentamethylbicyclo[3.2.0]hepta-2,6-dien-4-ol (2). To a stirred solution of 500 mg of ketone 1 in 25 mL of ether (freshly distilled from $LiAlH_4$), cooled to −10 °C, was slowly added 45 mg of $LiAlH_4$. This mixture was stirred for 1 h at −10 °C. After warming up to 0 °C a 20% NaOH solution and a 20% NH_4Cl solution were simultaneously added dropwise. After filtration the ether layer was washed with water untill neutral and dried ($CaCl_2$). The solvent was removed in vacuo using a rotary evaporator. The resulting white crystals were recrystallized from pentane (−30 °C) to give 381 mg (77%; one major stereoisomer) of **2**: IR 3320 cm^{-1} (broad); ^1H NMR (CCl_4) δ 5.00 (1 H, C-3, broad m), 4.07 (1 H, C-4, broad m), 1.65 (3 H, C-2 methyl, d, J = 1.5 Hz), 1.54 (6 H, C-6 and C-7 methyls), 1.08 and 0.93 (3 H each, C-1 and C-5 methyls), 1.01 (1 H, OH); mass spectrum parent peak m/e 178; correct elemental analysis.

1,5,6,7-Tetramethyl-2-trideuteriomethyl-3-deuteriobicyclo[3.2.0]hepta-2,6-dien-4-ol (2'). A solution containing 1 g of ketone 1 and 50 mg of CH_3ONa in 10 mL of CH_3OD was refluxed overnight. The methanol was evaporated under reduced pressure and the solid residue was treated with water and extracted with CH_2Cl_2. The organic layer was washed with water until neutral and dried over $MgSO_4$ and the solvent was removed in vacuo using a rotatory evaporator, giving a nearly quantitative yield of 1'. Compound 1' was treated with $LiAlH_4$ as described for ketone 1, affording alcohol **2'**, whose ^1H NMR spectrum differed from that of **2** by lacking the hydrogen signal at δ 5.00 (due to hydrogen at C-3) and the allylic methyl signal at δ 1.65 (due to the C-2 methyl). Mass spectrum parent peak m/e 182.

Registry No.—**1**, 15971-77-4; **1'**, 61463-56-7; **2**, 61463-57-8; **2'**, 61463-58-9; **3**, 61505-78-0; **4**, 61505-77-9; **5**, 61463-63-6; CH_3OD, 1455-13-6.

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(6) In ion **5** the CH_3 signal at δ 2.90 is observed as a doublet (J = 1.4 Hz). This is due to a coupling between the bridgehead hydrogen at C-1 (or C-5) and the CH_3 group at C-4 (or C-2), and not to a coupling between the hydrogen at C-1 (or C-5) and the CH_3 group at C-2 (or C-4). It is substantiated by the fact that in ion **5'** there is no such coupling.
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A Proposed Experimental Model for Molecular Orbital Calculations on Aryl Cations

Gerald F. Koser

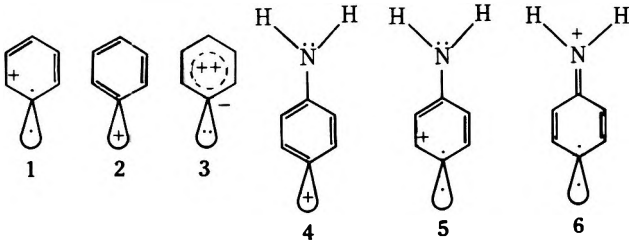
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Received August 16, 1976

A proposal, made 15 years ago, that the phenyl cation may exist as the σ,π triplet diradical 1 in its ground state[1,2] has now been examined by several molecular orbital methods. Extended Hückel,[3] INDO (with and without geometry optimization),[4,5] CNDO/S-CI,[6] and ab initio[7,8,9] calculations all

predict a ground *singlet* state for phenyl cation represented here, somewhat inadequately, with structure **2**.[10] CNDO/S–CI calculations on the singlet specie **3**, also proposed as a ground state alternative for phenyl cation,[2] predict that relative electronic state energies are **2** < **1** < **3**.[6]

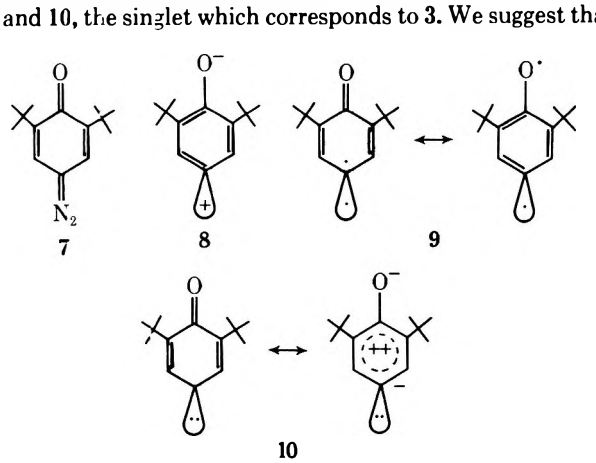
The effect of substituents on the energy of singlet phenyl cation has been analyzed by extended Hückel[3] and ab initio[7a] methods, but the effect of substituents on the *relative* electronic energies of singlet and triplet phenyl cation has not received much study.[7b] INDO calculations on the 4-aminophenyl cation constrained to a symmetric benzene geometry have been reported.[4] While the symmetric INDO singlet **2** is *more* stable than the symmetric INDO triplet **1** by at least 3.5 eV,[11] the symmetric INDO singlet **4** is less stable than the symmetric INDO triplet **5** by 0.01 eV. Although the quantitative validity of these calculations may be questioned, the



predicted substituent effect is reasonable. Stabilization of triplet phenyl cation, with its positive charge in the π system, by appropriately placed +R substituents is implicit in canonical structures such as **6** for the 4-aminophenyl cation.

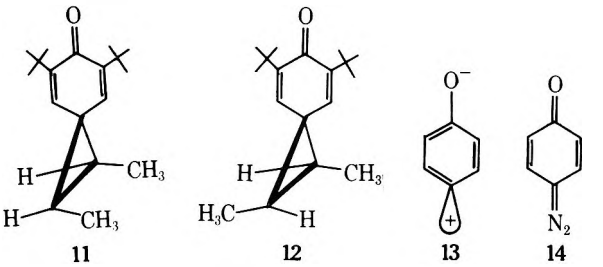
Multiplicities of the ground and low-lying excited states of the phenyl and 4-aminophenyl cations have not been experimentally determined, and it is, therefore, impossible to assess the validity of state multiplicity predictions made on those species by the various molecular orbital methods. Without an appropriate experimental model, the theoretical predictions are tenuous and of limited value. *It is the purpose of this note to point out that there is an available model; a substituted phenyl cation has been studied, and it has a triplet ground state.*

Pirkle and Koser investigated the photochemical decomposition of 3,5-di-*tert*-butylbenzene 1,4-diazooxide (**7**) in a variety of solvents including aromatic and aliphatic halides, benzene, cyclohexane, and a number of alkenes.[12-14] The reactive intermediate in those photolyses was regarded as the carbene, 3,5-di-*tert*-butyl-4-cyclohexadienonylidene. However, it may also be viewed as 3,5-di-*tert*-butyl-4-oxidophenyl cation (**8**), the oxido group of which is an outstanding +R substituent.[15] Other electronic states of **8** are represented by the carbenic structures **9**, the triplet which corresponds to **1**, and **10**, the singlet which corresponds to **3**. We suggest that



this phenylium ion may be used as a model to test the reliability of molecular orbital calculations on aryl cations.

Pirkle and Koser found that the photolysis of **7** (λ >480 nm) in neat *cis*-2-butene gave the *cis*-spirooctadienone **11** with a high degree of stereoselectivity. When the olefin was diluted with hexafluorobenzene, the relative yield of the *trans*-spirooctadienone **12** increased, and it increased in proportion to the extent of dilution.[12-14] Skell's hypothesis[16] was applied to these data. It was reasoned that the singlet carbene **10** forms initially upon photolysis of **7** and adds stereospecifically to *cis*-2-butene to give **11**. Collision of **10** with the "inert" diluent hexafluorobenzene causes thermal deactivation of **10** to its triplet ground state **9** which then adds nonstereospecifically to *cis*-2-butene giving a mixture of **11** and **12**.[13,17,18] That the ground state is indeed a triplet was confirmed by direct observation.[17,18] When the *solid* diazo oxide **7** was photolyzed in an ESR probe at −180 °C, the spectrum of the triplet was recorded (D = 0.3141 cm^{-1}, E = 0.0051 cm^{-1}).[17]



The state energy order for the 3,5-di-*tert*-butyl-4-oxidophenyl cation thus appears to be **9** < **10** < **8** and is, therefore, quite different from that predicted for phenyl cation. Here, then, is a test for the validity of any molecular orbital analysis of aryl cations. That is, if the calculations on phenyl cation, which predict a ground singlet state, are valid, similar calculations should predict a triplet ground state for the 3,5-di-*tert*-butyl-4-oxidophenyl cation.

Finally, we note that the olefin addition reactions of the 4-oxidophenyl cation (**13**) have not been studied nor has its ESR spectrum been observed even though benzene 1,4-diazooxide (**14**) is well known.[19] The *tert*-butyl groups in **7** are not innocuous; they impart solubility to **7** in nonpolar solvents, and they prevent the intermediate carbene (aryl cation) from reacting through its oxygen atom. However, it does not seem likely that attachment of *tert*-butyl groups to C-3 and C-5 in **13** would seriously alter *relative* electronic state energies, and computations on **13** would certainly be more economical than computations on **8**. Even so, the *tert*-butyl group perturbation needs to be determined.

Registry No.—**8**, 61446-34-2; **13**, 42766-45-0.

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(10) The optimal geometry and charge distribution of singlet phenyl cation predicted by molecular orbital calculations are quite different from those depicted by structure **2**. See, for example, ref. 5 and 6.
(11) Calculations on the σ,π triplet were not performed. The INDO method generates the lowest energy triplet specie which, in this case, was predicted to be of the σ,σ type and to be 3.5 eV less stable than the ground singlet cation.
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(15) The transient species formed during the decomposition of other benzene 1,4-diazooxides have also been viewed as possible oxidophenyl cations. See, for example, (a) M. J. S. Dewar and K. Narayanaswami, *J. Am. Chem. Soc.*, **86**, 2422 (1964); (b) J. K. Stille, P. Cassidy, and L. Plummer, *ibid.*, **85**, 1318 (1963); (c) T. Kunitake and C. C. Price, *ibid.*, **85**, 761 (1963).
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Hypervalent Organoiodine. Reactions of Silver Arylsulfonates with Iodosobenzene Dichloride

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Received April 30, 1976

The synthesis of iodosobenzene diacetate (**1**) from iodosobenzene dichloride (**2**) and silver acetate, reported by Alcock and Waddington in 1963,[1] suggests that a similar synthesis of iodosobenzene ditosylate (**3**) should be possible. However, when we allowed 1 equiv of **2** to react with 2 equiv of silver tosylate in acetonitrile, compound **3** was not obtained. Instead, phenylhydroxytosyloxyiodine (**4a**, 46%) and *p*-toluenesulfonic acid (39%) were isolated, and silver chloride was obtained in only 62% yield. Compound **4a** was identified by its spectral (IR, NMR) comparison with authentic material prepared by the action of toluenesulfonic acid on **1**, a reaction described by Neiland and Karele in 1970.[2] That phenylhydroxytosyloxyiodine exhibits structure **4a** and not the tautomeric structure **5** has recently been established by x-ray analysis.[3] The simplest explanation for the formation of **4a** and toluenesulfonic acid in comparable yields rests on the assumption that ditosylate **3** enjoys intermediate existence. Hydrolysis of **3**, either by atmospheric moisture or by adventitious moisture in the reaction solvent, would lead to the observed products.

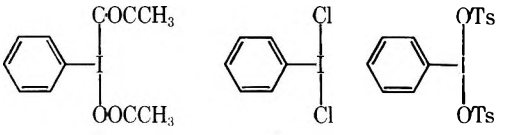
Indeed, when the reaction between **2** and silver tosylate was conducted under extremely dry conditions, compound **4a** was *not* obtained. However, all attempts to isolate **3** failed. The crude product, a waxy, yellow solid, was resolved by trituration with ether into silver tosylate and a nearly colorless semisolid which rapidly changed to a black oil upon solvent removal. That the oil is an iodine-containing (not molecular I_2) compound was verified by elemental analysis, but a definitive structural assignment could not be made. When the oil was allowed to stand in air, it crystallized to a brown solid which was shown to consist *partially* of toluenesulfonic acid.

When **2** was allowed to react, in turn, with silver benzenesulfonate, silver *p*-chlorobenzenesulfonate, and silver *p*-nitrobenzenesulfonate, the hydroxysulfonates **4b** and **4c** and, presumably, the hydroxysulfonate **4d** were obtained (yields are given in Table I). Note that the yield of silver chloride failed to exceed 65% in all of those reactions. Compounds **4a–d** are insoluble in acetonitrile (the reaction solvent) and crystallize from solution subsequent to the removal of silver chloride. Crystallization may occur shortly after filtration or hours may pass before crystals appear. In the latter instance, addition of a small quantity (ca. 0.1 g) of water to the filtrate has been observed to facilitate product formation.

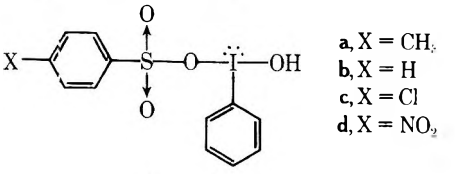
Authentic samples of **4b**, **4c**, and **4d** were prepared by treatment of **1** with the appropriate sulfonic acid in acetonitrile and were characterized by elemental (C, H, I) and spectral analysis. The structures assigned to the materials derived from iodosobenzene dichloride (**2**) were then confirmed by spectral (IR, NMR) comparisons.

Table I

	$PhICl_2 + Ag^+ {}^-O_3SC_6H_4X$		$PhI(OAC)_2 + HO_3SC_6H_4X$	
X	Yield of **4**, %	Yield of AgCl, %	X	Yield of **4**, %
CH_3	46	62	CH_3	93
H	64	61	H	72
Cl	39	60	Cl	51
NO_2	32	47	NO_2	91

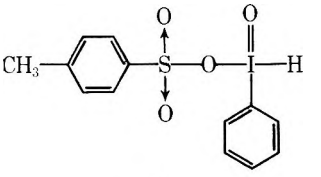


1 **2** **3**



a, X = CH_3
b, X = H
c, X = Cl
d, X = NO_2

4



5

Compound **4d** exhibited erratic behavior. For example, for three different $PhICl_2/AgO_3SC_6H_4NO_2$ runs, product melting points of 126–129, 141–143, and 153–156 °C were recorded. Similarly, for two different $PhI(OAc)_2/HO_3SC_6H_4NO_2$ runs, product melting points of 126–128.5 and 142–144.5 °C were observed, although most products derived from **1** melted in the 140–150 °C range. Melting points as high as 166–167.5 and 169–171.5 °C have been noted for "purified" **4d**. The NMR spectrum of **4d** in Me_2SO-d_6 has been difficult to reproduce. Two types of NMR spectra have been observed, and they exhibit significantly different aromatic patterns. One of these is nearly identical with the spectrum of a 1:1 mixture of iodobenzene and *p*-nitrobenzenesulfonic acid, and it seems that **4d** may undergo reductive decomposition in Me_2SO-d_6. We have been unable to isolate dimethylsulfone-d_6, the likely oxidation product, but if it is formed, it would be present in very small quantities. The NMR spectra of **4a**, **4b**, and **4c** are clearly distinct from those of 1:1 mixtures of iodobenzene and the corresponding benzenesulfonic acids.

Finally, we have found that **4a** can be synthesized directly from iodobenzene. When a solution of iodobenzene (5 mmol) and silver tosylate (10 mmol) in acetonitrile was subjected to a stream of chlorine gas, **4a** was formed and was isolated in 48% yield.

Experimental Section

General. NMR spectra were recorded on a Varian Model A-60 NMR spectrometer, Me_4Si being used as an internal reference. IR spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer and were calibrated with polystyrene. However, reported band positions in the 8–24 μ range should be regarded as approximate

(±0.05 μ). Melting points are uncorrected. Elemental analyses were performed at Galbraith Laboratories, Knoxville, Tenn.

The silver salts employed in this study were prepared by treatment of the corresponding benzenesulfonic acids in acetonitrile with silver(I) oxide. The sulfonic acids were purchased from Eastman Organic Chemicals, both toluenesulfonic and benzenesulfonic acids as their monohydrates. Some silver tosylate was purchased from Eastman Organic Chemicals. Iodosobenzene diacetate (98%) was purchased from the Aldrich Chemical Co., and silver(I) oxide was purchased from MCB. Iodosobenzene dichloride was synthesized from iodobenzene and chlorine and was recrystallized from nitromethane just prior to use.

Compounds **4a–d**, derived from iodosobenzene dichloride, were identified by IR and ^{1}H NMR spectral comparisons with authentic materials derived from iodosobenzene diacetate (as described herein). Spectra are *nearly* identical in such comparisons but there are occasional minor differences, sometimes due, we believe, to instrument fluctuations.

Reaction of 1 with *p*-Toluenesulfonic Acid in CH_3CN. *p*-Toluenesulfonic acid monohydrate (7.61 g, 40 mmol), dissolved in a minimum quantity of CH_3CN, was added to a solution/suspension of **1** (6.44 g, 20 mmol) in CH_3CN (45 mL) at room temperature. The reaction mixture immediately cleared and turned yellow and, upon standing at room temperature, gave phenylhydroxyltosyloxyiodine (**4a**) as fine white needles with a yellowish hue. Two crops were isolated, yield 7.62 g (92%). The crude product was washed with acetone (removes *p*-toluenesulfonic acid) and ether (removes acetic acid) and dried: mp 135–138 °C; the NMR spectrum of this material has been thoroughly described elsewhere;[3] IR (KBr) bands at 6.18, 6.25, 6.37, 6.68, 6.80, 6.96, 7.15, 8.01 (sh), 8.5, 8.9, 9.6, 9.9, 10.02, 12.33, 12.82, 13.21, 13.68, 14.35, 15.22, 17.38, 17.65, 21.8, 22.3 μ.

Anal. Calcd for $C_{13}H_{13}ISO_4$: C, 39.81; H, 3.34; I, 32.36. Found: C, 39.53; H, 3.09; I, 32.89.

Reaction of 2 with Silver *p*-Toluenesulfonate in Acetonitrile. A solution of **2** (1.00 g, 3.64 mmol) in CH_3CN (20 mL) was added dropwise to a solution of silver *p*-toluenesulfonate (2.03 g, 7.28 mmol) in CH_3CN (20 mL) over a period of ca. 15 min at room temperature. The reaction mixture was then allowed to stir for 45 min at room temperature after which time the AgCl which had precipitated was isolated and dried, yield 0.647 g (62%). Upon refrigeration, the filtrate yielded phenylhydroxyltosyloxyiodine (**4a**) as white needles which have a yellowish hue in light: yield 0.580 g (46.1%); mp 135–137 °C.

The final filtrate was concentrated at reduced pressure and 0 °C to a mushy, yellow-white solid. The solid was treated with ether, and 0.205 g of silver *p*-toluenesulfonate was recovered. The resulting ether phase was then concentrated at reduced pressure to a pungent, waxy solid, tan to gray in color. The solid was triturated with acetone and dried in vacuo and had an ^{1}H NMR spectrum identical with that of *p*-toluenesulfonic acid: yield 0.55 g; mp 89–91 °C.

Reaction of Iodobenzene with Cl_2 in the Presence of $AgO^{+-}O_3SC_6H_4CH_3$. Iodobenzene (1.08 g, 5 mmol) and silver *p*-toluenesulfonate (2.79 g, 10 mmol) were dissolved in CH_3CN (20 mL). The resulting solution was stirred vigorously while Cl_2 gas was blown across the surface. The precipitation of AgCl began immediately, and the solution yellowed. After the AgCl (1.23 g, 64.1%) was removed, phenylhydroxyltosyloxyiodine (**4a**) crystallized from the filtrate as fine white needles with a pale yellow hue: yield, 0.92 g, (48%); mp 132–134 °C.

Reaction of 1 with Benzenesulfonic Acid. A solution of benzenesulfonic acid monohydrate (0.88 g, 5.0 mmol) in a minimum quantity of CH_3CN was added at once to a solution of **1** (1.6 g, 5 mmol) in CH_3CH (35 mL). After ca. 2 min, fine crystals formed throughout the solution, and, after 1 h, the product, **4b**, was isolated by filtration, washed with acetone and ether, and dried: yield 1.58 g (71.5%); mp 127–128 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.15–7.85 (complex multiplet, aromatic hydrogens), 8.05–8.35 (complex multiplet, aromatic hydrogens), 8.90 (s, OH), integration 8:1.8:1.3 (theoretical 8:2:1); IR (KBr) bands at 6.15, 6.36, 6.80, 6.92, 6.96, 7.15, 8.44, 8.85, 9.6, 9.8, 10.05, 13.2, 13.6, 14.45, 14.9, 15.25, 15.95, and 17.6 μ.

Anal. Calcd for $C_{12}H_{11}SO_4I$: C, 38.11; H, 2.93; I, 33.56. Found: C, 38.11; H, 2.95; I, 33.71.

Reaction of 2 with Silver Benzenesulfonate in CH_3CN. A solution of silver benzenesulfonate (3.26 g, 12.3 mmol) in CH_3CN (20 mL) was added dropwise to a solution of **2** (1.56 g, 5.7 mmol) in CH_3CN (40 mL) with *immediate* precipitation of AgCl which was subsequently isolated and dried (1.00 g, 61.2%). Upon refrigeration, the yellow filtrate yielded phenylhydroxybenzenesulfonoxyiodine (**4b**) as well-crystallized needles which were isolated, washed with acetone, and dried: yield 1.36 g (63.5%); mp 123–125 °C.

Reaction of 1 with *p*-Chlorobenzenesulfonic Acid. A solution of *p*-chlorobenzenesulfonic acid (2.05 g, 10.6 mmol) in CH_3CN (~10 mL) was added at once to a cloudy solution of **1** (3.22 g, 10 mmol) in CH_3CN (50 mL). The reaction mixture cleared to a yellow solution and was allowed to stand for several hours at room temperature (after a small amount of insoluble matter had been removed by filtration) during which time **4c** crystallized from solution. The product was isolated as fine, pale yellow needles, washed with ether, and dried: yield 2.10 g (50.9%); mp 119–120 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.2–7.8 (complex multiplet, aromatic hydrogens), 8.0–8.4 (complex multiplet, aromatic hydrogens), 9.01 (broad singlet, O–H), integration 7:1.76:0.84 (theoretical 7:2:1); IR (KBr) bands at 6.37, 6.75, 6.80, 6.95, 7.18, 8.13, 8.45, 8.9, 9.1, 9.2, 9.45, 9.65, 9.95, 10.05, 11.9, 12.1, 13.2, 13.4, 13.65, 14.05, 14.6, 15.35, 17.6, 17.95, 20.4, 22.3 μ.

Anal. Calcd for $C_{12}H_{10}SO_4ICl$: C, 34.93; H, 2.44; I, 30.71. Found: C, 34.71; H, 2.73; I, 30.62.

Reaction of 2 with Silver *p*-Chlorobenzenesulfonate in CH_3CN. A solution of **2** (0.93 g, 3.3 mmol) in CH_3CN (30 mL) was added dropwise to a solution of silver *p*-chlorobenzenesulfonate (2.03 g, 6.7 mmol) in CH_3CN (15 mL) over a period of 15 min with *immediate* precipitation of AgCl. After an additional 1 h, the AgCl was isolated (0.58 g, 59.7%) by filtration. The filtrate, upon standing, yielded phenylhydroxy-*p*-chlorobenzenesulfonoxyiodine (**4c**) as fine, white needles: yield 0.55 g (39.2%); mp 119–121 °C.

Reaction of 1 with *p*-Nitrobenzenesulfonic Acid. A solution of *p*-nitrobenzenesulfonic acid (2.03 g, 10 mmol) in a minimum quantity of CH_3CN was added at once to a translucent solution of **1** (1.61 g, 5 mmol) in CH_3CN (25 mL). The reaction mixture immediately cleared to a yellow solution, and, after 1 min, dense, pale yellow plates began to crystallize from solution. After 1 h, the solution was chilled in ice, and the product, **4d**, was isolated, yield 1.92 g (90.8%). The product, after recrystallization from methanol–ether, melted at 145–147 °C; NMR (Me_2SO-d_6, presumably nondecomposed **4d**) δ 7.5–8.4 (complex multiplet, aromatic hydrogens), this multiplet exhibits lines at δ 7.58, 7.62, 7.68, 7.71, 7.85, 8.17, 8.20, 8.30, and 8.35; 8.75 (very broad singlet, OH), integration 9.1:1 (theoretical 9:1); IR (KBr) bands at 6.19, 6.24, 6.38, 6.59, 6.81, 6.96, 7.13, 7.39, 7.75, 8.05, 8.20, 8.9, 9.6, 9.85, 11.40, 11.65, 13.42, 13.62, 14.4, 15.55, 17.6, 18.0, 21.1 μ.

Anal. Calcd for $C_{12}H_{10}INSO_6$: C, 34.06; H, 2.38; I, 29.99. Found: C, 33.90; H, 2.48; I, 29.86.

Reaction of 2 with Silver *p*-Nitrobenzenesulfonate. A solution of silver *p*-nitrobenzenesulfonate (3.22 g, 10.4 mmol) in CH_3CN (40 mL) was added dropwise at room temperature to a solution of **2** (1.43 g, 5.2 mmol) in CH_3CN (40 mL). After an additional 0.5 h the AgCl which had precipitated was isolated and dried, yield 0.70 g (47.3%). The filtrate was placed under refrigeration and yielded 0.71 g (32.1%) of **4d** as dense plaques of fine, pale yellow crystals, mp 143–145 °C.

Reaction of 2 with Silver *p*-Toluenesulfonate in CH_3CN under Anhydrous Conditions. The following experiment was conducted under dry nitrogen in a controlled atmosphere glovebox.

Dry silver tosylate (2.78 g, 0.01 mol) was mixed with acetonitrile (freshly distilled from P_2O_5) in a quantity just sufficient to effect solution, and **2** (1.38 g, 0.005 mol, freshly recrystallized from CH_3NO_2) was likewise dissolved in a minimum quantity of dry CH_3CN. The latter solution was added dropwise to the former over a period of about 10 min. After an additional 10 min, the AgCl which had precipitated was isolated, dried, and weighed (0.94 g, 65.5%). The clear, yellow filtrate, when it was allowed to stand overnight, *did not* yield phenylhydroxytosyloxyiodine (**4a**).

The filtrate was then concentrated in vacuo to a yellow, waxy solid (2.98 g): NMR (CD_3CN) δ 1.9 (s, CH_3CN impurity), 2.75 (s, 66 mm), 7.1–7.9 (m, 123 mm), 13.7 (s, 14 mm). A portion (0.48 g) was redissolved in CH_3CN, an observation which indicates clearly that the *insoluble* **4a** was not present in the crude product. A sample (2.00 g) of the crude product was triturated with ether, and 0.80 g of an ether-insoluble, water-soluble, tan-gray solid was obtained and found to consist primarily of unreacted silver tosylate; duplicate gravimetric silver analyses (by the NaCl precipitation method) gave values of 23.1 and 27.1% for the percentage by weight of silver. The ether *solution* from the trituration experiment was concentrated to a colorless to pale yellow semisolid (0.85 g) which rapidly changed to a black oil. After several days, the oil crystallized *partially* to a brown solid: NMR (CD_3CN) δ 1.2 and 3.6 (t and q of occluded ether), 2.40 (s, 14.5 mm), 7.0–8.0 (m, 25.5 mm), 10.82 (s, 7 mm).

Anal. C, 41.43; H, 4.98; I, 35.22.

The brown solid is water soluble and gives a brown, cloudy, acidic solution (pH ~2–3). Titration of those solutions with NaOH (0.099 N) gave an equivalent weight of ~300. The solid material is only slightly soluble in $CHCl_3$, but "recrystallization" of a portion from that solvent gave a solid, mp 102–105 °C, identified by NMR analysis as toluenesulfonic acid.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the Research Corporation for partial support of this research.

Registry No.—**1**, 3240-34-4; **2**, 932-72-9; **4a**, 27126-76-7; **4b**, 61477-31-4; **4c**, 61477-32-5; **4d**, 61477-33-6; *p*-toluenesulfonic acid, 104-15-4; benzenesulfonic acid, 98-11-3; *p*-chlorobenzenesulfonic acid, 98-66-8; *p*-nitrobenzenesulfonic acid, 138-42-1; silver *p*-toluenesulfonate, 16836-95-6; silver benzenesulfonate, 39938-06-2; silver *p*-chlorobenzenesulfonate, 39938-10-8; silver *p*-nitrobenzenesulfonate, 39938-18-6; iodobenzene, 591-50-4.

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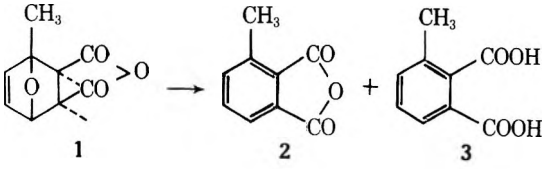
Improved Synthesis of 3-Methylphthalic Anhydride[1]

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Received August 17, 1976

The Diels–Alder reaction of furans with maleic anhydride (MA) is known to occur in excellent yield in many cases.[3] However, the aromatization of these adducts to derivatives of phthalic anhydride is less well documented. In an early paper *exo-cis*-1-methyl-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride (**1**), the adduct of 2-methylfuran and MA, **2**, was converted to 3-methylphthalic anhydride (**2**) by treatment with hydrogen bromide in acetic acid but no details or yields were given.[4]



1 2 3

In this laboratory, 3,6-dimethylphthalic anhydride was prepared in 45% yield[5] by adding the 2,5-dimethylfuran–MA adduct to 90% sulfuric acid at −6 to 0 °C. Similarly, 3-methylphthalic anhydride was prepared from **1** in 38% yield.[6] The adduct of 2-acetoxyfuran and MA was converted into 3-acetoxyphthalic anhydride in 57% yield by heating with acetic anhydride containing sulfuric acid.[7] In this paper we report on our efforts to improve the yield of **2** by treatment of **1** with acidic reagents. In addition to the isolation of **2**, we also examined the reaction mixtures for 3-methylphthalic acid (**3**) and other compounds, but the side products, when isolated, proved to be tars, except in one experiment (no. 5, Table I). No attempt was made to isolate highly water-soluble compounds.

Of the acidic reagents tried, 98% sulfuric acid proved the most promising. The best result (expt 2), a 66% yield, was obtained when the mixing of reagents was done at very low temperatures. In order to attain a low-temperature liquid medium with sulfuric acid a cosolvent, sulfolane, was needed. The desirability of having a low temperature may be explained by assuming that one reason for getting a low yield in these reactions is that an acid-catalyzed reversal of the Diels–Alder reaction[8,9] competes with acid-catalyzed dehydration to the desired product. This reversal of the Diels–Alder reaction is less important at lower temperatures and hence a higher yield of dehydration product results. In support of this concept, the fact that a 25% yield of 5-acetyl-2-methylfuran[10] was obtained in a BF_3–Ac_2O–AcOH medium (expt 5, Table I) is pertinent. This compound undoubtedly arises from acetylation of the 2-methylfuran formed by reversion of the Diels–Alder adduct to its components. In other acidic media used any 2-methylfuran formed was converted either into water-soluble products or tars.

Experimental Section[11]

***exo-cis*-1-Methyl-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic Anhydride (1).** In the best of several large-scale runs, 216 g (2.20 mol) of freshly distilled maleic anhydride was dissolved in 600 mL of dry ether freshly distilled from Grignard reagent.[12] To this solution 4 g of hydroquinone and 200 g (2.44 mol) of freshly distilled 2-methylfuran were added at room temperature. After 4 h the mixture was placed in a refrigerator overnight. The crystals (322 g, 81.3% based on MA) which had separated were collected and washed with an ether–petroleum ether mixture and melted at 80–81 °C. Further cooling of the combined filtrates yielded 48.6 g (12.3%) of **1**, mp 79–80 °C.[13] The total yield was thus 94.6% based on MA and 85% based on 2-methylfuran. In order to obtain such high yields it is important that all reactants and solvents be freshly distilled. As we never tried a run without hydroquinone we do not know if the presence of hydroquinone is necessary.

3-Methylphthalic Anhydride (2). The highest yields obtained are represented by expt 3, Table I. On a large scale 250 mL of concentrated H_2SO_4 (98%) was dissolved in 100 mL of freshly distilled sulfolane[14] and the solution was cooled to −55 °C (alcohol thermometer) with dry ice–isopropyl alcohol. Finely powdered, freshly

Table I. Conversion of 1 to 2[a]

Expt	Acid medium	Conditions	Yield, % 2	3	Tar, other
1[a]	98% H_2SO_4	−20 to −10 °C, 4 h 25 °C, 1 h	38	0	0
2	85% H_2SO_4	0–26 °C, 2 h	1	25	0
3[a]	98% H_2SO_4 in sulfolane	−55 to −45 °C, 3 h −45 to 26 °C, 3 h	66	0	0
4[a]	HF (liq)	−78 to 26 °C, 24 h	30	5	65
5	BF_3, Ac_2O, HOAc	25 °C, 3 h	0	0	25[b]
6	80% H_3PO_4, 20% H_2SO_4	0–27 °C, 2 h	5	5	0
7	71% CH_3SO_3H, P_2O_5[c]	0–26 °C, 5 h	10	0	0
8	71% CH_3SO_3H	0–26 °C, 5 h	0	0	100[d]
9	Dry HCl in ether	0–25 °C, 3 h	0	0	100[d]

[a] The reactions were carried out in general with 5–10 g of **1** and appropriate volumes of the acidic reagents, e.g., 50–100 mL. All productive experiments were run in duplicate with excellent agreement of results. [b] 5-Acetyl-2-methylfuran. [c] 1 equiv of P_2O_5 added for the 29% of H_2O. [d] Starting material, **1**.

prepared 1 (60.0 g) was added at such a rate that the temperature did not exceed −45 °C. After 3 h at −55 to −45 °C the mixture was allowed to come to room temperature during 3 h and was then poured on 2 L of cracked ice. As soon as the ice was melted the solid was collected and washed with cold water. After drying by suction overnight the distilled solid, bp 125 °C (0.4 mm), was recrystallized from benzene–petroleum ether to yield 33.0 g (61%) of colorless 2, mp 115–116 °C.

Registry No.—1, 941-63-9; 2, 4792-30-7; 3, 37102-74-2; 5-acetyl-2-methylfuran, 1193-79-9; maleic anhydride, 108-31-6; 2-methylfuran, 534-22-5.

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(14) Sulfolane, tetramethylenesulfone, was kindly provided by the Phillips Petroleum Co., Bartlesville, Okla.

A Direct Method for the Preparation of Phenols from Aryl Bromides Utilizing Molybdenum Peroxide–Pyridine–Hexamethylphosphoramide

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Received October 12, 1976

We wish to report a convenient synthetic method for the conversion of aryl bromides to phenols by reactions of arylmagnesium bromide Grignard reagents with molybdenum peroxide–pyridine–hexamethylphosphoramide. The reported procedure represents a novel synthetic use of the molybdenum complex and provides a mild, one-flask reaction sequence for the synthesis of phenols under basic conditions. We obtained good to excellent yields with several prototype compounds.

Vedejs[1] had reported a method for the hydroxylation of enolate anions using transition metal peroxide MoO_5–Py–HMPA (MoOPH) as the hydroxylating agent. This MoOPH had been previously described by Mimoun for the epoxidation of olefins.[2,3] Regen and Whitesides[4] noted that a related reagent, MoO_5–HMPA, reacted with *n*-butyllithium to form *n*-butoxide and Vedejs[1] observed that a number of enolate anions reacted with this reagent at low temperature presumably by nucleophilic attack at peroxide oxygen. A variety of esters, lactones, and ketones having enolizable methine or methylene groups have been hydroxylated with this complex. Synthetic pathways under investigation in our laboratories made it desirable to study the effectiveness of MoOPH in converting aryl bromides to their respective phenolate anions. Aqueous workup with careful acidification yielded the phenolic products. We can now describe our application of MoOPH for the preparation of phenolic compounds.

Starting with an appropriate aromatic bromide we formed the arylmagnesium bromide in anhydrous THF and immediately reacted the Grignard reagent with MoOPH[5,6] at dry ice–acetone bath temperatures. After aqueous workup, the phenolic compounds were isolated in high yields (Table I). The method described is a straightforward and convenient one. Reactions run at temperature to 20 °C gave similar results but caution is advised when utilizing the MoOPH complex at room temperature.[7] Reactions of bromobenzene (1), 1-bromo-4-methoxybenzene (2), 1-bromo-4-ethylbenzene (3), and 1-bromonaphthalene (4) with MoOPH afforded the corresponding phenolic compounds in yields of 67–89%.[9]

Table I

Starting material[a]	Product[a]	Yield, %
Bromobenzene (1)	Phenol (1a)	89
1-Bromo-4-methoxybenzene (2)	4-Methoxyphenol (2a)	67
1-Bromo-4-ethylbenzene (3)	4-Ethylphenol (3a)	70
1-Bromonaphthalene (4)	1-Hydroxynaphthalene (4a)	85

[a] Compounds 1 and 4 were purifed by distillation. Compounds 2 and 3 were purified by column chromatography on silica gel (50:1, $CHCl_3$).

Experimental Section

All melting points were taken on a Thomas-Hoover melting point apparatus. IR spectra were obtained on a Beckman Model 4230 infrared spectrophotometer; NMR data were recorded on a Varian Model A-60A spectrometer in $CDCl_3$ using Me_4Si as an internal standard. TLC analysis was performed on silica gel plates using $CHCl_3$ as the mobile phase.

General Procedure for Making Arylmagnesium Bromides. Dry THF (15 mL) and 0.12 g (5.0 mmol) of Mg metal were placed in a three-necked flask equipped with a gas inlet tube, a gas outlet tube, and a dropping funnel. The aryl bromide (5.0 mmol) in 10 mL of dry THF was added dropwise with stirring under N_2 to the Mg–THF suspension. The reaction was allowed to proceed at room temperature and complete dissolution of Mg was taken as an indication of complete Grignard formation.

Reaction of the Grignard Reagent with MoOPH. After the formation of Grignard reagent, the dropping funnel was replaced with a ground glass stopper. The contents of the flask were cooled to −78 °C (dry ice–acetone bath). To this solution was added 5.0 mmol of powdered MoOPH.[2] The reaction was allowed to continue at −78 °C for 1 h at which time the flask was gradually warmed to 10 °C and 75 mL of H_2O was added. The reaction mixture was allowed to stir for an additional 1.0 h. The contents of the flask were extracted with $CHCl_3$ (3 × 100 mL), and the extracts washed with 10% HCl (1 × 30 mL) and 10% $NaHCO_3$ (1 × 30 mL). The solvent was removed under reduced pressure at 35 °C and the residue treated with 10% aqueous NaOH (25 mL). The alkaline solution was washed with $CHCl_3$ (2 × 50 mL), neutralized with 10% HCl to pH 4, and extracted with $CHCl_3$ (3 × 100 mL). The $CHCl_3$ layer was dried (Na_2SO_4) and evaporated to give the arylhydroxy compounds. The low-melting solids were purified by column chromatography (50:1 silica gel, $CHCl_3$) or by distillation. IR, NMR, and melting point data of all phenolic products were compared with those of authentic samples.

Registry No.—1, 108-86-1; 1a, 108-95-2; 2, 104-92-7; 2a, 150-76-5; 3, 1585-07-5; 3a, 123-07-9; 4, 90-11-9; 4a, 90-15-3; MoOPH, 23319-63-3.

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(5) MoOPH was prepared according to the procedure of Mimoun (ref 2). We noted that while preparing the complex MoO_5–H_2O–HMPA allowing the temperature to rise above 40 °C results in a strongly exothermic reaction which is difficult to control.
(6) The reaction of phenylmagnesium bromide and MoOPH was studied between −78 and 20 °C. The reaction proceeded smoothly at 20 °C without any

explosion and without change in phenolic yields.
(7) Vedejs (ref 1) reported that MoO_5–H_2O–HMPA may be unstable when stored at room temperature. We stored this complex for 2 weeks and there was no indication of any instability. However, if the complex was exposed to air for 2–3 days it absorbed moisture and was exceedingly difficult to recrystallize.
(8) All compounds **1a–4a** were compared with the authentic samples for TLC, IR, NMR and melting point data.
(9) M.R.D. supported as NIH Trainee, 1973–1976.

A Convenient Synthesis of 1-Bromo-8-iodonaphthalene and 1,8-Dibromonaphthalene from 8-Bromo-1-naphthoic Acid

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Received October 13, 1976

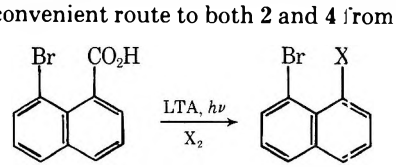
1,8-Dihalonaphthalenes, especially those containing bromine and/or iodine, are important intermediates for the preparation of naphthalene-based heterocycles and other naphthalene derivatives. Fieser and Seligman[2] prepared several 1,8-disubstituted naphthalenes from 1,8-diaminonaphthalene employing a modified stepwise diazotization procedure.[3] This method is time consuming and does not give satisfactory results.[4] Direct tetraazotization of 1,8-diaminonaphthalene is useful for preparing 1,8-diiodonaphthalene (**1**)[5] but does not give good yields of 1,8-dibromonaphthalene (**2**)[4] and is not a feasible route to mixed dihalonaphthalenes.

A synthesis of **2** using the Hunsdiecker reaction on 8-bromo-1-naphthoic acid (**3**) was reported[4] and 1-bromo-8-iodonaphthalene (**4**) has been prepared by treating 8-bromo-1-naphthoic acid with red mercuric oxide and iodine.[6a] For large scale preparations of these compounds both routes have disadvantages: the former requires expensive silver salts and the latter gives modest yields (28%).

Since our work requires that we have ready access to all three dihalonaphthalenes, **1**, **2**, and **4**, we investigated all of the reported methods for making these compounds in order to find the most reliable and efficient routes. The diazotization procedures[2] for preparing **2** and **4** gave yields varying from 0 to 30%. These reactions are apparently very sensitive to the state of the catalyst. We were not successful in finding a way to make it consistently active.

Although we found the tetraazotization procedure[5] useful for preparing **1**,[7] we could not extend this method to **2**, an observation consistent with that made earlier.[4] Our efforts to improve the yields of the mercuration–iodination reaction[6a] to produce **4** were unsuccessful. When we substituted iodine monochloride for iodine we isolated no product from the reaction mixture.

We did find that lead tetraacetate (LTA) induced halodecarboxylation, a procedure usually inefficient for aromatic acids,[8] is a convenient route to both **2** and **4** from **3**.



3 **2**, X = Br; **4**, X = I

We have found the yields consistently good for **4** (≥75%, isolated) using LTA, halogen, and **3**. The yields of **2** run lower (~50%, isolated) but are still in the useful range.

Attempts to extend this method to making **1**, **2**, **3**, and 8-iodonanaphthoic acid (**5**) from 1,8-naphthalenedicarboxylic acid (**6**) failed using pure benzene and pure tetrahydrofuran solvent systems.

Experimental Section

Melting points were determined on a Thomas-Hoover Mel-Temp melting point apparatus and are corrected. Infrared spectra were taken on a Perkin-Elmer Infracord 137 using pressed KBr pellets. NMR spectra were obtained from a Varian A60-A spectrometer in $CDCl_3$ with Me_4Si as internal standard. IR, NMR, and mass spectra of **4** and **2** are consistent with the assigned structures.

1-Bromo-8-iodonaphthalene (4). In a three-necked 1-L round-bottom flask equipped with heating mantle, reflux condenser, magnetic stirrer, and a syringe needle for bubbling N_2 through the solution were placed 750 mL of dry benzene and 14 g of 8-bromo-1-naphthoic acid.[9] This slurry was warmed to near reflux to dissolve **3**. Nitrogen was bubbled through the solution and moist lead tetraacetate freshly made from 57 g of Pb_3O_4 in 98 mL of glacial acetic acid and 32 mL of acetic anhydride[10] was added to give a deep red solution. The solution was irradiated with a 275-W sunlamp and turned yellow after 5 min. Iodine was added in small portions with time allowed between additions for the iodine color to discharge. Large amounts of lead salts precipitated during the addition of the iodine. When the iodine color did not discharge after 15 min of irradiation, the reaction was assumed to be complete and the light was turned off. The red solution was cooled, filtered, and washed with saturated sodium thiosulfate solution. The resulting yellow benzene solution was dried with anhydrous $MgSO_4$ and filtered, and the solvent was removed in vacuo. The brown solid obtained was placed on a 10 × 5 cm column of alumina (Alcoa F-20, neutral, activated) and eluted with hexane as one large fraction. Removal of the hexane gave 13.6 g (75%) of a pale yellow solid, mp 92–93 °C (lit. mp[6] 91–92 °C). A second run on the same scale produced 13.7 g (76%) of **4**.

1,8-Dibromonaphthalene (2). The procedure was the same as that for **4** with the exception that bromine was added in small portions by syringe. Six grams of 8-bromo-1-naphthoic acid (**3**) gave 4.5 g (66%) of a pale yellow solid after chromatography on alumina with hexane, mp 82–85 °C. Recrystallization from ethanol gave 3.4 g (50%) of an off-white solid, mp 104–105 °C.[6a,b] A second run on 4 g of **3** gave 1.8 g (40%) after recrystallization, mp 104–105 °C (lit. mp 109–110[2] and 106–108 °C[6]).

Acknowledgments. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. Financial support from the Research Corporation is also gratefully acknowledged.

Registry No.—**2**, 17135-74-9; **3**, 1729-99-3; **4**, 4044-58-0.

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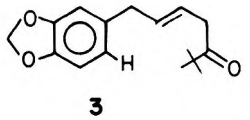
Cyclizations of Enolates onto Aromatic Rings via the Photo-$S_{RN}1$ Reaction. Preparative and Mechanistic Aspects

Summary: Six-, seven-, eight-, and ten-membered rings are obtained by photostimulated aromatic nucleophilic substitution by enolate anions, but only when internal H-atom transfer from the γ position of the ketone is blocked, as shown by deuterium labeling.

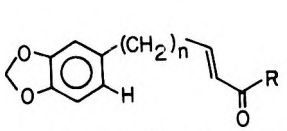
Sir: The photoinitiated substitution of carbanions for halide in aromatic rings, discovered by Bunnett and Rossi,[1] promises to be an important new method of nucleophilic aromatic substitution. Following the initial reports of simple intermolecular examples,[2] we found an efficient application of the reaction in the synthesis of cephalotaxine,[3] and thus became interested in the factors which govern the generality of the reaction for organic synthesis, particularly in cyclizations. Here we report preliminary results which begin to delineate the conditions under which the intramolecular photo-$S_{RN}1$ reaction is likely to be successful, and demonstrate that hydrogen atom migration can provide a serious side reaction in both intra- and intermolecular examples.

The studies have involved methylenedioxophenyl derivatives (Table I) which were chosen to test questions of ring size preferences in the cyclizations, including regioselectivity with ketones that can give two enolate anions. The reactions were carried out by dissolving the aryl halo ketone (1 mmol) and potassium *tert*-butoxide (6 mmol) in liquid ammonia (75–80 mL, reflux) in a Pyrex flask and irradiating with an external medium-pressure mercury arc (Hanovia 450 W) until the aryl halo ketone was consumed. Conventional isolation procedures provided the crude organic products from which the cyclized product was isolated by short-path distillation and chromatography. The yields are based on isolated material, unless otherwise indicated.[4]

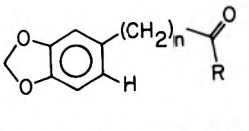
Entries 1–3 of Table I demonstrate the cyclizations can be achieved efficiently; the ten-membered ring (entry 4) was obtained in reasonable yield assuming no special preference for medium-sized rings in this method. However, in cases where the more substituted (internal) enolate can appear (entries 5–9) the cyclizations are much less efficient. For example, compound **1** leads to the tetralin derivative **2** in only 11% yield (entry 5). The major monomeric product (67%) was the β,γ-unsaturated ketone **3** (presumably from isomerization of the α,β isomer, **4a**),[5] while a trace of the reduction product, **5a**, was detected by GC–MS. Where a four- and a six-membered ring could reasonably be expected, neither was obtained (entry 6) and the reduction product (**5b**) could be isolated in 21% yield as the only monomeric product. Compound **6** produced mainly the seven-membered ring (**7** entry 7) along with approximately equal amounts of five-membered ring, the



3

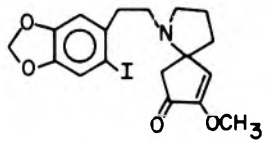
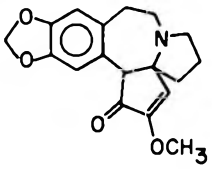
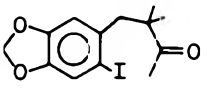
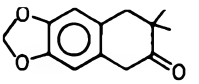
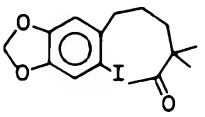
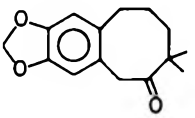
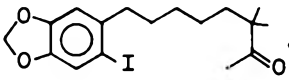
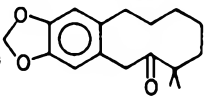
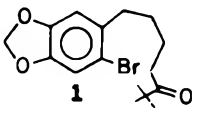
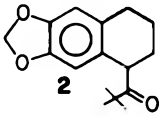
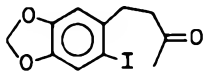
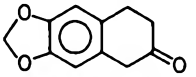
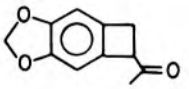
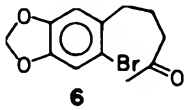
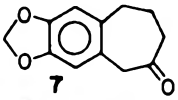
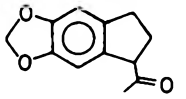
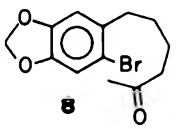
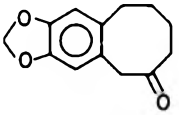
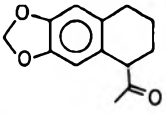


4a: R = $C(CH_3)_3$, n = 2
b: R = CH_3, n = 1
c: R = CH_3, n = 2



5a: R = $C(CH_3)_3$, n = 4
b: R = CH_3, n = 2
c: R = CH_3, n = 3
d: R = CH_3, n = 4

Table I. Photocyclization of Keto Halo Aryls

Entry	Halo ketone	Cyclzn products (yield[a] %)
1.		 (94)
2.		 (99)
3.		 (71,[b] 28)[c]
4.		 (35)
5.		 (11)
6.		 (0)[d]  (0)[d]
7.		 (42)[d]  (4)[d]
8.		 (19)[d]  (3)[d]

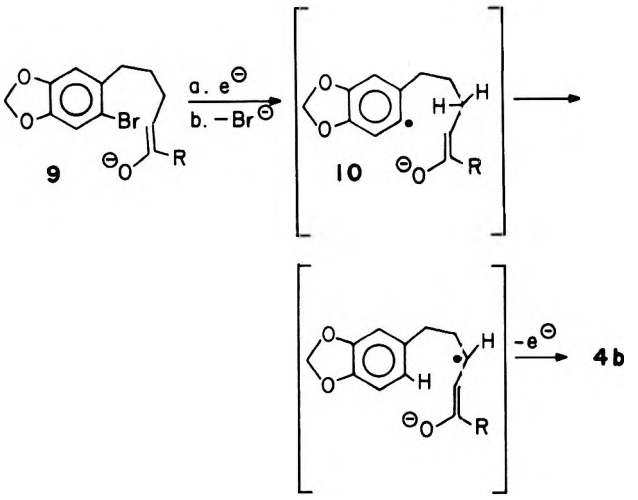
[a] The yields are based on isolated material unless otherwise noted. [b] This yield was obtained at low concentration, ~0.00125 M. [c] This yield was obtained at the usual concentration, ~0.05 M. [d] The product ratios are based on uncalibrated GLC analyses; the combined yield is based on the weight of the mixture obtained after purification.

α,β-unsaturated ketone (**4b**) and the reduction product (**5c**). From **8**, the yield of monomeric material was 31%, trace amounts of reduction product (**5d**, 3%) and the six-membered ring (entry 8, 3%), and larger amounts of the α,β-unsaturated ketone (**4c**, 7%) and the eight-membered ring (entry 8, 19%).

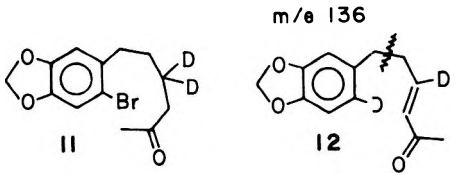
In related experiments, the enolate anions were generated quantitatively using potassium amide. Irradiation produced a larger proportion of product resulting from cyclization through the unsubstituted (presumably, kinetic) enolate. From **6** (entry 7) under these conditions, only reduction product **5c** (23% yield) and the seven-membered ring (21% yield) were obtained. From **8** (entry 8), the reduction product **5d** (3%) and the eight-membered ring (11%) were obtained. There was only a trace of the six-membered ring.

The formation of unsaturated ketones with concomitant replacement of halogen by hydrogen suggested the possibility of intramolecular hydrogen atom transfer from the β position of the enolate (e.g., **9** in Scheme I) to the transient phenyl

Scheme I



radical (i.e., in **10**);[6] then hydrogen-atom abstraction through a six-atom transition state would produce the enone–radical anion (Scheme I), the usual species formed in electron transfer to α,β-unsaturated ketones. This reaction would serve as a propagation step in the radical-chain mechanism,[7] and intermolecular reactions of the intermediates might explain the low yields of monomeric products sometimes observed. Consistent with this hypothesis, the dideuterated analogue **11** under the usual reaction conditions produced the unsaturated ketone (i.e., **12**) with 2.0 ± 0.1 deuterium atoms/molecule and 1.0 ± 0.1 deuteriums/unit in the mass spectral fragment at *m/e* 136, the piperonyl ring unit.



There has been no direct evidence reported which implicates hydrogen-atom transfer from the enolate anion as a significant side reaction in intermolecular examples of the photo-$S_{RN}1$ reaction.[8] However, alkyl-substituted enolate anions, where the β hydrogen is available, are known[9] to undergo the photo-$S_{RN}1$ reaction much less efficiently than unsubstituted analogues. For example, the lithium enolate of *tert*-butyl 2-methylpropionate reacted with *p*-bromoanisole upon irradiation to give *tert*-butyl 2-(*p*-methoxyphenyl)-2-methylpropionate in 5% yield; the major product was anisole (35–50%). Lithio *tert*-butyl acetate reacted under the same conditions, affording *tert*-butyl (*p*-methoxyphenyl)acetate (67%) and *tert*-butyl di(*p*-methoxyphenyl)acetate (29%). Irradiation of the enolate from *tert*-butyl 2-(trideuteriomethyl)-3,3,3-trideuteriopropionate with *p*-bromoanisole under the usual conditions produced anisole in 54% yield, with 35% of it labeled with one deuterium, confirming the major role of H-atom abstraction from the enolate.

These studies suggest that the photo-$S_{RN}1$ reaction of enolate anions with aryl halides can be efficient for intramolecular cases as well as in the well-established intermolecular examples, but, when a hydrogen atom is present at the β carbon in the enolate anion, hydrogen-atom transfer to the transient phenyl radical is generally the dominant process.[10]

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(4) All new compounds showed satisfactory spectral data (^{1}H NMR, IR, low resolution mass spectra). The starting compounds in entries 1, 2, 3, 5, 6, 7, and 8 and the products in entries 1, 2, and 3 of Table I have given satisfactory combustion analysis.
(5) The α,β ketone **4b** was prepared by aldol condensation between pinacolone and 3-(3,4-methylenedioxophenyl)propionaldehyde and fully characterized. Upon treatment with potassium *tert*-butoxide in liquid ammonia (approximately the conditions for the photo-$S_{RN}1$ reaction except in darkness), the α,β isomer was converted essentially quantitatively to the β,γ isomer **3**. Therefore we believe the α,β-unsaturated ketone **4b** to be the first-formed product from the photo-$S_{RN}1$ reaction of **1**.
(6) The intermediacy of phenyl radicals in the photo-$S_{RN}1$ reaction has been suggested and supported by Bunnett and his coworker.[2]
(7) The radical-chain mechanism has been proposed by R. A. Rossi and J. F. Bunnett, *J. Am. Chem. Soc.*, **92**, 683 (1972).
(8) Bunnett and Sundberg have obtained hexamethyloctanedione as a rate-depressing side product in the reaction of diisopropyl ketone enolate with iodobenzene.[1]
(9) (a) T. Bargar, unpublished work at Cornell; (b) ref 1.
(10) We wish to acknowledge generous financial support from the Public Health Service through NIH Grant AI-08687. In addition we are grateful to Mr. Jeffery Hayes who carried out the experimental tests for one of the entries in the table (entry 4).
(11) Recipient of a Camille and Henry Dreyfuss Teacher-Scholar Grant, 1973–1978
(12) National Institutes of Health predoctoral trainee, 1973–1976.

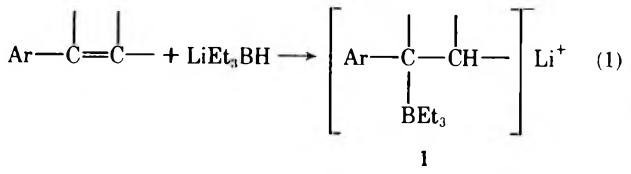
M. F. Semmelhack,*[11] Thomas M. Bargar[12]
Spencer T. Olin Research Laboratories
Department of Chemistry, Cornell University
Ithaca, New York 14853

Received March 1, 1977

Nucleophilic Hydroboration of Substituted Styrenes with Lithium Triethylborohydride. A Simple Convenient Procedure for the Markownikoff Hydroboration of Aromatically Conjugated Olefins and the Synthesis of Mixed Organoboranes with the Benzylic (α-Arylalkyl) Moiety

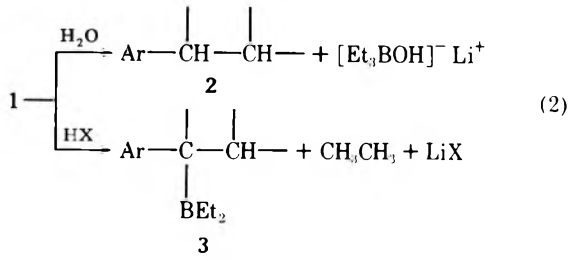
Summary: Lithium triethylborohydride ($LiEt_3BH$) adds to substituted styrenes under relatively mild conditions to give the corresponding tetraalkylborates, readily hydrolyzed to the corresponding saturated hydrocarbons or protonolyzed with strong acids to the mixed trialkylboranes containing a benzylic group.

Sir: We wish to report a simple regiospecific addition of lithium triethylborohydride to aromatically conjugated olefins under remarkably mild conditions to give the addition product **1** (eq 1). Furthermore, by the treatment of **1** with water, the



1

corresponding saturated hydrocarbon 2 is obtained in excellent yield (eq 2). On the other hand, treatment of 1 with strong



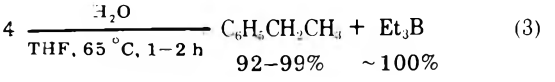
3

acids, such as methanesulfonic acid or hydrochloric acid, yields the Markownikoff mixed trialkylborane 3 in excellent yield (eq 2). Consequently, this procedure provides a new synthetic route to mixed organoboranes containing the reactive benzylic (α-arylalkyl) moiety.

Recently, trialkylborohydrides have received considerable attention owing to their remarkable nucleophilic characteristics in the reduction of organic functional groups.[1] However, only one example of the addition of these reagents to olefins has been reported, namely, addition of sodium triethylborohydride to ethylene, which requires drastic conditions of high temperature (~150 °C) and pressure (1000 psi).[2] A related reaction which proceeds much more readily is the conjugate addition of trialkylborohydrides to α,β-unsaturated carbonyl derivatives.[3]

In the course of an investigation of the reducing properties of lithium triethylborohydride toward representative functional groups in tetrahydrofuran (THF), we observed that at 0 °C the reagent slowly adds in a 1:1 molar ratio to styrene.[4] At 65 °C, the reaction is over in 6 h. These observations prompted us to examine the reaction in detail.

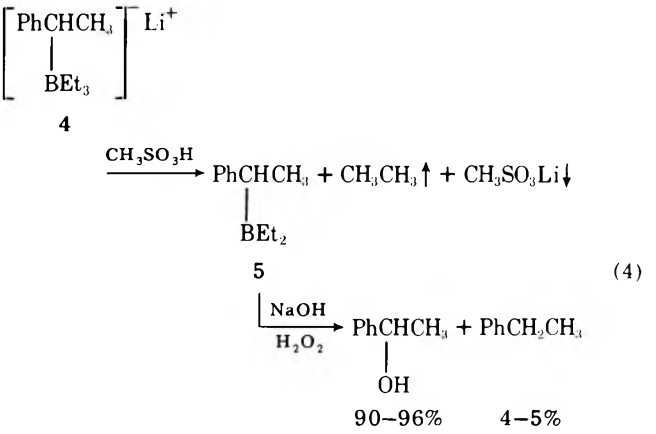
The product is reasonably stable thermally, resisting dissociation.[5] Hydrolysis of the product (4) of the above reaction is readily achieved by water in 1–2 h at 65 °C. GC analysis of this mixture, after oxidation with alkaline hydrogen peroxide, showed that ethylbenzene had been formed in nearly quantitative yield (based on the styrene used). Also, the amount of ethanol formed indicated that a quantitative yield of triethylborane was present (eq 3).



(3)

Deuterolysis with D_2O using similar conditions yielded pure α-deuterioethylbenzene, indicating that boron must be attached in the position α to the phenyl group.

4 behaves quite differently toward strong acids. Treatment of 4 with an equimolar quantity of methanesulfonic acid[6] at room temperature brings about an immediate evolution of gas with formation of white precipitate. GC analysis of the resulting mixture, after oxidation, revealed a 90–96% yield of 1-phenylethanol (free of the 2 isomer) with a 4–5% yield of ethylbenzene.[7] The analysis also revealed the loss of approximately one-third of the ethyl groups. This establishes that the acid selectively protonates one of the ethyl groups in 4 to form 5 (eq 4). The absence of 2-phenylethanol confirms the conclusion that boron must be attached exclusively to the carbon atom α to the phenyl group. Thus the procedure provides a convenient new route to mixed organoboranes containing the reactive benzylic (α-arylalkyl) moiety.



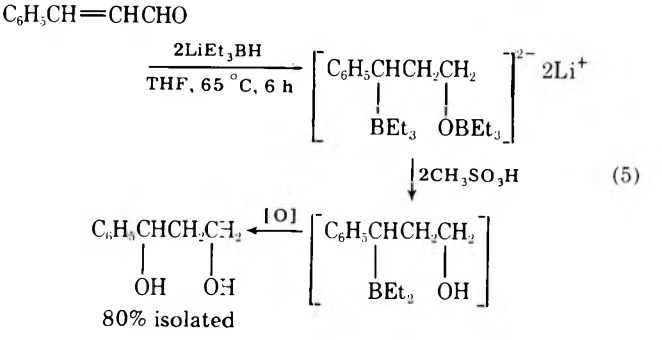
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5

(4)

Substituted styrenes (p-methoxy, p-chloro) give similar results. As anticipated for a nucleophilic hydroboration reaction, the rate of the addition is faster for p-chloro and slower for p-methoxy, a trend which is opposite to that observed in the electrophilic hydroboration by 9-BBN.[8] Methyl substitution on the double bond, as in *trans*-propenylbenzene and isopropenylbenzene, reduces the rate of reaction, compared with the parent compound, styrene, itself. Some of these slow reactions can be greatly facilitated by running them at 100 °C in diglyme (DG).[9]

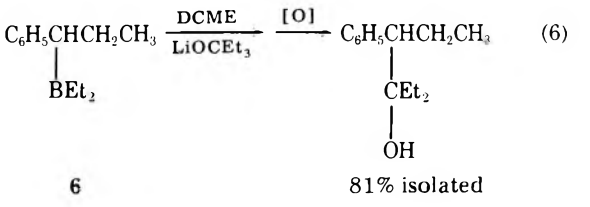
The double bond in cinnamaldehyde also adds the reagent readily, following the initial reduction of the aldehyde group. Oxidation of the intermediate provides 1-phenyl-1,3-propanediol (isomerically pure) in good yield (eq 5).



80% isolated

(5)

The intermediate trialkylborane 5 and 6 were also isolated (64% each) and characterized.[10] The DCME reaction[11] of 6 gave an excellent yield of the corresponding tertiary alcohol (eq 6).



6

81% isolated

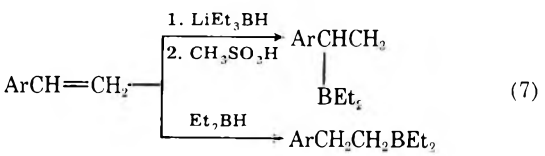
(6)

1,1-Diphenylethylene rapidly adds the reagent (9 h, 0 °C). However, the ate complex is evidently unstable and dissociates into the organolithium derivative and triethylborane. Thus, the reaction mixture immediately develops a deep reddish color, not present in the other reactions, indicating the probable presence of 1-lithio-1,1-diphenylethane, rather than its triethylborane complex.[12] The color immediately disappears upon addition of either water or strong acid, yielding only a single product, 1,1-diphenylethane, 96%.

The following procedure for the reaction of styrene is representative. A dry 50-mL flask equipped with a septum-covered inlet, a magnetic stirring bar, and a reflux condenser connected to a mercury bubbler was flushed with nitrogen.

The flask was charged with 17.2 mL of a 1.54 M solution of $LiEt_3BH$ (26.4 mmol) in THF,[13] 8 mL of a 3 M solution of isopropylbenzene in THF (internal standard), and 2.8 mL of THF. To this well-stirred solution, 8 mL of a 3 M solution of styrene (24 mmol) in THF was injected and the mixture was refluxed overnight.[14] The mixture was cooled to room temperature and a 7.5-mL aliquot (equivalent to 5.0 mmol of styrene) was transferred to another flask. Then 0.35 mL (5.5 mmol) of methanesulfonic acid was added dropwise while vigorously stirring. Gas evolution was observed with concurrent formation of a white precipitate. The mixture was stirred for 15 min at room temperature and oxidized in the usual manner. After the aqueous layer was saturated with potassium carbonate, GC analysis (Carbowax 20M) indicated a 91% yield of 1-phenylethanol and a 4% yield of ethylbenzene. The remaining reaction mixture was treated with 5 mL of water and refluxed for 2 h. After oxidation, GC analysis showed a 96% yield of ethylbenzene. There was no 1-phenylethanol detectable.

The present procedure provides a new type of hydroboration leading to synthesis of Markownikoff organoboranes. Consequently, it is now possible to control the direction of the hydroboration of aromatically conjugated olefins by choosing an appropriate reagent (eq 7). This development also provides



(7)

a valuable new route to mixed organoboranes containing the highly reactive benzylic (α-arylalkyl) moiety.

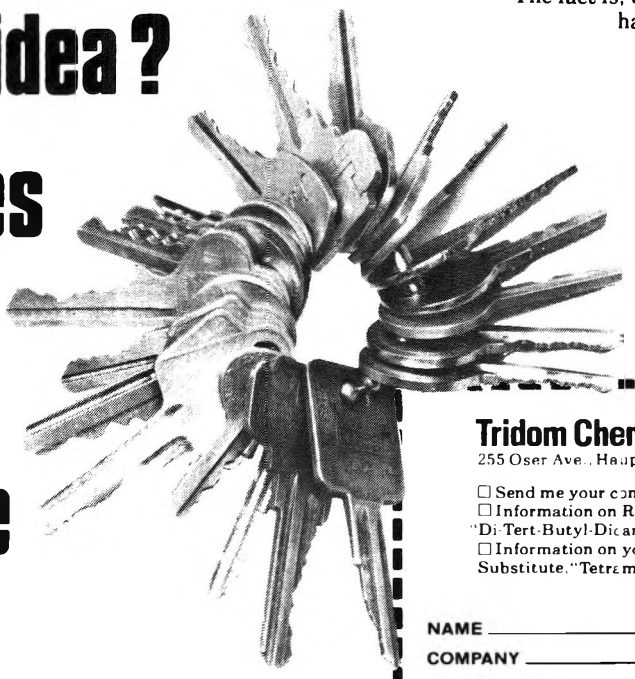
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(3) B. Ganem et al., *J. Org. Chem.*, **40**, 146, 2846 (1975); **41**, 2194 (1976).
(4) By using 4 equiv of the reagent (1.0 M), styrene utilizes 0.44 equiv of hydride in 24 h at 0 °C. At 25 °C, 1.0 equiv is utilized in ~12 h.
(5) GC analysis using low injector-port temperature (30 °C) showed that the product exists as a strong triethylborane complex.
(6) Hydrogen chloride or concentrated hydrochloric acid works equally well.
(7) Formation of the hydrolyzed product during the oxidation stage is a well-known phenomenon for benzylic-type organoboranes. See H. C. Brown and R. L. Sharp, *J. Am. Chem. Soc.*, **88**, 5851 (1966); A. J. Weinheimer and W. E. Marsico, *J. Org. Chem.*, **27**, 1926 (1962). Such ready hydrolysis has rendered difficult the synthesis of benzylic organoboranes through application of benzylic Grignards or the corresponding lithium derivatives.
(8) H. C. Brown , R. Liotta, and C. G. Scouten, *J. Am. Chem. Soc.*, **98**, 5297 (1976).
(9) $LiEt_3BH$ in diglyme is prepared from LiH and Et_3B using a procedure similar to that for preparation of the reagent in THF: H. C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.*, **94**, 7159 (1972).
(10) The ^1H and ^{11}B NMR spectra of the organoborane intermediates 5 and **6** corresponded to the structures. Oxidation with alkaline hydrogen peroxide gave the corresponding alcohol (GC).
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(12) Lithium aluminum hydride reacts with 1,1-diphenylethylene to give the corresponding benzylic carbanions: I. Granoth and Y. Segall, *J. Chem Soc., Chem. Commun.*, 887 (1974).
(13) The reagent is available from Aldrich Chemical Co., as 1 M solution in THF.
(14) Although 1 mol of the reagent is consumed per mole of styrene in 6 h, it is sometimes necessary to reflux the solution for longer time (overnight is sufficient) to realize a quantitative yield of the products.
(15) Graduate research assistant on Grant No. DA-ARO-D-31-124-73-G148, supported by the U.S. Army Research Office (Durham).

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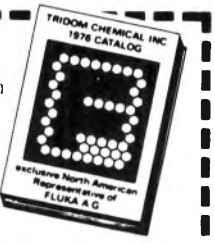
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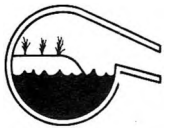
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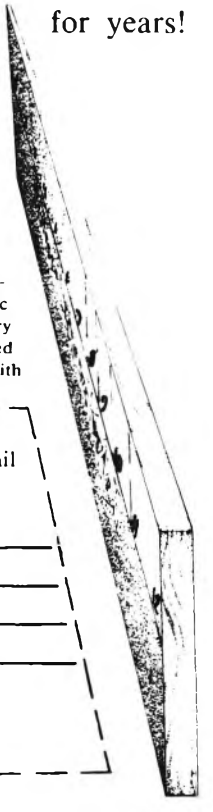
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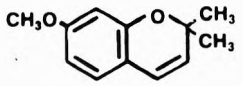
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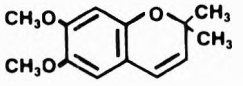
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Precocenes

Juvenile hormones are necessary throughout most stages of the insect life cycle for development of ovaries, sex pheromone production and larval diapause.[1] Application of



Precocene I



Precocene II

exogenous juvenile hormones to insect populations can upset development only during the brief period of metamorphosis that occurs when an immature insect molts to the adult stage.[2,3]

Bowers and co-workers[4] have found that introduction of some anti-juvenile hormones (antiallatotropins) into an insect colony terminates juvenile hormone secretion and induces:

1) precocious molting of insects to sterile adults,
2) inability of larvae which are dependent on a high titer of juvenile hormones to diapause,
3) sterility in adult insects which are dependent on juvenile hormone for ovarian development, and
4) artificial diapause in species which diapause through a lack of juvenile hormones.

Bowers isolated 7-methoxy-2,2-dimethylchromene and 6,7-dimethoxy-2,2-dimethylchromene from extracts of the plant *Ageratum houstonianum*. Since these compounds were found to induce precocious metamorphosis in insects, he named them **Precocene I** and **Precocene II**, respectively.[4]

In tests performed by Bowers[4] with the **Precocenes**, milkweed bugs underwent precocious metamorphosis, and in several other species of insects, sterilization was induced. **Precocene II** was also found to induce diapause in Colorado potato beetles.

In these tests, the biological effect of the **Precocenes** is equivalent to that of the surgical removal of the corpora allata which produce juvenile hormones in insects. Indeed, **Precocene II** was found to inhibit the biosynthesis of juvenile hormone by the cockroach corpora allata.[5] Thus, the **Precocenes** depress juvenile hormone titer and can be highly effective insecticides. Moreover, Bowers,[4] in some instances, succeeded in reversing the antiallatotropic activity in precocious acults by treatment with exogenous juvenile hormones.

We believe that this remarkable discovery of antiallatotropic activity could guide the way to safe, economical and insect-specific pesticides.[6]

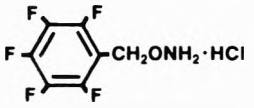
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Pentafluorobenzylhydroxylamine



PFBHA·HCl

***O*-(2,3,4,5,6-Pentafluorobenzyl)hydroxylamine hydrochloride (PFBHA · HCl)** has recently been introduced as a very sensitive derivatizing agent for the *gas chromatographic analysis of ketosteroids* using electron capture detection.[1,2] For this type of detection technique to be effective, the compound to be analyzed must contain a strong electron-withdrawing group. Since most ketosteroids do not contain a sufficiently strong electron-withdrawing group, a suitable derivative must be prepared.

Clark and Wotiz[3] first suggested the use of heptafluorobutyrate ester derivatives for the chromatography of hydroxysteroids such as testosterone. Although these derivatives are sensitive to electron capture detection, they suffer from the difficulty encountered in controlling the reaction to prepare selectively the 17-hydroxy mono ester, the 3-enol mono ester or the 3-enol-17-hydroxy diester. As a result, one steroid may be resolved into several peaks in the chromatogram, leading to confusion and error in the analysis. Koshy and co-workers have shown **PFBHA·HCl** to be a more effective derivatizing reagent. **PFBHA·HCl** converts ketosteroids to their oximes, and glc conditions can be chosen such that both the *syn* and *anti* oximes appear as one peak.[1]

Steroid *O*-(2,3,4,5,6-pentafluorobenzyl) oximes are readily prepared under mild conditions by treating the ketosteroid with a solution of **PFBHA·HCl** in pyridine at 60 to 65°C.[1] After evaporation of the solvent, the oxime is extracted into cyclohexane, and the cyclohexane solution is washed with water and dried over Na_2SO_4. Derivatives can be prepared from less than one nanogram of steroid. PFB-oxime derivatives of testosterone have been detected with samples as small as 5 picograms.

Nambara and co-workers have used **PFBHA·HCl** for the determination of dehydroepiandrosterone in human plasma with satisfactory results.[2] It has been suggested that this analytical technique may also be applicable to the determination of specific prostaglandins in tissues, and the analysis of ketosteroid levels in meat carcasses to ascertain if they fall within federal standards.[4]

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