VOLUME 39 SEPTEMBER 6, 1974 NUMBER 18 JOCEAH

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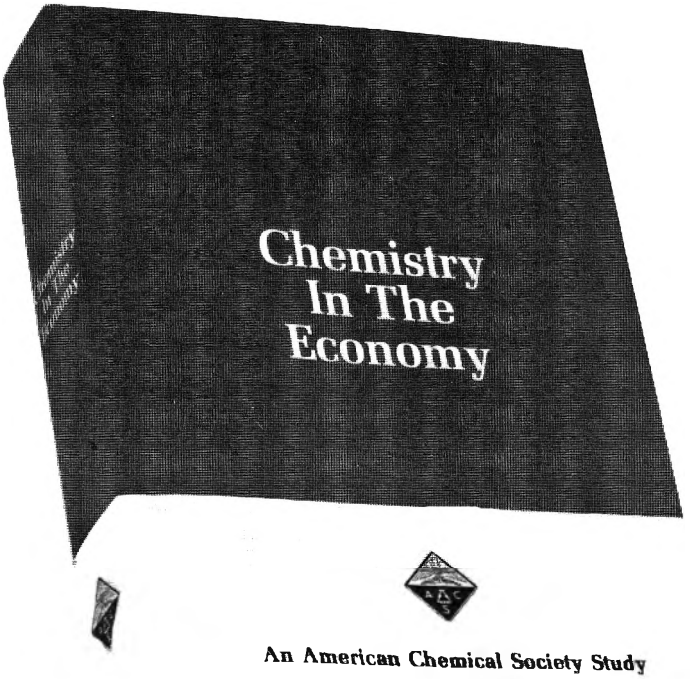

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Published biweekly by the American Chemical Society at 20th and Northampton Sts., Easton, Pa. 18042. Second-class postage paid at Washington, D. C., and at additional mailing offices.

Editorial Processing Department, American Chemical Society, 20th and Northampton Sts., Easton, Pa. 18042: Department Head, Charles R. Bertsch; Assistant Department Head, Marianne C. Brogan, Production Editor, Eileen B. Segal; Assistant Editor, Fern S. Jackson; Editorial Assistant, Andrew J. D'Amelio.

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Notice to Authors last printed in the issue of June 1, 1973

JOCEAH(18) 2665-2818 (1974)
ISSN 0022-3263

THE JOURNAL OF Organic Chemistry®

VOLUME 39, NUMBER 18 SEPTEMBER 6, 1974

NOTES

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THE JOURNAL OF Organic Chemistry®

VOLUME 39, NUMBER 18

SEPTEMBER 6, 1974

Stereoselective Total Syntheses of (±)-Longicyclene, (±)-Longicamphor, and (±)-Longiborneol

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Received April 19, 1974

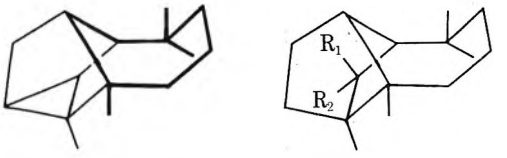
Stereoselective total syntheses of (±)-longicyclene (1), (±)-longicamphor **2A**), and (±)-longiborneol (**2B**) from tetrahydroeucarvone (**5**) *via* intermediate aldehyde **15** are reported. The synthetic approach contains a reductive cyclization reaction utilizing diisobutylaluminum hydride to construct bicyclic ketol **12.** A new sequence of reactions for converting cyclopropyl ketone **17** to (±)-longicyclene (1) without fragmentation is described.

The number of syntheses of sesquiterpene natural products has increased dramatically over the past 20 years, as indicated in recent reviews.[2] The sesquiterpene group of naturally occurring compounds contains a fantastic variety of intricately bridged molecular structures. This diversity of complex carbon skeletons provides the organic chemist with an excellent reservoir for exploring new synthetic methods and designs. The profusion of structural types requires a multitude of synthetic approaches challenging the imagination of many a synthetic organic chemist.

Synthetic quests within the longifolane class of sesquiterpenes have included such elaborately bridged structures as longifolene,[3,4] isolongifolene,[5] α-longipinene,[6,7] and culmorin.[8] The tetracyclic member of this interesting group of naturally occurring compounds, namely, longicyclene (1),[9] has evaded synthesis for nearly 10 years. A tricyclic member of the longifolane class, namely, longicamphor (**2A**), has previously been synthesized from (+)-longifolene *via* (+)-longiborneol (**2B**).[10] We wish to report herein stereoselective total syntheses of (±)-longicyclene (1), (±)-longicamphor (**2A**), and (±)-longiborneol (**2B**)[11] (Chart I).

Longicyclene (1), isolated from turpentine oil of *Pinus longifolia,* was assigned structure and absolute configuration 1 on the basis of spectral evidence and an acid-catalyzed conversion to longifolene.[9,12] Longicamphor (**2A**) is the corresponding oxidation product of longiborneol (**2B**). Longiborneol (juniperol, macrocarpol) was isolated from *Cupressus macrocarpa,* the famous Monterey cypress.[13,14]

Chart I
Longicyclene, Longicamphor, and Longiborneol



1 **2A**, $R_1, R_2 = O$
B, $R_1 = OH; R_2 = H$

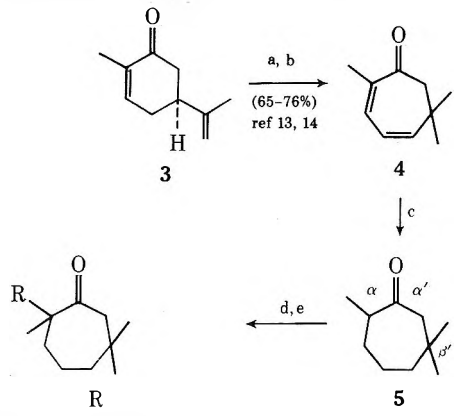
Results and Discussion

The starting material chosen for the synthesis of these sesquiterpenes is tetrahydroeucarvone (**5**). This ketone is readily available from (−)-carvone (**3**). Sequential treatment of carvone (**3**) with hydrogen bromide in glacial acetic acid followed by dehydrohalogenation using potassium hydroxide in methanol affords eucarvone (**4**) in 65–76% yield.[15,16] The mechanism of this rearrangement was studied by van Tamelen and coworkers. The reaction proceeds *via* a carenone intermediate which, in the presence of excess base, opens to give eucarvone (**4**).[17] Catalytic hydrogenation of dienone **4** neat over 10% palladium on carbon produces the desired starting ketone **5** in 94% yield.[18,19]

The basic carbon skeleton of ketone **5** can be seen in longicyclene (1) as outlined with heavy lines. The synthetic strategy was to prepare a bicyclo[4.2.1]nonane intermediate by constructing an appropriately functionalized two-carbon bridge between carbon-2 and carbon-7 of ketone **5.** With this goal in mind, the plan was to sequentially alkylate tetrahydroeucarvone selectively at the α-methine position and then to construct the two-carbon bridge by an intramolecular carbon–carbon bond-forming process at the α′-methylene position. In recent reviews both Conia[20] and House[21] point out that alkylation of an unsymmetrical cyclic ketone such as tetrahydroeucarvone (**5**), where the corresponding enolate is generated under thermodynamically controlled conditions, is favored at the α-methine position. The presence of an alkyl group, such as a methyl group, at an α position favors α-alkylation. The presence of alkyl substituents at the β′ position also favors α-alkylation. Whenever the two effects are combined, as in tetrahydroeucarvone (**5**), then α-alkylation should predominate.

Alkylation of Tetrahydroeucarvone (Chart II). Alkylation of tetrahydroeucarvone (**5**) by generating the enolate anion using stirred sodium hydride in 1,2-dimethoxyethane (DME) at 80 ± 5° for 24–48 hr followed by addition of allyl bromide gives keto olefin **6A** in 80% yield. Alkylation of the sodium enolate of ketone **5** with ethyl 2-bromoacetate affords keto ester **6B** in 53% yield. The structures of both alkylation products **6A** and **6B** were confirmed by spectroscopic data. Both compound **6A** and **6B** show an AB quartet in the nmr spectrum for two methylene protons adjacent to a ketone carbonyl (–$COCH_2$ centered at δ 2.38,

Chart II
Alkylation of Tetrahydroeucarvone[a]



3 4 5

6 R

A $-CH_2CH{=}CH_2$ (80%)
B $-CH_2CO_2Et$ (53%)
C $-CH(CH_3)CH{=}CHCH_3$ (86%)
D $-CH(CH_3)CO_2Et$ (33%)

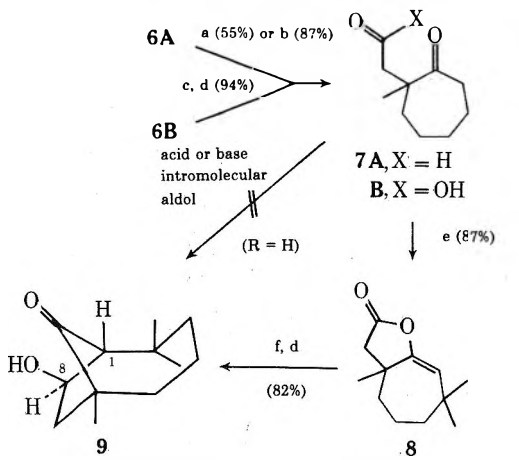
[a] a, HBr, HOAc; b, KOH, CH_3OH; c, H_2, 10% Pd/C; d, NaH, DME, Δ 24–48 hr; e, $BrCH_2CH{=}CH_2$, $BrCH_2CO_2Et$, $CH_3CHClCH{=}CHCH_3$, or $CH_3CHBrCO_2Et$ for products **6A**, **6B**, **6C**, and **6D**, respectively.

J_{AB} = 11 Hz, and δ 2.37, J_{AB} = 14 Hz, for compounds **6A** and **6B**, respectively). No isomeric alkylated products at the methylene position were observed spectroscopically (nmr) or detected chromatographically (glc). The sodium enolate of tetrahydroeucarvone was also alkylated, similarly, with 4-chloro-2-pentene[22,23] to produce keto olefin **6C** in 86% yield, and with ethyl 2-bromopropanoate to give keto ester **6D** in 33% yield.[8,24]

Model Study to Prepare an Appropriately Functionalized Bicyclo[4.2.1]nonane Intermediate (Chart III). Oxidative cleavage of keto olefin **6A** using osmium tetroxide and 2.1 equiv of sodium metaperiodate in aqueous tetrahydrofuran (THF) produced keto aldehyde **7A** in 55% yield.[25] All attempts to affect an intramolecular aldol cyclization to ketol **9** using either acid or base catalysis gave only recovered starting keto aldehyde **7A**.[26]

Oxidative cleavage of keto olefin **6A** using a catalytic amount of ruthenium tetroxide and 5.4 equiv of sodium metaperiodate in aqueous *tert*-butyl alcohol gave keto acid **7B** in 87% yield.[27] Keto acid **7B** was also prepared from

Chart III
Model Study[a]



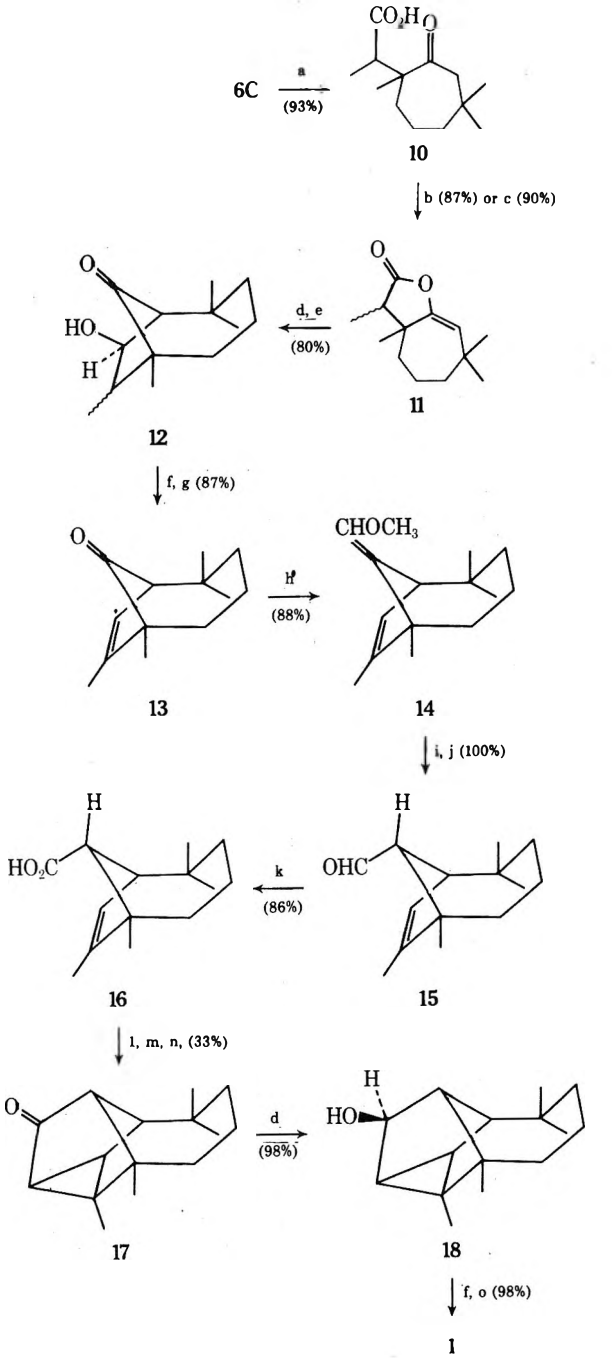
9 8

[a] a, OsO_4, $NaIO_4$, H_2O, THF, for **7A**; b, RuO_4, $NaIO_4$, H_2O, *t*-BuOH, for **7B**; c, KOH, CH_3OH, H_2O; d, H_3O^+; e, NaOAc, Ac_2O, Δ; f, *i*-Bu_2AlH, THF.

keto ester **6B** in 94% yield by saponification with potassium hydroxide in aqueous methanol followed by acidification with dilute hydrochloric acid. Keto acid **7B** was converted to enol lactone **8** in 87% yield by treatment with anhydrous sodium acetate in refluxing acetic anhydride for 5 hr.[28] Reduction of enol lactone **8** with 1.1 equiv of diisobutylaluminum hydride in anhydrous tetrahydrofuran (THF) at room temperature for 22 hr followed by neutralization with dilute hydrochloric acid at 0° (ice bath) gave crystalline bicyclic ketol **9** in 82% yield. Other reducing agents such as lithium tri-*tert*-butoxyaluminum hydride or lithium trimethoxyaluminum hydride proved unsuccessful.[28] The β configuration for the alcohol group was assigned on the basis of nmr data. A vicinal coupling constant of $J_{1,8}$ = 2 Hz was observed for the bridgehead proton at carbon-1 coupled with the hydroxymethine proton at carbon-8. The magnitude of this coupling constant is in accord with a dihedral angle near 130°.[29,30] Examination of a Dreiding model of exo alcohol **9** shows an expected dihedral angle near 130° in keeping with the observed coupling constant. The endo isomer of structure **9** would have an expected dihedral angle near 15° (from Dreiding models) which should exhibit a vicinal coupling constant near J = 7.7 Hz for the bridgehead proton on carbon-1.

Synthesis of (±)-Longicyclene (1) (Chart IV). Oxidative cleavage of keto olefin **6C** using catalytic amounts of ruthenium tetroxide–osmium tetroxide and 5 equiv of sodium metaperiodate in aqueous *tert*-butyl alcohol gave keto acid **10** in 93% yield.[27] The use of catalytic amounts of only ruthenium tetroxide resulted in much lower yields. Keto acid **10** was converted to enol lactone **11** by two methods. First, treatment of compound **10** with anhydrous sodium acetate in refluxing acetic anhydride for 5 hr gave enol lactone **11** in 87% yield.[28] Second, a solution of keto acid **10**, acetic anhydride, and a catalytic amount of 60% perchloric acid in dichloromethane was allowed to stir at room temperature for 4 hr to afford enol lactone **11** in 90% yield.[31] Reductive cyclization of enol lactone **11** using 1.1 equiv of diisobutylaluminum hydride in anhydrous tetrahydrofuran (THF) at 60° (bath temperature) for 18 hr followed by neutralizing the reaction mixture with dilute hydrochloric acid at 0° (ice bath) produced liquid bicyclic ketol **12** as a 66:34 mixture of diastereomers (glc) in 80% yield.[28] This bicyclic ketol was found to be extremely sensitive to either base- or acid-catalyzed fragmentation to a keto aldehyde. Bicyclic ketol **12** was immediately esterified with methanesulfonyl chloride in dichloromethane in the presence of triethylamine.[32] The crude mesylate ester was stirred in collidine at 170–175° for 16 hr to afford bicyclic enone **13** in 87% overall yield from ketol **12**.[33] The infrared data for bicyclic enone **13** were in good agreement with that reported for the same structure as a degradation product of culmorin by Barton and Werstiuk.[34] A Wittig reaction on enone **13** using methoxymethylenetriphenylphosphorane in dimethyl sulfoxide at 60° gave methoxyvinyl ether **14** in 88% yield.[35] Hydrolysis of methoxyvinyl ether **14** in a homogeneous solution of 50% perchloric acid in ether for 1.75 hr followed by epimerization of the resulting mixture of aldehydes with anhydrous potassium carbonate in methanol at room temperature for 1.75 hr produced aldehyde **15** in quantitative yield.[35] Aldehyde **15** was smoothly oxidized to carboxylic acid **16** utilizing Jones reagent in acetone at room temperature for 30 min.[36,37] Acid **16** was converted to an acid chloride using oxalyl chloride in benzene. The crude acid chloride was then treated with anhydrous diazomethane in ether to afford an intermediate diazo ketone. This diazo ketone was stirred with a suspension of copper powder in refluxing tetrahydrofuran to produce crystalline

Chart IV
Synthesis of (±)-Longicyclene[a]

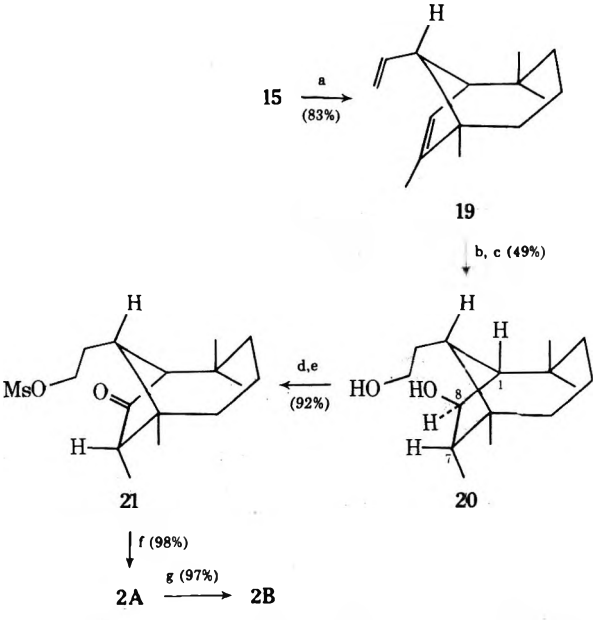


[a] a, RuO_4, OsO_4, H_2O, *t*-BuOH, $NaIO_4$; b, NaOAc, Ac_2O, Δ; c, Ac_2O, CH_2Cl_2, $HClO_4$ (catalytic); d, *i*-Bu_2AlH, THF; e, H_3O^+; f, MsCl, CH_2Cl_2, Et_3N; g, collidine, Δ; h, $Ph_3P{=}CHOCH_3$, DMSO, Δ; i, $HClO_4$, H_2O, Et_2O; j, K_2CO_3, CH_3OH; k, CrO_3, H_2SO_4, acetone; l, $(COCl)_2$, PhH; m, CH_2N_2, Et_2O; n, Cu, THF, Δ; o, $LiAlH_4$, Et_2O.

tetracyclic cyclopropyl ketone **17** in 33% overall yield from carboxylic acid **16**.[38] Two modificiations of the Wolff–Kishner reduction of cyclopropyl ketone **17** were attempted and both (Huang-Minlon procedure and Nagata–Itazaki modification) were unsuccessful.[39-41] Both attempts afforded mostly starting material plus minor amounts of unidentified cleavage products. Even an attempt to prepare the tosylhydrazone derivative of ketone **17** under forcing conditions gave only recovered starting material. Examination of a Drieding model of cyclopropyl ketone **17** shows that the β side of the carbonyl carbon atom is hindered by the methyl substituents at carbon-1 and carbon-11, but relatively unhindered on the α side of the carbonyl. Reduction of ketone **17** with diisobutylaluminum hydride in tetrahydrofuran produced crystalline cyclopropylcarbinyl alcohol **18** in 98% yield. The stereochemistry of alcohol **18** was assigned on the basis of "steric approach control."[42] The bulky hydride reagent should approach from the less hindered face of the carbonyl to afford an alcohol with the stereochemistry indicated by structure **18**. Alcohol **18** was esterified with methanesulfonyl chloride in dichloromethane in the presence of triethylamine at −15° (freezer) for 72 hr.[32] The entire reaction mixture was then added to a mixture of lithium aluminum hydride in ether. This mixture was stirred at reflux to afford (±)-longicyclene (**1**) in 98% overall yield from alcohol **18**. No fragmentation of the cyclopropane ring to give olefinic products was observed (nmr, glc). The synthetic (±)-longicyclene was identical with an authentic sample of (+)-longicylene[9] with respect to ir, nmr, and glc retention times on five columns.

Synthesis of (±)-Longicamphor (2A) and Longiborneol (2B) (Chart V). The synthesis of (±)-longicamphor (**2A**) and (±)-longiborneol (**2B**) utilizes bicyclic aldehyde **15** as the key synthetic intermediate. A Wittig reaction on aldehyde **15** using methylenetriphenylphosphorane in dimethyl sulfoxide at room temperature for 13.5 hr gave diene **19** in 83% yield.[35] Hydroboration of diene **19** with diborane in anhydrous tetrahydrofuran followed by oxidation using basic hydrogen peroxide produced crystalline diol **20** in 49% yield.[43] An attempt to increase the yield for this conversion utilizing disiamylborane in tetrahydrofuran followed by basic hydrogen peroxide gave nearly identical results.[43] First-order analysis of the coupling constants for the hydroxymethine proton at carbon-8 (the X part of an AMX system) shows coupling constants of J = 2.6 and 7.8 Hz. Routine use of europium(DPM)$_3$[44] sufficiently dispersed the nmr spectrum so that the bridgehead proton on carbon-1 was clearly observable, thus establishing the coupling constant $J_{1,8}$ = 2.6 Hz. The magnitude of this coupling constant is in agreement with a dihedral angle near 120° for the vicinal protons on carbon-1 and carbon-8. This dihedral angle is what would be expected for exo alcohol **20**

Chart V
Synthesis of (±)-Longicamphor and (±)-Longiborneol[a]



[a] a, $Ph_3P{=}CH_2$, DMSO, room temperature; b, BH_3-THF; c, H_2O_2, OH^-; d, MsCl, CH_2Cl_2, Et_3N; e, CrO_3-py_2, CH_2Cl_2; f, $NaN(SiMe_3)_2$, PhH, DME; g, Ca, NH_3, *n*-PrOH.

based on examination of the Dreiding model for structure **20**.[29,30] Examination of the Dreiding model for the endo isomer of structure **20** shows an expected dihedral angle near 0° and the predicted coupling constant would have to be near 8 Hz.[29,30] The tricyclic carbon framework of longicamphor (**2A**) was constructed from diol **20** using an intramolecular alkylation sequence similar to that employed by Johnson and coworkers in their synthesis of aldosterone.[45] The primary alcohol was selectively esterified using 1.1 equiv of methanesulfonyl chloride in dichloromethane in the presence of triethylamine.[32] The crude liquid hydroxymesylate ester was oxidized using chromium trioxide–dipyridine complex in dry dichloromethane[46,47] to afford crystalline keto mesylate **21** in 92% overall yield from diol **20**. Treatment of keto mesylate **21** with sodium bis(trimethylsilyl)amide[48] in benzene–1,2-dimethoxyethane at room temperature for 40 min gave (±)-longicamphor (**2A**) in 98% yield.[49] The synthetic (±)-longicamphor was identical with natural (+)-longicamphor with respect to ir, nmr, and glc retention times on five columns. Reduction of (±)-longicamphor (**2A**) with calcium metal in liquid ammonia in the presence of 1-propanol produced (±)-longiborneol (**2B**) in 97% yield.[10,12,13,34,49] The synthetic (±)-longiborneol was identical with natural (+)-longiborneol (prepared from (+)-longicamphor) with respect to ir, nmr, and glc retention times on five columns.

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. All boiling points are uncorrected. Analyses were performed by Elek Microanalytical Laboratories, Torrance, Calif., and Spang Microanalytical Laboratory, Ann Arbor, Mich.

Analytical gas phase chromatography (glc) was performed using the following types of columns of flow rates: (A) 50-ft, stainless steel, 0.02-in. capillary column coated with Carbowax 6000, flow rate 5 ml/min at ambient temperature; (B) 300-ft, stainless steel, 0.02-in. capillary column coated with OV-17 (Varian), flow rate 5 ml/min at ambient temperature; (C) 300-ft, stainless steel, 0.02-in. capillary column coated with FFAP (Varian), flow rate 5 ml/min, at ambient temperature; (D) 5-ft, stainless steel, 0.125-in. column, packed with 3% SE-30 on Varaport 30, 100/120 mesh (Varian), flow rate 15 ml/min at ambient temperature; (E) 6-ft, stainless steel, 0.125-in. column, packed with 5% FFAP on Varaport-30, 80/100 mesh (Varian), flow rate 15 ml/min at ambient temperature; (F) 6-ft, stainless steel, 0.125-in. column, packed with 5% OV-17 on Varaport-30, 80/100 mesh (Varian), flow rate 15 ml/min at ambient temperature.

Silica gel $PF_{254+366}$ (E. Merck No. 7748) and silica gel 60 (E. Merck No. 7734, 70–230 or 75–325 mesh) available from Brinkmann Instruments were used for thin layer and column chromatography, respectively.

Infrared (ir) spectra were recorded on a Perkin-Elmer Model 337 or 700 spectrophotometer. Solid samples were recorded in spectroquality carbon tetrachloride or chloroform using 0.10-mm sodium chloride cells. Liquid samples were taken as thin films between sodium chloride plates.

Nuclear magnetic resonance (nmr) spectra were measured on a Varian Associates Model T-60 or HA-100 spectrometer. The following abbreviations are used to describe nmr spectral bands reported in the Experimental Section: broad (b), singlet (s), doublet (d), triplet (*t*), quartet (q), AB quartet (AB), multiplet (m), and δ (parts per million, ppm) downfield from tetramethylsilane.

Finally, for all reactions performed under an atmosphere of dry nitrogen, the equipment was dried in an oven at 120° for several hours, then allowed to cool in an atmosphere of dry nitrogen using an apparatus designed by Johnson and Schneider.[50] All liquid transfers were made with nitrogen-filled syringes. Petroleum ether refers to Baker Analyzed reagent, bp 30–60°.

Eucarvone (4).[15,16] Freshly distilled carvone (**3**, 200 g, 1.33 mol) was slowly added to a solution of anhydrous hydrogen bromide (295 g, 3.66 mol) in glacial acetic acid (1.0 l.) at 5–10° with rapid stirring and efficient cooling. The cooling bath was removed and stirring was continued for 15 min.

The resulting orange solution was poured into water (2 l.), the lower layer was separated, and the aqueous layer was extracted with ether (three times). The combined ethereal extracts were washed with water (three times), saturated potassium bicarbonate solution until basic to litmus paper, and finally water until neutral. The organic solution was dried (Na_2SO_4) and then added dropwise to a well-stirred and cooled solution of potassium hydroxide (145 g) and anhydrous methanol (550 ml).

After completion of the addition, the resulting suspension was stirred at reflux for 15 min and then poured into ice–sulfuric acid. The yellow liquid was separated and the aqueous layer was extracted with ether (three times). The combined ethereal extracts were washed with 10% sodium hydroxide (three times) to remove the carvacrol and then with water until neutral, dried (Na_2SO_4), concentrated *in vacuo*, and distilled to give 130 g (65%) of eucarvone (**4**): bp 46–49° (1.5 mm) [lit.[16] bp 81.5–84.0° (8 mm)]; ir (film) 3010 (CH=CH), 1660 (CO), 1385, 1365 (*gem*-CH_3), and 728 cm^{-1} (CH=CH); nmr (CCl_4) δ 5.5–6.54 (m, 3, CH=CH), 2.57 (s, 2, $COCH_2$), 1.85 (d, 3, J = 1.8 Hz, CH_3C=), and 1.06 ppm (s, 6, *gem*-CH_3).

Tetrahydroeucarvone (5).[18,19] Eucarvone (**4**, 223 g, 1.49 mol) was carefully mixed with 10% palladium on charcoal (8.5 g) in a Parr Shaker bottle. The unsaturated ketone was hydrogenated on a Parr Shaker at 15–50 psi until no further hydrogen uptake was observed. The product was filtered through Celite and distilled to give 215 g (94%) of tetrahydroeucarvone (**5**): bp 47–50° (1.5 mm) [lit.[18,19] bp 46–49° (1.5 mm)]; ir (film) 1700 (CO), 1385, and 1370 cm^{-1} (*gem*-CH_3); nmr (CCl_4) δ 2.34 (distorted AB, 3, J_{AB} = 12 Hz, CHCO and $COCH_2$), 1.02 (d, 3, J = Hz, CH_3CH), 0.95 and 0.91 ppm (s, s, 6, *gem*-CH_3); nmr (100 Hz, CCl_4) δ 2.21 (distorted AB, 3, J_{AB} = 12 Hz, CHCO and $COCH_2$), 0.88 (d, 3, J = 7 Hz, CH_3CH), 0.83 and 0.78 ppm (s, s, 6, *gem*-CH_3).

2-(3′-Propene)-2,6,6-trimethylcycloheptanone (6A). Sodium hydride (1.63 g, 40 mg-atoms of a 59% dispersion) was transferred to the reaction flask and washed with anhydrous 1,2-dimethoxyethane (DME, 5 × 10 ml freshly distilled from lithium aluminum hydride). Dry DME (10 ml) was added and the apparatus was sealed under dry nitrogen. Tetrahydroeucarvone (**5**, 6.00 g, 38.9 mmol) dissolved in dry DME (10 ml) was added. The mixture was allowed to stir at 80 ± 2° for 48 hr.

The resulting light yellow slurry of sodium enolate was cooled to room temperature and allyl bromide (7.0 ml, 80 mmol, freshly distilled) dissolved in dry DME (5 ml) was added over a period of 1 hr. The pale yellow slurry was allowed to stir at room temperature for 24 hr and then poured into a mixture of acetic acid, ice, and ether. The ether layer was separated, washed with 10% sodium bicarbonate solution (three times) and water (three times), and then dried (Na_2SO_4) and concentrated *in vacuo*. Distillation gave 6.05 g (80%) of colorless alkylated ketone **6A**: bp 49.5–50.5° (0.17 mm); ir (film) 3075 ($CH=CH_2$), 1695 (CO), 1640 ($CH=CH_2$), 1460 (CH), 1390, 1370, 1365 (*gem*-CH_3), 993 and 912 cm^{-1} ($CH=CH_2$); nmr (CCl_4) δ 4.8–6.1 (m, 3, $CH=CH_2$), 2.38 (AB, 2, J_{AB} = 11 Hz, $COCH_2$), 2.14 (d, 2, J = 8 Hz, $CH_2CH=CH_2$) 0.99, 0.95 and 0.89 ppm (s, s, s, 9, CH_3); glc analysis on column A (column temperature 120°, retention time 12.1 min) shows the product to be greater than 99.6% of a single product.

Anal. Calcd for $C_{13}H_{22}O$: C, 80.36; H, 11.41. Found: C, 80.39; H, 11.46.

2-(Ethyl 2′-acetate)-2,6,6-trimethylcycloheptanone (6B).[24] Sodium hydride (1.79 g, 44 mg-atoms of a 59% dispersion) was transferred to the reaction flask and washed with anhydrous 1,2-dimethoxyethane (DME, 3 × 10 ml, freshly distilled from lithium aluminum hydride). Dry DME (35 ml) was added and the flask was sealed under dry nitrogen. Tetrahydroeucarvone (**5**, 6.00 g, 38.9 mmol, dissolved in dry DME, 5 ml) was added to the stirred sodium hydride in refluxing DME. The mixture was allowed to stir at 82 ± 3° for 46 hr.

The resulting light yellow slurry of enolate anion was cooled to 15° and ethyl 2-bromoacetate (4.9 ml, 44 mmol, freshly distilled) dissolved in dry DME (5 ml) was added over a period of 5 min. The reaction mixture was allowed to warm to 25° over a period of 90 min and then poured into acetic acid–ice and extracted with ether. The combined ethereal extracts were washed with saturated sodium bicarbonate solution (three times) and with saturated sodium chloride solution until neutral, and then dried ($MgSO_4$) and concentrated *in vacuo*. Distillation gave 4.80 g (53%) of colorless keto ester **6B**: bp 76.5–79° (0.08 mm); ir (film) 1735 (CO_2Et), 1700 (CO), 1395, 1380, 1365 (*gem*-CH_3), 1228, 1200, 1161 (asymmetric COC), 1118, 1066, and 1033 cm^{-1} (symmetric COC); nmr (CCl_4) δ 4.06 (q, J = 7 Hz, OCH_2CH_3), 2.43 (bs, 2, CH_2CO_2Et), 1.10 (s, 3,

CH_3), and 0.91 ppm (s, 6, *gem*-CH_3O); glc analysis on column A (column temperature 120° retention time 20.5 min) shows the keto ester to be greater than 99.6% of a single product.

Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.06. Found: C, 70.25; H, 10.03.

3-Penten-2-ol.[22,23] **Method A.** An ethereal solution of methyllithium (Alfa Inorganics, 1.6 *M* solution, 550 ml) was transferred to the reaction flask under nitrogen. Freshly distilled crotonaldehyde (60.0 g, 856 mmol) was placed in a dropping funnel. The apparatus was sealed under dry nitrogen. The crotonaldehyde was added dropwise to the rapidly stirred methyllithium solution at 0° (ice bath) over a period of 2 hr.

The resulting light yellow reaction mixture was allowed to stir for 30 min and then carefully quenched with distilled water (100 ml). The inorganic salts were removed by filtration and the ether layer was separated. The ethereal solution was washed with saturated sodium chloride solution (three times), dried (Na_2SO_4), and concentrated *in vacuo* at room temperature. A trace of anhydrous calcium oxide was added and the crude product was distilled to give 35 g (47%) of 3-penten-2-ol, bp 119–122° (lit.[22,23] bp 119–122°).

Method B. Approximately 3.0 l. of anhydrous ether and 122 g (5.0 g-atoms) of magnesium turnings were placed in a 5-l. three-necked flask. Methyl iodide (324 ml, 5.2 mmol) was placed in a pressure-compensating dropping funnel.

After the first 50 ml of methyl iodide had been added, the flask was gently warmed to initiate the reaction. The remainder of the methyl iodide was added at a rate which would maintain the reaction at gentle reflux.

When most of the magnesium had reacted, crotonaldehyde (284 g, 4.04 mol, dissolved in anhydrous ether, 300 ml) was added dropwise with vigorous stirring and cooling (ice bath). The mixture was then allowed to stir at room temperature for 30 min, quenched with saturated sodium chloride solution (500 ml) with cooling (ice bath), the ether layer decanted, washed with 10% sodium sulfite solution (three times), dried (K_2CO_3–Na_2SO_4), filtered, and concentrated *in vacuo* at room temperature. A trace of anhydrous calcium oxide was added and the crude product was distilled to give 286 g (82%) of colorless 3-penten-2-ol: bp 119–122°; ir (film) 3650–3050 (OH), 3025 (CH=CH), 1675 (trans CH=CH), 1450, 1375, 1360 (CH_3), 1060, 1021 (OH), 962 (trans CH=CH), 909, and 858 cm^{-1}; nmr (CCl_4) δ 5.17–5.97 (m, 2, CH=CH), 4.36 (bm, 1, CHOH), 4.13 (bm, 1, CHOH), 1.67 (doublet of doublets, 3, J_1 = 1, J_2 = 4.2 Hz, CH_3CH=CH), and 1.14 ppm (d, 3, J_3 = CH_3CH).

4-Chloro-2-pentene.[22] **Method A.** Zinc chloride (53.6 g, 395 mmol, previously dried at 110° for 24 hr) was dissolved in concentrated hydrochloric acid (100 ml) and cooled at 0° (ice bath). 3-Penten-2-ol (34.0 g, 395 mmol) was added all at once and the solution was stirred at 1–10° for 90 min. The mixture was transferred to a separatory funnel. The organic layer was separated, washed with saturated sodium chloride solution (three times), dried ($CaCl_2$), and distilled to give 28.1 g (68%) of 4-chloro-2-pentene, bp 99–102° (lit.[22] bp 100.5°).

Method B. 3-Penten-2-ol (73.1 g, 849 mmol) was placed in a 100-ml round-bottomed flask and cooled to 0° (ice bath). Anhydrous hydrogen chloride gas was slowly bubbled through the alcohol for 3 hr. The mixture was then transferred to a separatory funnel and the aqueous layer was separated. The crude chloride was dried ($CaCl_2$) and distilled to give 68.8 g (77%) of 4-chloro-2-pentene: bp 99–102°; ir (film) 3040 (w, CH=CH), 1670 (trans CH=CH), 1450, 1375 (CH_3), 961 (trans CH=CH), and 643 cm^{-1} (CHCl); nmr (CCl_4) δ 5.28–6.06 (m, 2, CH=CH), 4.22–5.0 (m, 1, CHCl), 1.63 (doublet of doublets, 3, J_1 = 1, J_2 = 5 Hz, CH_3 CH=CH), and 1.49 ppm (d, 3, J_3 = 6.3 Hz, CH_3CHCl).

2-(4′-Pent-2′-ene)-2,6,6-trimethylcycloheptanone (6C).[8,24] Sodium hydride (17.9 g, 440 mg-atoms of a 59% dispersion) was transferred to the flask and washed with anhydrous 1,2-dimethoxyethane (DME, 3 × 25 ml, freshly distilled from lithium aluminum hydride). Dry DME (250 ml) was added and the apparatus was sealed under dry nitrogen. Tetrahydroeucarvone (**5**, 60.0 g, 389 mmol, dissolved in dry DME, 50 ml) was added rapidly. The reaction mixture was allowed to stir at 80 ± 5° for 72 hr.

To the resulting light yellow slurry of sodium enolate at 5° (ice bath) was added 4-chloro-2-pentene (46.5 g, 440 mmol, dissolved in dry DME, 50 ml). The reaction mixture was allowed to stir at room temperature for 72 hr.

The resulting milky-white slurry was heated to reflux (2 hr), cooled, poured into ice–water, and extracted with ether. The combined ethereal extracts were washed with saturated sodium chloride solution until neutral, dried ($MgSO_4$), and concentrated *in vacuo*. Distillation gave 74 g (86%) of colorless alkylated ketone **6C**: bp 70–71° (0.16 mm); ir (film) 3025 (CH=CH), 1695 (CO), 1675 (trans CH=CH), 1390, 1380, 1370 (*gem*-CH_3) and 966 cm^{-1} (trans CH=CH); nmr (CCl_4) δ 4.67–5.16 (m, 2, CH=CH), 2.63, 2.47 (two doublets, 1, J = 2.2, J_2 = 1.7, J_4 = 1.7 Hz, CH_3CHCH=CH), 0.92, 0.85, 0.77 (s, s, s, 9, CH_3), and 0.74 ppm (d, 3, J_5 = 6.6 Hz, CH_3CH).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.14; H, 11.73.

2-(Ethyl 2′-propanoate)-2,6,6-trimethylcycloheptanone (6D).[8,24] Sodium hydride (17.9 g, 440 mg-atoms of a 59% dispersion) was transferred to the reaction flask and washed with anhydrous 1,2-dimethoxyethane (DME, 3 × 25 ml, freshly distilled from lithium aluminum hydride). Dry DME (500 ml) was then distilled directly into the flask. The apparatus was sealed under dry nitrogen. The slurry was stirred at 82 ± 2° while tetrahydroeucarvone (**5**, 60.0 g, 389 mmol, dissolved in dry DME, 100 ml) was added. The mixture was allowed to stir at 82 ± 2° for 73 hr.

The resulting light yellow slurry of sodium enolate was cooled to 0° (ice bath) and ethyl 2-bromopropanoate (57.4 ml, 441 mmol, freshly distilled) dissolved in dry DME (100 ml) was added very rapidly. The reaction mixture was allowed to warm to room temperature over a period of 1 hr, poured into acetic acid–ice, and extracted with ether. The combined ethereal extracts were washed with saturated sodium bicarbonate solution (three times) and saturated sodium chloride solution until neutral, and then dried ($MgSO_4$) and concentrated *in vacuo*. Distillation gave 32 g (33%) of colorless keto ester **6D**: bp 84–104° (0.06 mm); ir (film) 1735 (CO_2Et), 1700 (CO), 1385, 1365 (*gem*-CH_3) 1280, 1260, 1250, 1220 (asymmetric COC), 1190–1160 cm^{-1} (symmetric COC); nmr (CCl_4) δ 4.12 (q, J = 7.2 Hz, OCH_2CH_3), 4.04 (q, J = 7.2 Hz, OCH_2CH_3), two diastereomers), 1.24 (d, J = 3.2 Hz, CH_3CH), 1.04 (t, J = 7.2 Hz, OCH_2CH_3), and 0.85 ppm (s, CH_3).

Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 71.00; H, 10.05.

2-(2′-Ethanal)-2,6,6-trimethylcycloheptanone (7A).[25] Osmium tetroxide solution was prepared by dissolving 1.00 g (3.94 mmol) of osmium tetroxide in distilled water (100 ml).

Unsaturated ketone **6A** (5.00 g, 25.8 mmol) and an aqueous solution of tetrahydrofuran [100 ml of a 1:3 solution (v/v) of water–THF] were transferred to the reaction flask. Sodium metaperiodate (11.6 g, 54.5 mg-atoms, Matheson) was placed in the solid addition funnel. The solution was stirred under a constant flow of nitrogen while osmium tetroxide solution (5.0 ml, 1.97 × 10^{-1} mmol) was added. Immediately a light brown color appeared. The sodium metaperiodate was added in small portions over a period of 1 hr. The reaction flask was sealed under dry nitrogen and allowed to stir at room temperature for 3 hr. The resulting white slurry was filtered and the filtrate was extracted with ether. The combined ethereal extracts were washed with water (three times), dried ($MgSO_4$), and concentrated *in vacuo*. Distillation gave 2.80 g (55%) of colorless keto aldehyde **7A**: bp 78–79° (0.20 mm); ir (film) 2735, 1720 (CHO), 1695 (CO), 1390, 1375, 1365 cm^{-1} (*gem*-CH_3); nmr (CCl_4) δ 9.75 (t, 1, J = 2.3 Hz, CHO), 2.46 (AB, 2, J_{AB} = 11 Hz, $COCH_2$), 2.45, 2.32 (pair of d, 2, J = 2.3 Hz, CH_2CHO), 1.22, 0.96, and 0.90 ppm (s, s, s, 9, CH_3).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.15; H, 10.11.

2-(2′-Ethanoic acid)-2,6,6-trimethylcycloheptanone (7B). Method A.[27] A solution of sodium metaperiodate (45 g, 210 mg-atoms), keto olefin **6A** (6.94 g, 38.9 mmol), aqueous ruthenium trichloride solution (0.6 ml, 0.038 g/ml, 0.0231 g) in distilled water (1600 ml), and *tert*-butyl alcohol (500 ml) was stirred at room temperature for 72 hr. The solution was transferred to a separatory funnel and extracted with dichloromethane (6 × 150 ml). The combined organic extracts were washed with 10% sodium hydroxide solution (5 × 100 ml). The combined basic extracts were washed with dichloromethane (50 ml). The aqueous layer was acidified with concentrated hydrochloric acid and extracted with dichloromethane (5 × 100 ml). The combined latter organic extracts were washed with saturated sodium chloride solution, dried ($MgSO_4$), and concentrated *in vacuo* to 7.52 g of a yellow, viscous oil. Distillation gave 7.16 g (87%) of f a slightly yellow, viscous keto acid **7B**.

Method B. A solution of keto ester **6B** (12.36 g, 5.13 mmol) and potassium hydroxide (10.0 g) in methanol (150 ml) and water (50 ml) was stirred at room temperature for 13 hr and then allowed to reflux for 1 hr.

The light yellow solution was cooled to room temperature and extracted with ether in order to remove neutral side products. The

aqueous layer was acidified with concentrated hydrochloric acid and again extracted with ether. The combined latter ethereal extracts were washed with saturated sodium chloride solution, dried ($MgSO_4$), and concentrated *in vacuo* to give 10.2 g (94%) of slightly yellow, viscous keto acid **7B**: bp 100° (bath temperature, 0.30 mm); ir (film) 2450–3650 (CO_2H), 1735, 1700 (CO_2H), 1380, 1360 (*gem*-CH_3), 1291, 1224, 1200 cm^{-1} (CO); nmr (CCl_4) δ 10.0 (s, 1, CO_2H), 2.40 (m, 0.4, CH_2CO), 1.19, 0.95, 0.92 ppm (s, s, s, 9, CH_3).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.65; H, 9.41.

3,3,7-Trimethyl-9-oxo-10-oxabicyclo[5.3.0]dec-1-ene (8).[28] A solution of keto acid **7B** (9.10 g, 42.9 mmol) and anhydrous sodium acetate (0.5 g) in acetic anhydride was allowed to stir at 140 ± 2° (bath temperature) for 5 hr.

The resulting orange-brown solution was cooled to room temperature, poured into ice-saturated sodium bicarbonate solution (300 g–150 ml), and extracted with ether (5 × 50 ml). The combined ethereal extracts were washed with water (3 × 50 ml) and saturated sodium chloride solution (50 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The remaining traces of acetic anhydride were removed by codistillation *in vacuo* with toluene (3 × 50 ml) and with methanol (3 × 50 ml, containing a trace of pyridine). The orange oil was dissolved in hexane (50 ml), concentrated to approximately 25 ml, and cooled in the freezer overnight. The crude, slightly yellow crystals were purified by sublimation (40 ± 2°, 0.5 mm) to give 7.26 g (87%) of pure white, crystalline enol lactone **8**: mp 68.7–69.2°; ir ($CHCl_3$) 1800, 1790 (CO), 1685 (OC=CH), 1390, 1380, 1365 (*gem*-CH_3), 857 and 848 cm^{-1} (C=CH); nmr (CCl_4) δ 5.06 (s, 1, OC=CH), 2.36 (AB, 2, J_{AB} = 17 Hz, CH_2CO), 1.28 (s, 3, CH_3), and 1.05 ppm (bs, 6, *gem*-CH_3).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.38; H, 9.35.

2,2,6-Trimethyl-8-*exo*-hydroxybicyclo[4.2.1]nonan-9-one (9).[28] Enol lactone 8 (0.120 g, 0.619 mmol) was stirred in anhydrous tetrahydrofuran (10.0 ml, freshly distilled from lithium aluminum hydride) at −78° (Dry Ice) under Ar while a solution of diisobutylaluminum hydride in benzene (0.45 ml, 1.50 *M*, 0.68 mmol) was added dropwise. After 10 min the cooling bath was removed and the clear solution was allowed to stir at room temperature for 22 hr. The reaction mixture was quenched at 0° (ice bath) with 10% hydrochloric acid (1.0 ml), poured into water (50 ml), and extracted with ether (4 × 25 ml). The combined ethereal extracts were washed with water (3 × 50 ml) and saturated sodium chloride solution (50 ml), dried (Na_2SO_4), and concentrated *in vacuo* to give 0.117 g of a colorless oil. Preparative thin layer chromatography on a 20 × 20 cm silica gel plate using 50% ether–50% petroleum ether eluent gave 0.099 g (82%) of white, crystalline ketol **9** (R_f 0.16–0.34): mp 65.5–66° ir ($CHCl_3$) 3600, 3460 (OH), 1725 (CO), 1395, 1389, 1375 cm^{-1} (*gem*-CH_3); nmr ($CDCl_3$) δ 4.37–4.67 (symmetrical multiplet, coupled ABX, 1, $J_{C\text{-}1,C\text{-}8}$ = 2, J_{AB} = 14 Hz, CHOH), 2.95 (s, 1, -OH), 2.50 and 2.27, 1.80 and 1.60 (two doublets, 2, J = 8 Hz, and two doublets, J = 5 Hz, CH_2 at C-7), 1.97 (d, 1, J = 2 Hz, bridgehead at C-1, dihedral angle between protons on C-1 and C-7 must be near 130°), 1.15 (s, 9, -CH_3).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.31; H, 10.14.

2-(2′-Propanoic acid)-2,6,6-trimethylcycloheptanone (10).[8,24,27] **Method A.** A mixture of keto olefin **6C** (10.0 g, 45.0 mmol), sodium metaperiodate (48.0 g, 225 mg-atoms), and distilled water (1.0 l.) was stirred until all the sodium metaperiodate dissolved. *tert*-Butyl alcohol (525 ml) was added with stirring and the solution became homogeneous. Catalytic amounts of ruthenium trichloride solution (2 ml, 0.0385 g/ml) and osmium tetroxide solution (10 ml, 0.0025 g/ml) were added. The flask was then filled completely with distilled water, carefully stoppered, and allowed to stir for 188 hr at room temperature. The reaction mixture was poured into water (2 l.) and extracted with ether (10 × 200 ml). The combined ethereal extracts were washed with 10% sodium hydroxide solution (5 × 100 ml). These combined aqueous extracts were washed with ether (100 ml). The aqueous layer was then carefully acidified with cooling (ice bath) with concentrated hydrochloric acid. The slightly acidic aqueous mixture was extracted with ether (5 × 100 ml) and the combined ethereal extracts were washed with water (50 ml) and saturated sodium chloride solution (50 ml), dried ($MgSO_4$), and concentrated *in vacuo* to give 9.46 g (93%) of pale yellow, crystalline keto acid **10**: mp 125–125.5°; ir ($CHCl_3$) 2400–3580 (CO_2H), 1710, 1700 (CO_2H, CO), 1380, 1370 cm^{-1} (*gem*-CH_3); nmr (CCl_4) δ 8.05 (bs, 1, CO_2H), 3.49 (distorted AB, 3, J_{AB} = 7 Hz, CHCO and $COCH_2$), 1.18 (s, 3, CH_3), 1.04 (bs, 6, *gem*-CH_3), and 0.90 ppm (d, 3, J = 5.6 Hz, CH_3CH).

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.81; H, 9.70.

3,3,7,8-Tetramethyl-9-oxo-10-oxabicyclo[5.3.0]dec-1-ene (11).[28] **Method A.** A solution of keto acid **10** (13.3 g, 58.9 mmol) and anhydrous sodium acetate (0.274 g) in acetic anhydride (50 ml) was stirred at reflux for 5 hr. After cooling to room temperature the orange-brown mixture was poured into ether (250 ml). This ethereal solution was washed with water (3 × 50 ml), 5% disodium hydrogen phosphate solution (3 × 25 ml), and saturated sodium chloride solution (3 × 50 ml), and dried overnight (Na_2SO_4) containing methanol (150 ml) and pyridine (0.5 ml). The resulting mixture was filtered and concentrated *in vacuo* to give 11.6 g (95%) of a red oil. Distillation gave 10.6 g (87%) of colorless liquid enol lactone **11**, bp 86–89° (0.4 mm).

Method B.[31] A solution of keto acid **10** (16.5 g, 72.9 mmol) and acetic anhydride (20.0 ml, 212 mmol, freshly distilled), in anhydrous dichloromethane (400 ml, freshly distilled from phosphorous pentoxide) containing 60% perchloric acid (20 μl) was allowed to stir at room temperature for 4 hr. The reaction mixture was washed with water (3 × 100 ml), saturated sodium bicarbonate solution (100 ml) and water (100 ml), dried ($MgSO_4$), and concentrated *in vacuo*. The last traces of acetic anhydride were removed with methanol (50 ml) containing a trace of pyridine (0.2 ml) and again concentrated *in vacuo* to give 14.8 g (97.4%) of an orange oil. Distillation gave 13.7 g (90%) of colorless liquid enol lactone **11**: bp 86–89° (0.4 mm); ir (film) 3040 (OC=CH), 1790 (CO), 1685 (OC=CH), 1390, 1375 (*gem*-CH_3), 855 and 841 cm^{-1} (OC=CH); nmr (CCl_4) δ 5.19 (m, 1, OC=CH), 1.30 (s, 3, CH_3), and 1.10 ppm (s, 6, *gem*-CH_3); glc analysis on column D shows the product to be a 70:30 mixture of diastereomers (column temperature 145°, retention times 7.2 and 9.1 min).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.91; H, 9.72.

2,2,6,7-Tetramethyl-8-*exo*-hydroxybicyclo[4.2.1]nonan-9-one (12).[28] A solution of enol lactone **11** (1.796 g, 8.62 mmol) in anhydrous tetrahydrofuran (80 ml, freshly distilled from lithium aluminun hydride) was stirred under nitrogen at −78° (Dry Ice) while a benzene solution of diisobutylaluminum hydride (6.00 ml, 1.50 *M*, 9.0 mmol) was added dropwise. After 30 min the cooling bath was removed and the clear solution was allowed to stir at 60° (bath temperature) for 18 hr. The reaction mixture was cooled to room temperature and poured into an ice–water mixture (200 ml) containing 10% hydrochloric acid (6 ml). The mixture was extracted with ether (6 × 50 ml). The combined ethereal extracts were washed with water (4 × 100 ml) and saturated sodium chloride solution (100 ml), dried (Na_2SO_4), and concentrated *in vacuo* to give 1.90 g of crude oil. The crude product was immediately chromatographed on silica gel (190 g, 75–325 mesh, E. Merck) in a 2.5-cm diameter column. A 50:50 mixture of ether and petroleum ether was used to develop the column, taking 80-ml sized fractions. Fractions 7–11 gave 1.45 g (80%) of pure ketol **12** as a colorless liquid. Analysis by glc on column D showed the ketol **12** to be a 66:34 mixture of diastereomers: bp 105° (0.2 mm, bulb to bulb, external temperature); ir (film) 3440 (-OH), 1725 cm^{-1} (CO). This compound was found to be very sensitive to acid- or base-catalyzed fragmentation and was immediately carried on to the next reaction.

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.25; H, 10.65.

2,2,6,7-Tetramethylbicyclo[4.2.1]non-7-en-9-one (13).[32,33] A solution of ketol **12** (1.835 g, 8.72 mmol) in anhydrous dichloromethane (60 ml, freshly distilled from phosphorus pentoxide) was stirred at 0° (ice bath) while triethylamine (1.337 g, 13.2 mmol, freshly distilled from calcium hydride) and methanesulfonyl chloride (1.105 g, 9.05 mmol, freshly distilled) were added sequentially. The resulting pale yellow solution was stored in a refrigerator at 3° for 17 hr. The solution was transferred to a separatory funnel with dichloromethane (600 ml) and water (150 ml). The organic layer was separated, washed with water (150 ml), 5% hydrochloric acid (150 ml), and saturated sodium chloride solution (150 ml), dried (Na_2SO_4), and concentrated *in vacuo* to give 2.52 g of a crude oil. This oil was dissolved in collidine (55 ml, dried over barium oxide). After stirring under nitrogen at 170–175° (bath temperature) for 16 hr, the dark brown solution was cooled to room temperature and diluted with ether (500 ml) and water (150 ml). The ether layer was separated, washed with 5% hydrochloric acid (6 × 150 ml), water (150 ml), saturated sodium bicarbonate solution (150 ml), water (150 ml), and saturated sodium chloride solution (150 ml), dried (Na_2SO_4), and concentrated *in vacuo* to give 1.66 g of crude ketone **13**. Distillation gave 1.46 g (87%) of pure ketone **13**: bp 46° (0.2 mm, external temperature); ir ($CHCl_3$) 1735 (CO),

1645, 850 cm^{-1} (C=CH) [lit.[34] ir ($CHCl_3$) 1738, 1650, 850 cm^{-1}]; nmr (CCl_4) δ 5.80 (q, 1, J = 2 Hz, CH=C), 2.35 (q, 1, J = 2 Hz, bridgehead at C-1), 1.66 (t, 3, J = 2 Hz, CH_3C=CH), 1.04 (s, 6, CH_3), 0.97 ppm (s, 3, CH_3).

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 80.97; H, 10.52.

2,2,6,7-Tetramethyl-9-methoxymethylenebicyclo[4.2.1]non-7-ene (14).[35] Sodium hydride (1.288 g of a 57% dispersion in oil, 30.6 mg-atoms) was washed with anhydrous ether (3 × 20 ml, freshly distilled from lithium aluminum hydride) under nitrogen. The remaining traces of ether were removed by warming the sodium hydride in a stream of dry nitrogen. After cooling to room temperature dimethyl sulfoxide (85 ml, freshly vacuum distilled from calcium hydride) was added. The mixture was stirred under nitrogen at 50–60° (bath temperature) for 2.75 hr. After the solution was cooled to room temperature methoxymethyltriphenylphosphonium chloride (10.42 g, 30.42 mmol) was added. The resulting deep red solution was stirred for 15 min, and then enone **13** (2.94 g, 15.6 mmol) dissolved in dry dimethyl sulfoxide (3 × 5.0 ml, freshly vacuum distilled from calcium hydride) was added. The resulting reaction mixture was stirred at 59° ± 2° (bath temperature) for 23.5 hr. The orange solution was cooled to room temperature and poured into water (500 ml) and ether (500 ml). The aqueous layer was separated and extracted further with ether (3 × 250 ml). The combined ethereal extracts were washed with 10% hydrochloric acid (200 ml), water (10 × 200 ml), and saturated sodium chloride solution (200 ml), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting concentrate (7.45 g) was dissolved in petroleum ether (10 ml) and allowed to stand overnight. The liquid was separated from the crystalline triphenylphosphine oxide and concentrated *in vacuo* to give 4.10 g of crude product. This crude liquid was chromatographed on silica gel (400 g, 75–325 mesh) in a 4.0-cm diameter column using a 2.5% ether–97.5% petroleum ether solution to develop the column, taking 200-ml sized fractions. Fractions 4–6 were concentrated and distilled to give 2.97 g (88%) of pure methoxyvinyl ether **14**: bp 45 ± 2° (0.2 mm, external temperature); ir (film) 3070 (C=CH), 1695 (C=CO), 1385 and 1365 cm^{-1} (*gem*-CH_3); nmr (CCl_4) δ 5.64 (m, 1, C=CHO), 5.4 (m, 1, CH=C), 3.5 (s, 3, CH_3O), 2.92 (m, 1, bridgehead H), 1.57 (m, 3, CH_3C=C), 1.01 (s, 3, CH_3), 0.92 (s, 3, CH_3), and 0.82 ppm (s, 3, CH_3).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.79; H, 10.82.

2,2,6,7-Tetramethylbicyclo[4.2.1]non-7-ene-9-*exo*-carboxaldehyde (15).[35] Perchloric acid (20 ml, 50%) was slowly added to a solution of methoxyvinyl ether **14** (1.477 g, 6.7 mmol) in ether (100 ml) under nitrogen. The resulting homogeneous solution was stirred for 1.75 hr at room temperature and then poured into pentane (100 ml) and water (100 ml). The aqueous layer was separated and extracted with pentane (4 × 50 ml). The combined organic extracts were washed with water (50 ml) and saturated sodium chloride solution (50 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The crude aldehyde was dissolved in dry methanol (100 ml) containing anhydrous potassium carbonate (1.0 g). The slurry was stirred at room temperature for 1.75 hr under nitrogen and then poured into water (100 ml). This aqueous solution was extracted with pentane (6 × 40 ml). The combined pentane extracts were washed with water (40 ml) and saturated sodium chloride solution (40 ml), dried (Na_2SO_4), and concentrated *in vacuo*. Distillation gave 1.40 g (100%) of pure aldehyde **15**: bp 45 ± 2° (0.2 mm, external temperature); ir (CCl_4) 3060 (C=CH), 2745 (-CHO), 1720 (CO), 1385, and 1365 cm^{-1} (*gem*-CH_3); nmr (CCl_4) δ 9.32 (d, 1, J = 7 Hz, -CHO), 5.42 (m, 1, C=CH), 2.35 (d, 1, J = 7 Hz, OCCH), 2.11 (m, 1, bridgehead H), 1.55 (m, 3, CH_3C=C), 1.03 (s, 3, CH_3), and 0.93 ppm (s, 6, CH_3).

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.38; H, 10.70.

2,2,6,7-Tetramethylbicyclo[4.2.1]non-7-ene-9-*exo*-carboxylic Acid (16).[36,37] Jones reagent (2.5 ml, 2.67 *M*, 6.67 mmol) was added dropwise to a solution of aldehyde **15** (1.25 g, 6.06 mmol) dissolved in anhydrous acetone (50 ml, dried over magnesium sulfate) at 0° (ice bath) with vigorous stirring. The ice bath was removed after the addition and after 30 min the reaction was quenched with reagent isopropyl alcohol (enough to remove the orange color). The reaction mixture was dissolved in water (150 ml) and extracted with ether (10 × 25 ml). The combined ethereal extracts were washed with water (25 ml) and then with 10% sodium hydroxide solution (5 × 50 ml). The basic extracts were carefully acidified with concentrated hydrochloric acid while cooling in an ice bath. This acidified solution was extracted with ether (5 × 50 ml). The combined ethereal extracts were washed with water (25 ml) and saturated sodium chloride solution (25 ml), dried (Na_2SO_4), and concentrated *in vacuo* to give 1.15 g (86%) of acid **16**. A small sample of this acid was recrystallized from pentane (three times) to give pure acid **16**: mp 127.5–128°; ir (CCl_4) 3060 (-CO_2H), and 1700 cm^{-1} (CO); nmr (CCl_4) δ 11.47 (s, 1, -CO_2H), 5.43 (m, 1, C=CH), 2.68 (s, 1, $CHCO_2H$), 2.37 (m, 1, bridgehead H), 1.52 (m, 3, CH_3C=C), 1.12 (s, 3, CH_3), 0.93 (s, 3, CH_3), and 0.88 ppm (s, 3, CH_3).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.62; H, 9.91.

2,2,6,10-Tetramethyltetracyclo[5.4.0.$0^{6,10}$.$0^{9,11}$]undecan-8-one (17).[38] A solution of the olefinic acid **16** (0.499 g, 2.25 mmol) dissolved in benzene (20 ml, freshly distilled from calcium hydride) was stirred at 0° (ice bath) under nitrogen while oxalyl chloride (1.35 ml, 2.0 g, 15.75 mmol) was added dropwise. The ice bath was removed and the solution was stirred at room temperature for 2 hr. The solvent and excess reagent were removed *in vacuo*. The resulting orange oil was dissolved in benzene (2 × 5.0 ml, freshly distilled from calcium hydride) under nitrogen. This solution was added dropwise at 0° (ice bath) to an anhydrous ethereal solution of diazomethane (50 ml, ~20 mmol, predried over sodium metal) with vigorous stirring under nitrogen. The resulting solution was stirred at 0° for 1 hr and then at room temperature for 1.5 hr. The solvents and excess reagent were removed *in vacuo*. Tetrahydrofuran (40 ml, freshly distilled from lithium aluminum hydride) and finely divided metalic copper powder (0.67 g, Fischer C-434) were added to the crude diazo ketone, sequentially. This suspension was vigorously stirred at reflux under nitrogen for 2 hr. The resulting suspension was allowed to stir at room temperature for an additional 14 hr. The solution was filtered into water (100 ml). The mixture was shaken vigorously for 5 min and then extracted with ether (3 × 50 ml). The combined ethereal extracts were washed with saturated sodium bicarbonate solution (4 × 40 ml), water (40 ml), and saturated sodium chloride solution (40 ml), dried (Na_2SO_4), and concentrated *in vacuo* to give 0.673 g of a crude brown oil. This crude oil was chromatographed on silica gel (67 g, 75–325 mesh, E. Merck) in a 2-cm diameter column using 10% ether–90% petroleum ether to develop the column, taking 37-ml sized fractions. Fractions 11–16 gave 0.164 g (33%) of pure ketone **17**: mp 64–64.5° (from pentane); ir (CCl_4) 3095 (cyclopropyl CH) and 1755 cm^{-1} (CO); nmr (CCl_4) δ 1.18 (s, 3, CH_3) 1.03 (s, 3, CH_3), 0.97 (s, 3, CH_3), and 0.90 ppm (s, 3, CH_3).

Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.61; H, 10.01.

2,2,6,10-Tetramethyltetracyclo[5.4.0.$0^{6,10}$.$0^{9,11}$]undecan-8β-ol (18). Diisobutylaluminum hydride in benzene (0.65 ml, 1.26 *M*, 0182 mmol) was added to a stirred solution of tetracyclic ketone **17** (0.164 g, 0.75 mmol) in anhydrous tetrahydrofuran (15 ml, freshly distilled from lithium aluminum hydride) at −78° (Dry Ice) under nitrogen. The resulting solution was stirred at −78° for 30 min, at 0° for 30 min, and at room temperature for 3 hr. The solution was then poured into a mixture of ice and 10% sodium hydroxide solution (25 g:25 ml). The mixture was extracted with ether (6 × 30 ml). The combined ethereal extracts were washed with water (3 × 30 ml) and saturated sodium chloride solution (30 ml), dried (Na_2SO_4), and concentrated *in vacuo* to give 0.169 g of crude crystalline alcohol **18**. Recrystallization from pentane (once) gave 0.162 g (98%) of pure alcohol **18**: mp 114–115°; ir (CCl_4) 3650 (free OH), 3325 (H-bonded OH), 3075 (cyclopropyl CH), 1380, and 1365 cm^{-1} (*gem*-CH_3); nmr (CCl_4) δ 3.63 (s, 1, CHO), 1.73 (s, 1, OH), 1.20 (s, 3, CH_3), 1.05 (s, 3, CH_3), 0.92 (s, 3, CH_3), and 0.87 ppm (s. 3, CH_3).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.80; H, 10.93.

(±)-Longicyclene (1).[9] To a stirred solution of tetracyclic alcohol **18** (0.1375 g, 0.625 mmol) in anhydrous dichloromethane (5.0 ml, freshly distilled from phosphorus pentoxide) at 0° (ice bath) under nitrogen were added sequentially triethylamine (0.13 g, 0.180 ml, 1.27 mmol, freshly distilled from calcium hydride) and methanesulfonyl chloride (0.147 g, 0.097 ml, 1.28 mmol, freshly distilled). The solution was stored in a freezer at −15° for 72 hr.[32] The reaction mixture was then poured into a mixture of lithium aluminum hydride (0.2033 g, 5.35 mg-atoms) and ether (20 ml, freshly distilled from lithium aluminum hydride). This mixture was stirred at reflux for 7.5 hr and left to stir at room temperature for 9.5 hr. The reaction mixture was poured into ice–10% sodium hydroxide solution (30 g:30 ml) and extracted with ether (5 × 30 ml). The combined ethereal extracts were washed with 10% hydrochloric acid (30 ml), saturated sodium bicarbonate solution (30 ml), water (2 × 30 ml), and saturated sodium chloride solution, dried (Na_2SO_4), and concentrated carefully *in vacuo* at room tem-

Table I

Column	Column temp, °C	Retention time, min
B	100	17.1
C	110	15.4
D	100	12.9
E	100	11.3
F	110	18.7

perature to give 0.136 g of crude (±)-longicyclene (**1**). The crude product was chromatographed on silica gel (10 g, 75–325 mesh, E. Merck) in a 1-cm diameter column using pentane to develop the column, taking 5-ml sized fractions. Fractions 3–5 gave after distillation 0.125 g (98%) of pure (±)-longicyclene (**1**): bp 82° (2.0 mm, external temperature); ir (CCl_4) 3085 (cyclopropyl H), 1385, and 1370 cm^{-1} (*gem*-CH_3); nmr (CCl_4) δ 1.04 (s, 3, CH_3), 0.98 (s, 3, CH_3), 0.92 (s, 3, CH_3), and 0.88 ppm (s, 3, CH_3). The spectral data are identical with those for natural (+)-longicyclene.[9]

Synthetic (±)-longicyclene was found to have identical retention times with those of natural (+)-longicyclene[9] on glc both in separate and coinjected samples using columns B–F. Glc data on separate and coinjected samples of longicyclene are listed in Table I.

Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.28; H, 11.78.

2,2,6,7-Tetramethyl-9-*exo*-vinylbicyclo[4.2.1]non-7-ene (19).[43] Sodium hydride (0.0840 g, 2.00 mg-atoms) of a 57% dispersion in oil was washed under nitrogen with anhydrous ether (3 × 2 ml, freshly distilled from lithium aluminum hydride) and the last traces of ether were removed by warming the sodium hydride in a stream of nitrogen. After cooling to room temperature, dry dimethyl sulfoxide (11 ml, freshly distilled from calcium hydride) was added and the mixture was stirred under nitrogen at 60 ± 2° until the evolution of hydrogen ceased. The resulting clear solution was cooled to room temperature and methyltriphenylphosphonium bromide (0.715 g, 2.00 mmol) was added. The yellow solution was stirred at room temperature for 15 min, and then aldehyde **15** (0.1961 g, 0.95 mmol) was added. The reaction mixture was allowed to stir at room temperature for 13.5 hr. The orange solution was poured into water (60 ml) and extracted with pentane (5 × 30 ml). The combined pentane extracts were washed with 10% hydrochloric acid solution (20 ml), saturated sodium bicarbonate solution (20 ml), water (20 ml), and saturated sodium chloride solution, dried (Na_2SO_4), and concentrated to approximately 10 ml *in vacuo* at room temperature. This solution was chromatographed on silica gel (20 g, 75–325 mesh, E. Merck) in a 1.5-cm diameter column using pentane to develop the column, taking 10-ml sized fractions. Fractions 5 and 6 gave after concentration and distillation 0.1603 g (83%) of pure diene **19**: bp 125° (30 mm, external temperature); ir (CCl_4) 3060 (C=CH, H_2C=CH), 1660 (C=CH), 1635 (H_2C=CH), 1385, 1375 (*gem*-CH_3), and 905 cm^{-1} (H_2C=CH); nmr (CCl_4) δ 5.3–6.0 (m, 2, H_2C=C**H** and C=CH), 4.88 (doublet of doublets, 1, J = 11 and 2.5 Hz, cis proton to R in $\mathbf{H_2C}$=CHR), 4.67 (overlapping doublet of doublets, 1, trans proton to R in $\mathbf{H_2C}$=CHR), 2.38 (d, 1, J = 9.5 Hz, H_2C=CHC**H**), 1.85 (m, 1, bridgehead H), 1.57 (t, 3, $\mathbf{CH_3}$C=CH), 0.97 (s, 3, CH_3), 0.95 (s, 3, CH_3), and 0.93 ppm (s, 3, CH_3).

Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.22; H, 11.85.

2,2,6,*endo*-7-Tetramethyl-9-*exo*-(2′-hydroxyethyl)bicyclo[4.2.1]nonan-*exo*-8-ol (20). Method A.[43] Diborane–tetrahydrofuran solution (2.3 ml, 0.75 *M*, 1.73 mmol, Alfa Inorganics) was added to a stirred solution of diene **19** (88.3 mg, 0.432 mmol) in anhydrous tetrahydrofuran (4.0 ml), freshly distilled from lithium aluminum hydride) at 0° (ice bath) under nitrogen. The resulting solution was allowed to stir at room temperature for 3 hr. The solution was cooled to 0° (ice bath) and a mixture of 30% hydrogen peroxide and 10% sodium hydroxide solution (5 ml:5 ml) was added dropwise. The reaction mixture was stirred vigorously at 0° (ice bath) for 1 hr and then stirred at room temperature for 1 hr. The solution was poured into water (50 ml) and extracted with ether (5 × 20 ml). The combined ethereal extracts were waawashed with 10% sodium hydroxide solution (10 ml) and saturated sodium chloride solution (2 × 10 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was chromatographed on silica gel (10 g, 70–230 mesh, E. Merck) in a 1-cm diameter column using 25% acetone–75% petroleum ether to develop the column, taking 5-ml sized fractions. Fractions 13–17 gave 0.0509 g (49%) of pure diol **20**, mp 130.5–131°.

Method B.[43] Diborane–tetrahydrofuran solution (30 ml, 0.75 *M*, 20.4 mmol, Alfa Inorganics) was added to a stirred solution of 2-methyl-2-butene (3.14 g, 44.8 mmol, distilled from sodium metal) in anhydrous tetrahydrofuran (30 ml, freshly distilled from lithium aluminum hydride) at 0° (ice bath) under nitrogen. The ice bath was removed and the solution was allowed to stir at room temperature for 3 hr and then recooled to 0° (ice bath). A solution of diene **19** (0.8324 g, 4.07 mmol) in dry tetrahydrofuran (5.0 ml, freshly distilled from lithium aluminum hydride) was added. The resulting solution was allowed to stir at room temperature for 11.3 hr and then cooled to 0° (ice bath) and carefully quenched with distilled water (3 ml). This was immediately followed by a mixture of 30% hydrogen peroxide and 10% sodium hydroxide solution (50 ml:50 ml). The resulting reaction mixture was stirred vigorously at 0° (ice bath) for 3 hr and then stirred at room temperature for 3 hr. The mixture was poured into water (400 ml) and extracted with ether (6 × 75 ml). The combined ethereal extracts were washed with 10% sodium hydroxide solution (50 ml), water (3 × 50 ml), and saturated sodium chloride solution (50 ml), dried (Na_2SO_4), and concentrated *in vacuo*. Excess isoamyl alcohol was removed under high vacuum. The crude product (1.58 g) was chromatographed on silica gel (158 g, 70–230 mesh) in a 2.5-cm diameter column using 25% acetone–75% petroleum ether solution to develop the column, taking 75-ml sized fractions. Fractions 14–18 gave 0.478 (49%) of diol **20**, mp 130–131°. Recrystallization of a small sample from ether–hexane (once) gave analytically pure diol **20**: mp 130.5–131°; ir ($CHCl_3$) 3625 (free OH), 3400 (H-bonded OH), 1385, and 1370 cm^{-1} (*gem*-CH_3); nmr ($CDCl_3$) δ 4.04 (doublet of doublets, an X part of an AMX system, 1, first-order analysis $J_{7,8}$ = 7.8 and $J_{1,8}$ = 2.6 Hz, RC**H**OHR′), 3.9–3.5 (m, 2, $\mathbf{CH_2}$OH), 2.03 (s, 2, OH), 1.03 (s, 3, CH_3), 0.93 (s, 3, CH_3), and 0.90 ppm (s, 6, CH_3).

Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 74.84; H, 11.71.

2,2,6*endo*-7-Tetramethyl-9-*exo*-(2′-ethyl methanesulfonate)bicyclo[4.2.1]nonan-8-one (21).[32,46,47] Triethylamine (0.046 g, 0.454 mmol, freshly distilled from calcium hydride) and methanesulfonyl chloride (0.0596 g, 0.433 mmol) were sequentially added to a stirred solution of diol **20** (0.0994 g, 0.413 mmol) in anhydrous dichloromethane (6.0 ml, freshly distilled from phosphorus pentoxide) at 0° (ice bath) under nitrogen. The reaction was monitored by tlc (silica gel) using 50% acetone–50% petroleum ether to develop the plates [R_f (product) 0.66, R_f (starting material) 0.59]. After 36 hr at 3° (refrigerator) the solution was diluted with dichloromethane (40 ml), washed with water (2 × 10 ml), 5% hydrochloric acid (10 ml), saturated sodium bicarbonate solution (10 ml), and water (10 ml), dried (Na_2SO_4), and concentrated *in vacuo* to give 0.1286 g (97.4%) of a crude liquid hydroxy mesylate: ir (CCl_4) 3400 (OH), 1370, and 1180 cm^{-1} (CH_3SO_2OR); nmr (CCl_4) δ 4.37–3.77 (m, 3, C**H**OH and $\mathbf{CH_2}$OMs), 2.93 (s, 3, CH_3SO_3–), 2.50 (s, 1, OH), 1.03 (((s, 3, CH_3), 0.94 (s, 3, CH_3), and 0.90 (s, 6, CH_3). This material was used immediately in the next step without further purification.

To a solution of dry pyridine (0.4465 g, 5.65 mmol, freshly distilled from calcium hydride) in anhydrous dichloromethane (5.0 ml, freshly distilled from phosphorus pentoxide) at 0° (ice bath) under nitrogen was added chromium trioxide (0.282 g, 2.82 mg-atoms, Alfa Inorganics No. 87844, dried in a desiccator over phosphorus pentoxide). The burgundy solution was stirred at 0° for 5 min and then at room temperature for 10 min. A solution of the crude hydroxy mesylate (0.1286 g, 0.403 mmol) in dry dichloromethane (1.0 ml) was added quickly. A heavy, black, tarry residue separated immediately. After stirring for 15 min the brown-black solution was filtered through a column of Woelm neutral alumina (10 g, in a 1-cm diameter column, activity III) using dichloromethane (4 × 25 ml) to elute. The combined colorless eluent was concentrated *in vacuo* to give 0.121 g (92% overall) of keto mesylate **21**: mp 126–127°; tlc (silica gel) using 20% ether–80% petroleum ether to develop the plate shows only one spot. A small sample was recrystallized from pentane to give analytically pure keto mesylate **21**: mp 126–127°; ir ($CHCl_3$) 1725 (CO), 1370 and 1180 cm^{-1} (CH_3SO_2OR); nmr ($CDCl_3$) δ 4.5–4.1 (m, 2, $\mathbf{CH_2}$OMs), 3.0 (s, 3, CH_3SO_3) 1.10 (s, 3, CH_3), 1.06 (s, 3, CH_3), 1.00 (s, 3, CH_3), and 0.97 ppm (d, 3, J = 7 Hz, $\mathbf{CH_3}$CH).

Anal. Calcd for $C_{16}H_{28}O_4S$: C, 60.65; H, 8.92; S, 10.22. Found: C, 60.72; H, 8.92; S, 10.13.

(±)-Longicamphor (2A).[48] A solution of sodium bis(trimethylsilyl)amide in benzene (0.33 ml, 0.97 *M*, 0.32 mmol) was added dropwise to a stirred solution of keto mesylate **21** (99.4 mg, 0.314 mmol) dissolved in anhydrous 1,2-dimethoxyethane (5.0 ml, freshly distilled from lithium aluminum hydride) under nitrogen

Table II

Column	Column temp, °C	Retention time, min
B	220	12.3
C	170	15.0
D	120	12.0
E	170	13.2
F	190	11.2

Table III

Column	Column temp, °C	Retention time, min
B	200	14.2
C	190	17.6
D	120	13.5
E	170	13.0
F	170	13.5

at 0° (ice bath). The solution turned yellow, the ice bath was removed, and the solution was stirred at room temperature for 40 min. The yellow solution was diluted with ether (50 ml), washed with water (10 ml), 10% hydrochloric acid (2 × 10 ml), saturated sodium bicarbonate solution (2 × 10 ml), water (10 ml), and saturated sodium chloride solution (10 ml), dried (Na_2SO_4), concentrated *in vacuo*, and distilled to give 68.0 mg (98%) of pure (±)-longicamphor (**2A**): bp 50° (20 mm, external temperature); ir (CCl_4) 1735 (CO), 1390, and 1375 cm^{-1} (*gem*-CH_3); nmr (CCl_4) δ 1.60 (s, 1, bridgehead H), 1.13 (s, 3, CH_3CO), 0.92 (s, 3, CH_3), and 0.87 ppm (s, 6, $-CH_3$). The spectral data are identical with those observed for natural (+)-longicamphor.

Synthetic (±)-longicamphor was found to have identical retention times with those of natural (+)-longicamphor[10,13,14] on glc both in separate and coinjected samples using columns B–F. Glc data on separate and coinjected samples of longicamphor are listed in Table II.

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.84; H, 11.08.

(±)-Longiborneol (2B).[34,49] Racemic longicamphor (**1**, 67 mg, 0.304 mmol) was added to a blue solution of calcium metal (120 mg) in liquid ammonia (30 ml, distilled through potassium hydroxide towers). 1-Propanol was immediately added dropwise until the blue color was dispelled. The ammonia was evaporated and the residue was taken up in water (100 ml) and ether (100 ml). The aqueous layer was separated and extracted with ether (3 × 25 ml). The combined ethereal extracts were washed with water (5 × 10 ml) and saturated sodium chloride solution (20 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The excess 1-propanol was removed under high vacuum. The crude product was recrystallized from pentane (once) to give 65.5 mg (97%) of pure (±)-longiborneol (**2b**): mp 100–102°; ir (CCl_4) 3640 (free OH), 3450 (H-bonded OH), 1370, 1385 (*gem*-CH_3), and 1050 cm^{-1} (COH); nmr (CCl_4) δ 3.68 (d, 1, J = 6 Hz, CHOH), 0.93 (s, 6, $-CH_3$), and 0.85 ppm (s, 6, CH_3). The spectral data are identical with those observed for natural (+)-longiborneol.

Synthetic (±)-longiborneol was found to have identical retention times with those of natural (+)-longiborneol[10,13,14] on glc both in separate and coinjected samples using columns B–F. Glc data on separate and coinjected samples of longiborneol are listed in Table III.

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.01; H, 11.77.

Acknowledgment. We graciously thank the Robert A. Welch Foundation (Grant E-518) and the University of Houston (Limited Grant-in-Aid, 1972–1973) for support of this research program. We would also like to express our sincere gratitude to Professor Sukh Dev for providing authentic samples of (+)-longicyclene and (+)-longicamphor. We are also indebted to Professor M. R. Willcott, III, and Mr. W. Bearden for their help in the nmr analysis of diol **20**.

Registry No.—**1**, 41437-68-7; **2A**, 51868-75-8; **2B**, 51897-51-9; **3**, 2244-16-8; **4**, 503-93-5; **5**, 4436-59-3; **6A**, 51830-59-2; **6B**, 51830-60-5; **6C**, 51830-61-6; **6D**, 51830-62-7; **7A**, 51830-63-8; **7B**, 51830-64-9; **8**, 51830-65-0; **9**, 51830-67-2; **10**, 51830-66-1; **11** epimer A, 51868-76-9; **11** epimer B, 51868-77-0; **12** epimer A, 51868-78-1; **12** epimer B, 51868-79-2; **13**, 41509-35-7; **14**, 51830-68-3; **15**, 41435-94-3; **16**, 41437-67-6; **17**, 41509-36-8; **18**, 51830-69-4; **19**, 51830-70-7; **20**, 51830-71-8; **20** mesylate, 51830-72-9; **21**, 51830-73-0; allyl bromide, 106-95-6; ethyl 2-bromoacetate, 105-36-2; *trans*-3-penten-2-ol, 3899-34-1; crotonaldehyde, 4170-30-3; *trans*-4-chloro-2-pentene, 18610-33-8; ethyl 2-bromopropanoate, 535-11-5.

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Regioselective Functionalization in the Oxymercuration of β,γ-Unsaturated Urethanes. Synthesis of γ-Ketourethanes

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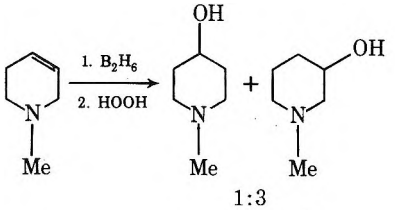
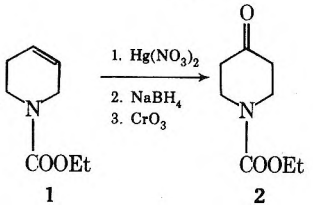
Received December 27, 1973

A specific directing effect on the regiochemistry of oxymercuration has been exerted by a proximate urethane functionality during the oxymercuration of selected β,γ-unsaturated urethanes. This effect has been utilized in the synthesis of γ-ketourethanes by reduction of initially formed oxymercurials with sodium borohydride followed by chromic acid oxidation. A mixture of products arising from spontaneous demercuration of an allylic mercurial has been obtained following oxymercuration of a dienic urethane.

The oxymercuration reaction, combined with *in situ* reduction of the oxymercuric intermediate, provides a convenient mild method to achieve Markovnikov hydration of a carbon–carbon double bond.[1] Additionally, for those cases where the rules of Markovnikov addition are not applicable, the synthetic utility of oxymercuration is often enhanced by the ability of proximate Lewis base groups to exert specific directing effects in promoting regioselective additions.[2] We here report a study of the utilization of such a directing effect in the synthesis of cyclic and bicyclic γ-ketourethanes from β,γ-unsaturated urethanes. Involved is a synthetic sequence of regioselective mercuric nitrate oxymercuration, sodium borohydride demercuration, and chromic acid oxidation.[3] Hereafter, the sequence of reactions will be referred to as ketofunctionalization.

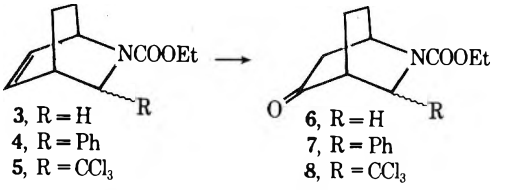
A study of the syntheses of hydroxypiperidines by the hydroboration of β,γ-unsaturated tetrahydropyridines followed by oxidation indicated a 3:1 preference for formation of 3-piperidinols.[4] The result probably reflects an electronic attraction between the boron and nitrogen atoms. By contrast, the mercuric nitrate ketofunctionalization sequence using *N*-carbethoxy-1,2,3,6-tetrahydropyridine (**1**) has been found to afford regiospecifically *N*-carbethoxy-4-ketopiperidine (**2**), which can be converted to *N*-methyl-4-hydroxypiperidine by lithium aluminum hydride reduction.





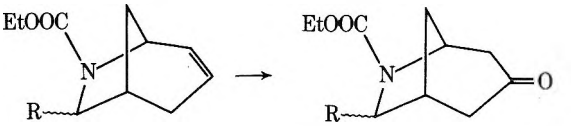
1 **2**

Introduction of bridging atoms did not change the regioselectivity of functionalization. *N*-Carbethoxydioscorone (**6**) was obtained[5] regiospecifically from 2-azabicyclo[2.2.2]oct-5-ene (**3**). This route to dioscorone from **3** offers a distinct advantage over two previous nonregiospecific synthetic approaches, one of which involved a hydroboration–oxidation route[6] and a second which utilized an epoxidation, reductive ring opening, oxidation sequence.[7] The introduction of a 3-phenyl substituent did not hinder the course of the reaction, and **4**, R = 80% *exo*-phenyl, afforded **7**, R = 80% phenyl. However, the mixture **5**, R = 75% *endo*-trichloromethyl, was unreactive toward the oxymercuration conditions. It is likely for **5** that, when the trichloromethyl group is endo, the urethane functionality is for steric reasons not in the endo configuration required for coordination of a cationic mercury species with both the olefinic bond and the urethane. Although plausible, this argument fails to account for failure of the remaining *exo*-trichloromethyl isomer to oxymercurate.



3, R = H
4, R = Ph
5, R = CCl_3

6, R = H
7, R = Ph
8, R = CCl_3

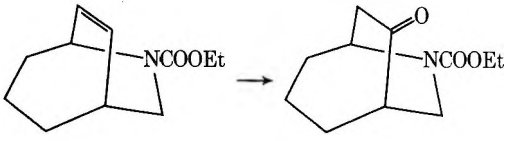


9, R = H
10, R = Ph
11, R = CCl_3

12, R = H
13, R = Ph
14, R = CCl_3

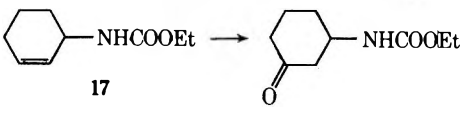
Actinobolamine,[8] reported as a degradation product of actinobolin, has a substituted 6-azabicyclo[3.2.1]octan-3-one skeleton (**12**). Ketofunctionalization of 7-azabicyclo[3.2.1]oct-5-ene (**9**) afforded **12**. The *N*-methyl[9] and *N*-benzyl[10] derivatives of **12** have been synthesized previously from 3,4,5-trimethoxybenzoic acid. Similarly, **10**, R = 85% *exo*-phenyl, afforded **13**, R = 85% *exo*-phenyl. An *exo*-trichloromethyl group did not deter reaction in this ring system and **11** afforded **14** in 75% yield.

The trimethylene bridged urethane **15** was functionalized to ketone **16**. The above examples have all utilized ure-



15 **16**

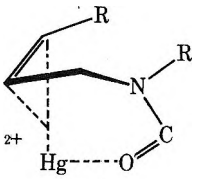
thanes of secondary amines; however, the urethane of a primary allylic amine **17** afforded *N*-carbethoxy-3-aminocyclohexanone (**18**), also in a regiospecific manner.



17 **18**

In the regiospecific additions of HgX and OH to the various β,γ-unsaturated urethanes, the urethane functionality, although exerting an obvious directing effect, remains unchanged at the end of the reactions. It is likely that the

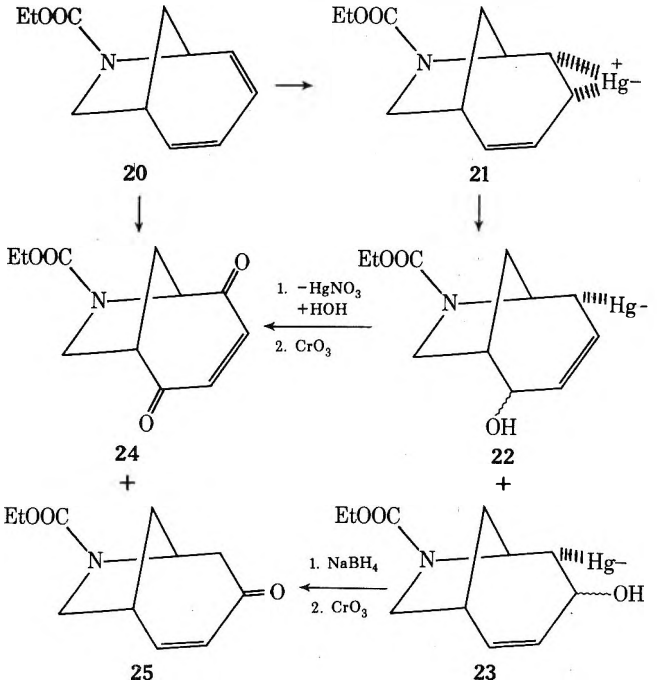
Lewis base group in the urethane, most probably the carbonyl oxygen,[11] is assisting by the formation of an intermediate nonsymmetrically disposed olefin–mercury complex **19** in which the mercuric salt is further complexed with the



19

Lewis base group.[12] Ultimately, reaction of this unsymmetrical complex with external nucleophile is most likely at the more weakly coordinated γ position, since a six-membered ring structure involving coordination of organomercurial with urethane can be maintained. Alternatively, the inductive effect of the nitrogen atom may favor attack at the γ position of a mercurinium ion by external nucleophile.

The ketofunctionalization procedure was also investigated for the bicyclic dienic urethane **20.** Two products, the diketone **24** and the monoketone **25,** were obtained. The formation of both products is explicable in terms of initial mercuration of the olefinic carbon nearest the urethane functionality to give **21.** Nucleophilic attack on the nonsymmetrical mercury complexed species **21** can occur at either of two allylic sites to form **22** and **23.** The allylic mercurial **22** under the reaction conditions can solvolyze with loss of mercury and nitrate ion to form an allylic cation,[13] which following attack by solvent leads to a diol which is oxidized to **24.** The mercurial **23,** following sodium borohydride demercuration, is oxidized to conjugated ketone **25.**



Experimental Section

The nmr spectra were determined on a Varian Associates XL-100-15 spectrometer, operated at 40°. Deuteriochloroform was used as solvent with 2% tetramethylsilane as internal standard (see Table I). Structural assignments were confirmed with the aid of decoupling experiments.

Analysis were performed by Micro-analysis, Inc., Wilmington, Del.

Gas chromatograph analyses (vpc) and collections were performed on a Varian Aerograph A-90-P3 instrument (thermal conductivity detector), using a 2 m × 0.25 in., 20% DC550 on 45/60 Chromosorb W column.

Table I
Nmr Spectra[a,b]

Compd[d]	Registry no.	Spectrum
2	29976-53-2	2.30 (4 H, t, J = 4.2 Hz), 3.60 (4 H, t)
6	37778-51-1	4.53 (1 H, m), 3.68 (1 H, dd), 3.52 (1 H, dd, J = 2, 11.5 Hz), 2.61 (1 H, dd, J = 19, 2.2 Hz), 2.27 (1 H, dd), 2.50 (1 H, m), 1.95 (4 H, m)
7	52003-25-5	4.82 (1 H, br), 5.12 (1 H, d, J = 3 Hz), 2.52–2.92 (2 H, m), 2.35 (1 H, dd, J = 2, 18 Hz), 1.82–2.0 (4 H, m)
12	52003-26-6	4.38 (1 H, br), 3.94–3.22 (2 H, m), 3.20–2.46 (4, H, m), 2.34 (1 H, dd, J = 2, 17 Hz), 1.84–2.22 (2 H, m)
13	52003-27-7	4.96 (0.15, *endo*-phenyl isomer, d, J = 5.0 Hz), 4.74 (0.85 H, *exo*-phenyl isomer, s), 4.52 (1 H, br), 3.20–2.32 (3 H, m), 2.76 (1, H, m), 2.36 (1 H, dd, J = 3, 17 Hz), 2.14–1.52 (2 H, m, J = 12 Hz)[c]
14	52003-28-8	4.48 (1 H, br), 4.55 (1 H, s), 3.30–2.76 (3 H, m), 2.74–2.52 (2 H, m), 2.37 (1 H, dd, J = 12.5, 2 Hz), 1.86 (1 H, m, J = 14 Hz)[c]
16	52003-29-9	4.60 (1 H, br), 3.84–3.40 (2 H, m, J = 12 Hz),[c] 2.86–2.18 (3 H, m, J = 18 Hz),[c] 2.12–1.40 (6 H, m)
18	38031-97-9	5.22 (1 H, br), 3.92 (1 H, br), 2.74 (1 H, dd, J = 14 Hz),[c] 2.60–2.24 (3 H, m), 2.24–1.46 (4 H, m)
24	52003-30-2	6.36 (2 H, s), 4.60 (1 H, br), 3.94–3.72 (2 H, m), 3.41 (1 H, br), 2.74–2.28 (2 H, m)
25	52003-31-3	6.26 (1 H, m, J = 13 Hz),[c] 5.82 (1 H, m, J = 13 Hz),[c] 4.38 (1 H, br), 3.72–3.54 (2 H, m), 3.40–2.84 (2 H, m), 2.60–2.40 (3 H, m)

[a] Reported in δ as parts per million from TMS in $CDCl_3$ solution: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. [b] Chemical shifts of OCH_2CH_3 are not listed. [c] Additional small couplings were noted. [d] Satisfactory elemental analyses were reported for all new compounds listed in the table.

General Procedure for Ketofunctionalization of β,γ-Unsaturated Urethanes. The procedure of Brown and Geoghegan[1] was used for the synthesis of alcohols from representative olefins. Mercuric nitrate in 50:50 tetrahydrofuran–water was substituted for mercuric acetate. Alcohols were oxidized in acetone solution using chromic acid according to established procedure.[14] Reaction conditions and yields of products are given in Table II. No traces of the isomeric β-amino ketones were observed in the expanded spin-decoupled spectra of **2, 6, 7, 12, 13, 14, 16,** or **18.** Gc spectra of **2, 6, 12, 14,** and **18** confirmed the isomeric purity. The β-keto derivative isomeric with **2** has been shown to be stable to the oxidation procedure used in this study and to the thermal gc conditions.[6] Because of the structural similarity of the molecules used in this study, it is thus unlikely that β-keto isomers were formed and then decomposed at some point in the synthetic sequence. Reported product yields represent recovered yields and were not optimized.

***N*-Carbethoxy-3-trichloromethyl-2-azabicyclo[2.2.2]oct-5-ene (5).** A solution of *N*-carbethoxytrichloromethylimine[20] (4.4 g, 20 mmol), cyclohexa-1,3-diene (1.6 g, 20 mmol) and boron trifluoride etherate (0.5 ml) in CCl_4 (200 ml) was stirred at 30° for 72 hr. Acid was removed by washing with water and aqueous sodium bicarbonate. Removal of solvent, extraction of the residue with *n*-heptane, and removal of solvent afforded 4.27 g (71%) of oil, bp 132–134° (0.05 mm). Nmr ($CDCl_3$) indicated 75 ± 3% *endo*-trichloromethyl isomer, δ 4.70 (d, H_{3x}, $J_{3,4}$ = 2.8 Hz), and 25 ± 3% exo isomer, δ 4.32 (dd, H_{3n}, $J_{3n,4}$ = 3.2, $J_{3n,8a}$ = 1.4 Hz).

Anal. Calcd for $C_{11}H_{14}NO_2Cl_3$: C, 44.22; H, 4.71; N, 4.71. Found: C, 44.30: H, 4.93: N, 4.74.

***N*-Carbethoxy-6-trichloromethyl-7-azabicyclo[3.2.1]oct-**

Table II
Results Realized for the Conversion of Representative β,γ-Unsaturated Urethanes into γ-Ketourethanes by the Solvomercuration–Demercuration[a]–Oxidation[b] Procedure Utilizing Mercuric Nitrate

Olefin	Registry no.	g (mmol)	Reaction time, hr	Product ketone	Yield, %	Molecular distillation pot temp, °C (pressure, mm)
1[c]	52003-32-4	1.55 (10)	5.0	**2**	80[d]	160 (0.05)
3[e]	3693-69-4	1.81 (10)	0.2	**6**	87[f]	*g*
4[h]	3693-55-8	0.50 (1.9)	72	**7**	86	179–190 (0.05)
5[i]	52003-33-5	0.50 (1.7)	48	**8**[t]	0	
9[j]	42793-16-8	0.50 (2.6)	48	**12**	79[k]	100–120 (0.1)
10[j]	52003-34-6	0.50 (1.9)	72	**13**	85	160–200 (0.05)
11[l]	52003-35-7	0.38 (1.3)	1.0	**14**	75	110–150 (0.05)
15[m]	40792-14-1	0.50 (2.5)	24	**16**	57	150–180 (0.1)
17[n]	1541-28-2	1.0 (6.2)	24	**18**	57[o]	120–125 (0.07)
20[p]	40792-18-5	1.0 (5.2)	168	24,[q] 25[r]	42[s]	

[a] Reference 1. [b] Reference 14. [c] Prepared from 1,2,3,6-tetrahydropyridine (Aldrich) and ethyl chloroformate. [d] 99% purity by vpc analysis. [e] Reference 6. [f] 2% unreacted starting material by vpc. [g] See ref 5 and 6. [h] 80% *exo*-phenyl, ref 6 and 15. [i] 75 ± 3% *endo*-CCl_3. [j] Reference 16. [k] 10% unreacted **9**. [l] 100% *exo*-CCl_3, mp 93–95° ($CHCl_3$). [m] Reference 17. [n] Reference 18. [o] Contains 10% unreacted **17**, vpc (190°) retention time 3 min, and 90% **18**, vpc retention time 9.5 min. [p] Reference 19. [q] Uv (95% EtOH) λ_{max} 270 mμ (log ε 3.8), 223 (4.2). [r] Uv (95% EtOH) λ_{max} 225 mμ (log ε 4.0). [s] Vpc (200°), **20** retention time (4.5 min, 40%), **24** (retention time 17.6 min, 29%), **25** (retention time 13 min, 23%). [t] Registry no., 52003-36-8.

2-ene (11). Trichloro adduct **5** (1.2 g, 0.4 mmol) and trifluorosulfonic acid (5 drops) in 70 ml of benzene was stirred for 48 hr at 30°. After washing with water to remove acid, drying over $MgSO_4$, and removal of solvent, 1.04 g (87%) of rearranged[16] *exo*-trichloromethyl adduct **11** was formed: mp 84–86°; vpc (2 m × 0.25 in., 5% DC550 on Chromosorb W, 190°, 27 min); ir (CCl_4) 1710 cm^{-1}; nmr ($CDCl_3$) δ 6.25 (1 H, m), 5.58 (1 H, m), 4.58 (1 H, s), 4.38 (1 H, m), 4.20 (2 H, q, J = 7 Hz), 2.90 (2 H, m), 2.45 (2 H, m), 1.83 (1 H, m), 1.25 (3 H, t, J = 7 Hz).

Anal. Calcd for $C_{11}H_{14}NO_2Cl_3$: C, 44.22; H, 4.71; N, 4.71. Found: C, 44.50; H, 4.81; N, 4.59.

Acknowledgment. This research was supported by Grant CA 12020 from the National Institutes of Health.

Registry No.—*N*-Carbethoxytrichloromethylimine, 16723-30-1; cyclohexa-1,3-diene, 592-57-4.

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Substituent Effects on the Regioselectivity of C–H Insertion Arising during Stereospecific Intramolecular Cyclization of 7-Norcaranylidenes

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Received May 9, 1974

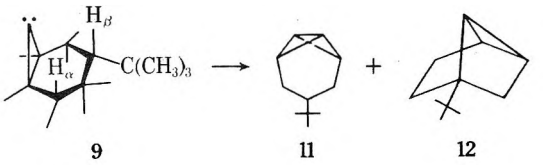
A number of 7,7-dibromo-2-methoxynorcaranes were prepared by addition of dibromocarbene to selected 3-methoxycyclohexenes. The reaction of these dibromides with ethereal methyllithium leads to intramolecular carbenoid insertion with formation of 3-methoxytricyclo[4.1.0.$0^{2,7}$]heptanes and *endo*-2-methoxytricyclo[4.1.0.$0^{3,7}$]-heptanes. The results require that the 7-norcaranylidenes undergo C–H bond insertion *via* that conformation in which the 2-methoxyl substituent is axially disposed. For comparison purposes, the behavior of the *cis*- and *trans*-3-methoxyl- and 3-methyl-7-norcaranylidenes was also examined. To accommodate the high levels of C–H_β reactivity in the 2-methoxyl series, it is proposed that neighboring ether oxygen participation gains importance in an effort to offset developing electron deficiency at C_3. All insertions are necessarily stereospecific and the role of conformational factors on the regioselectivity of these processes is presented. Electronic effects are also important, the 2-methoxyl group deterring attack at the geminal C–H bond because of its electronegativity influence on the bond nucleophilicity.

The capability of organolithium reagents to produce carbenoid intermediates when allowed to react with *gem*-dihalides has been amply documented in recent years.[2] In the specific instance of 1,1-dibromocyclopropanes, the α-bromocyclopropyllithium intermediate or the cyclopropylidene derived therefrom is capable of affording allenes[3] or products of intramolecular capture depending upon the structural elements of the molecule. If a suitably positioned double bond is available, spiropentane formation occurs.[4] In systems where ring opening to an allene is deterred for reasons of excessive product strain and/or lack of a suitable driving force for cyclopropane bond rupture, intramolecular C–H insertion becomes kinetically dominant.[5]

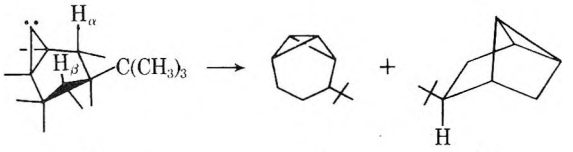
A relevant example is the carbenoid **2**, which has been shown not to experience ring opening to **3** prior to undergoing C–H insertion with formation of **4** and **5**.[5e,6] This finding contrasts markedly with the behavior of dibromide **6**, which reacts with methyllithium to give 1,2-cyclohexadiene (**7**) exclusively;[7] this reactive intermediate undergoes subsequent conversion to dimers and tetramers. Since the related [5.1.0] bicyclic molecule likewise is prone to ring opening (at least partially) with formation of 1,2-cyclooctadiene,[8] it is seen that the reactivity of **2** is somewhat anomalous. As Moore has pointed out,[5e] intermediate **2** is a species which possesses two characteristics not available simultaneously to the [3.1.0] and [5.1.0] bicyclic systems: (1) unlike the higher homolog, conversion to the orthogonal allene is not possible because of the highly strained nature of **3**; (2) unlike the lower homolog, the [4.1.0] carbenoid (the parent 7-norcaranylidene) lacks sufficient ground-state strain to promote ring opening despite the instability of the allene.

As a result of the unique reactivity profile of **2** and 7-norcaranylidenes in general,[5e,f,9] these chemical entities provide a unique opportunity to assess the influence of a number of conventional factors on competitive intramolecular C–H insertion reactions of carbenoids. The situation is illustrated in the case of **2** (shown as **2b** for simplicity in depiction) which very likely exists as a pair of rapidly equilibrating half-chair conformers (**8a** and **8b**).[5e] As with the simpler cyclohexane models, interconversion of these isoenergetic conformational isomers results in interchange of the axial and equatorial environments of the C–H bonds. Inspection of molecular models reveals that all equatorially disposed hydrogens are decidedly too remote from the carbenoid center to permit ready insertion, and therefore that axial C–H bonds are involved during intramolecular cyclization. However, in the parent system, the presumably rapid stereomutation between **8a** and **8b** does not perturb the statistical distribution of one α (H_5 in **8a**, H_2 in **8b**) and one β hydrogen (H_3 in **8a**, H_4 in **8b**) of axial disposition. Evidence has been obtained[5a] that **2** reacts to give a predominance of **4** over **5** (*ca.* 23:1). Thus there exists a sizable kinetic preference for C–H_α insertion in the structurally unbiased carbenoid.

When the conformation of the 7-norcaranylidene is "fixed" by appropriate *tert*-butyl substitution as in **9** and **10**, the H_α/H_β selectivity, equivalent to bicyclobutane *vs.* bicyclopentane formation, undergoes noteworthy modification.[5e] The trans isomer **9** affords a mixture of hydrocarbons **11** and **12** in a ratio of 1:1.5. There is clearly an appreciable enhancement of selectivity toward H_β which is believed[5e] to arise primarily from the added inductive contributions of the *tert*-butyl substituent. Cis isomer **10** in contrast undergoes insertion at relative rates such that bicyclobutane production (**13**) again dominates over that of bicyclopentane **14** by a factor of 22. It would appear on this basis that the *tert*-butyl group in **10** does not affect appreciably the conformation adopted by the unsubstituted compound.



9 11 12

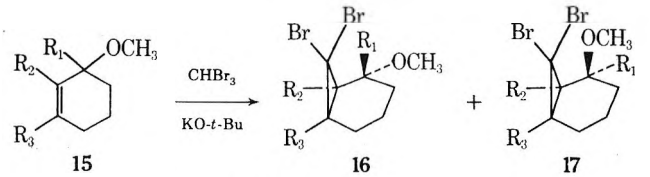


10 13 14

This is of course a rather skeletal assessment of the situation. It appeared that other phenomena which could affect the selectivity of such reactions had to be considered before reasonably accurate mechanistic comprehension of the process was realized. This paper, therefore, describes a study of the regioselectivity of intramolecular $C-H_\alpha/C-H_\beta$ carbenoid insertion reactions in 7-norcaranylidenes possessing methoxyl and methyl groups at C_2 and C_3 (*cf.* 8 for numbering). The perturbations introduced by the electronegative substituent were expected to be rather large yet not necessarily similar in direction to those of the methyl (or *tert*-butyl) substituent, depending upon inductive and resonance contributions which it remained to evaluate.

Results

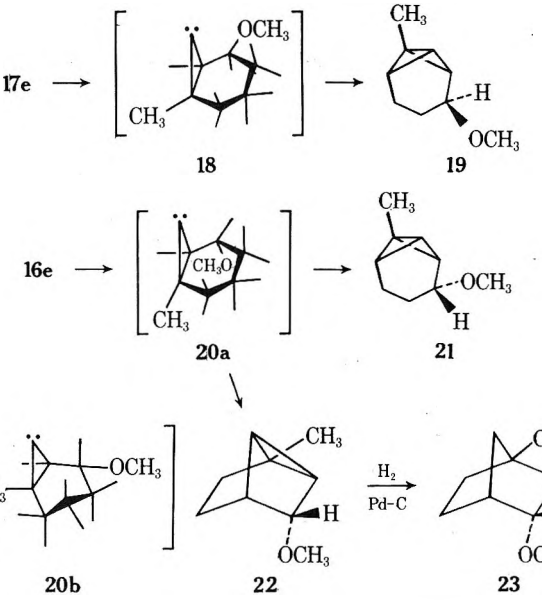
Preparation of the compounds selected for study was effected by a method modeled on the synthesis of dibromide **1**, bolstered by the observation of Seyferth and Mai[10] that high levels of stereoselectivity were realized upon reaction of 3-methoxycyclohexene with phenyl(bromodichloromethyl)mercury. In our hands, treatment of the variously substituted methoxy olefins **15** with dibromocarbene generated from bromoform and potassium *tert*-butoxide likewise gave rise in each case to one major product by far. In no instance was greater than 5% of cis isomers **17** formed. The structural assignments to **16** were made by analogy to those of Seyferth and Mai in the dichloro series and are supported by extensive pmr data (Table I). Of the seven examples studied, three (**16a, 16d,** and **16e**) are of primary importance in the present context. The four deuterated substrates were required for the program described in another paper[11] and are included herein because they demonstrate the reproducibility of the insertion ratios.



15 16 17

a, $R_1 = R_2 = R_3 = H$
b, $R_1 = D$; $R_2 = R_3 = H$
c, $R_1 = R_2 = H$; $R_3 = D$
d, $R_1 = R_3 = H$; $R_2 = CH_3$
e, $R_1 = R_2 = H$; $R_3 = CH_3$
f, $R_1 = D$; $R_2 = H$; $R_3 = CH_3$
g, $R_1 = H$; $R_2 = D$; $R_3 = CH_3$

Reaction of **16e–17e** (95:5)[12] with methyllithium in ether at −30° afforded in 68% yield a mixture consisting chiefly of **19** (5%), **21** (67%), and **22** (28%). These products were separated by preparative vpc methods and identified as the compounds indicated on the basis of their spectral properties (Table II) and chemical evidence. For example, the very characteristic pmr features of **22,** particularly the low-



field quartet ($J_{1,2}$ = 2.5 and $J_{2,3}$ = 7.5 Hz) due to the >CHO– proton, characterizes the substance as an *endo*-2-methoxytricyclo[4.1.0.$0^{3,7}$]heptane derivative.[13] Independent confirmation of structure **22** was derived from catalytic hydrogenation over Pd/C in ethanol at 1 atm exclusively to *endo*-1-methyl-3-methoxynorbornane (**23**). Tricycloheptanes **19** and **21** show complex pmr patterns which are strikingly similar to those of related molecules in the high-field region.[5f,9,14] In particular, both ethers display multiplets (1 H each) at approximately δ 2.4 and 2.1 assignable to the two dissimilar "wing" protons and in the δ 1.0 region due to the bridgehead hydrogen. The stereochemistry of **19** and **21** follows from the recognized stereospecificity of such carbenoid insertion reactions;[5e,9b,c] the epimeric relationship of the two isomers is recognized spectroscopically by the great similarity of their pmr spectra except for the C_1 methyl singlet signals (in C_6D_6) which in **19** appears δ 0.04 upfield to the corresponding absorption in **21.** As expected for the tricyclo[4.1.0.$0^{2,7}$]heptane nucleus, catalytic hydrogenation of **21** under conditions identical with those utilized for **22** led to the consumption of 1.91 equiv of hydrogen with formation of four products identified as $C_9H_{18}O$ isomers by accurate mass spectral measurements.

These results establish that 7-norcaranylidene **18** undergoes intramolecular insertion chiefly into H_α. Clearly it is not possible to rule out completely the H_β insertion pathway because of the low concentration of **17e** in the dibromide mixture. However, because **17e** is present to the extent of 5% in the starting material and **19** comprises 5% of the total reaction mixture, internal consistency requires that a high preference for bicyclobutane formation be operative. Such regioselectivity is not encountered with **20,** which is seen to exhibit a H_α/H_β selectivity of only 2.4. Strikingly, attack at the $C-H_\alpha$ bond adjoining the methoxyl substituent does not operate.[15] Also, in that half-chair conformation (**20b**) in which the methoxyl group is equatorially disposed, the remaining H_α is likewise oriented in the equatorial plane and consequently lacks adequate proximity for reaction with the carbenoid center. Moreover, were the lone axial H_β present in conformation **20b** to undergo intramolecular transfer to C_7, ether **24** would result and this is not

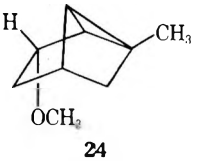


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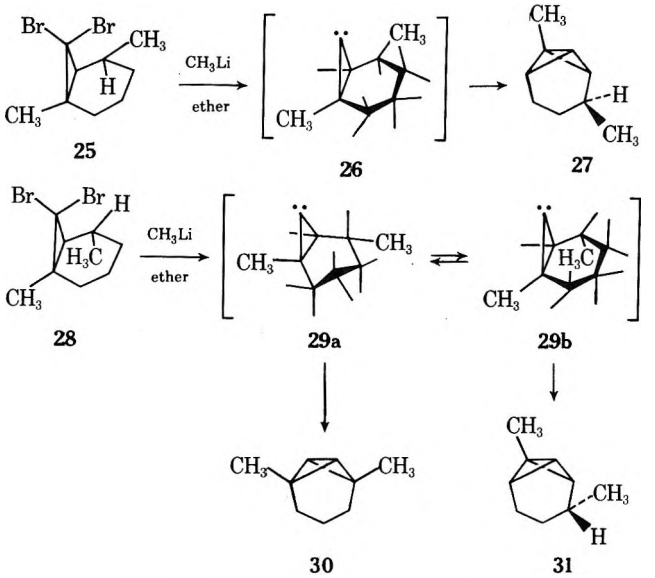
Table I
Physical Data for the 7,7-Dibromo-2-methoxybicyclo[4.1.0]heptanes

Compd	Bp, °C (mm)	Pmr, δ (CDCl₃, 60 MHz)	Anal. data
16a	97–107 (0.8)	3.44 (s, 3, $-OCH_3$), 3.44–3.10 (m, 1, >CHO–), and 2.33–1.00 (m, 8)[a]	Calcd for $C_8H_{12}Br_2O$: C, 33.84; H, 4.26. Found: C, 33.79; H, 4.30
16b	97–107 (0.8)	3.45 (s, 3, $-OCH_3$) and 2.20–0.92 (m, 8)	For $C_8H_{11}D^{79}Br_2O$: calcd *m/e* 282.9319; found 282.9313
16c	90–92 (0.7)	3.44 (s, 3, $-OCH_3$), 3.44–3.10 (m, 1), and 2.33–1.00 (m, 7)	For $C_8H_{11}D^{79}Br_2O$: calcd *m/e* 282.9319; found 282.9313
16d	96–100 (0.8)	3.52–3.18 (m, 1), 3.38 (s, 3), 2.25–0.75 (m, 7), and 1.35 (s, 3)[b]	Calcd for $C_9H_{14}Br_2O$: C, 36.27; H, 4.74; Br, 53.62. Found: C, 36.35; H, 4.80; Br, 53.64
16e	*c*		
16f	*c*		
16g	*d*		

[a] For **17a** (~3%): δ 3.53 (s, $-OCH_3$). [b] For **17d** (~5%): δ 3.28 (s, $-OCH_3$). [c] See ref 9b. [d] See ref 9c.

seen. These data taken together rule out the possibility that **20** undergoes intramolecular cyclization *via* conformer **20b**. Rather, **21** and **22** must be formed by competitive attack at the two available sites in **20a**.

That the methoxyl substituent is capable of a high level of control of product distribution is seen from the behavior of the related methyl-substituted dibromides **25** and **28**. In this instance,[9b] Zon realized vpc separation of the isomers and treated these substances separately with methyllithium in ether. As with **18**, carbenoid **26** exhibited a high level of regiospecificity for H_α insertion. Intermediate **29** is also characterized by a pronounced specificity for attack at $C-H_\alpha$ bonds. The larger proportion (90%) of bicyclobutane product arising from conformer **29a** indicates that the methyl group is fostering reactivity at C_2. Despite this, the assumedly less stable conformer **29b** is able to compete in the product-forming manifold, affording as it does 10% of **31**.

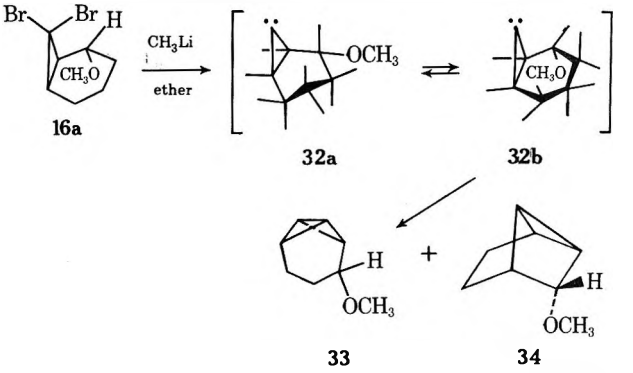


On this basis, it would seem that the cis carbenoid intermediates **18** and **26** compare favorably in their reactivity, perhaps as a consequence of the fact that the C_2 substituent is as remote as possible from the carbenoid center and that the remaining C_2–H bond resides trans to C_7, thereby rendering it unavailable for insertion. Neither entity gives evidence of C_3-H_β attack.

Utilizing the reactivity preferences of parent carbenoid **8** as a model, we see the marked H_α selectivity exhibited by dimethyl derivative **29** to be quite normal. What was somewhat unexpected was that conformer **29b** possesses a sufficient reactivity advantage to compete with **29a** in the product-forming step. If the assumption is allowed that the supportive electronic capabilities of methyl and *tert*-butyl groups are comparable,[16] then the reactivity of **29a** in proceeding to **30** should be about 30-fold more rapid than the **29b** → **31** cyclization. The results show that the partitioning is approximately 9:1 and that **29b** has therefore a somewhat greater reactivity than anticipated. A more important comparison is that of the behavior of the *trans*-2-methoxyl (**20**) and *trans*-2-methyl (**29**) carbenoid intermediates. It is obvious that there are important differences in product distribution, the main ones being that conformer **20b** is unreactive and that **20a** affords considerable $C-H_\beta$ insertion while **29a** and **29b** give no evidence of this. We shall return to these points later in the discussion.

When the deuterated isomer pairs **16f–17f** and **16g–17g** were exposed to methyllithium in ether, behavior nearly identical with that of the unlabeled dibromides was observed (see Experimental Section).

Attention was next turned to the somewhat simpler system **16a–17a** (97:3) which, when treated as before with methyllithium, underwent cyclization to give chiefly (89%) the tricyclic ethers **33** and **34**. The relative distribution of



these products was 23 and 77%, respectively, corresponding to a significant increase in H_β reactivity (H_α/H_β = 0.30). Structural assignment to **34** followed from its identity with authentic samples.[13a,b,17] The pmr spectrum of **33** is sufficiently similar to those of **19** and **21** to define the molecule

Table II
Physical Data for the Major Products of Carbenoid Insertion

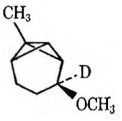
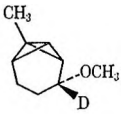
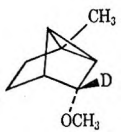
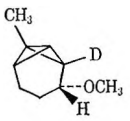
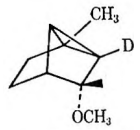
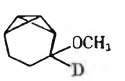
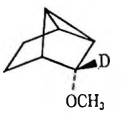
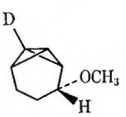
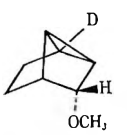
Starting dibromide	Vpc column employed for separation (°C)[a]	Products	Registry no.	Relative ratio, %	Pmr, δ (C_6D_6, 60 MHz)	Anal. data
16e–17e (95:5)	C (100)	**19**		5	3.29–2.99 (m, 1, H_3), 3.20 (s, 3, $-OCH_3$), 2.54–2.23 (m, 1, H_2 or H_6), 2.23–1.93 (m, 1, H_2 or H_6), 1.81–1.23 (m, 4, methylenes), 1.44 (s, 3, $-CH_3$), and 1.23–0.89 (m, 1, H_7)	For $C_9H_{14}O$: calcd *m/e* 138.1045; found 138.1046
		21		67	3.39–2.99 (m, 1), 3.20 (s, 3), 2.54–2.23 (m, 1), 2.23–1.93 (m, 1), 1.81–1.23 (m, 4), 1.48 (s, 3), and 1.23–0.89 (m, 1)	Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.39; H, 10.18
		22		28	3.79–3.55 (dd, J = 7.5 and 2.5 Hz, 1, H_2), 3.01 (s, 3, $-OCH_3$), 2.71–2.35 (m, 1, H_3), 1.99–1.56 (m, 6), and 1.00 (s, 3, $-CH_3$)	Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.07; H, 10.22
16f–17f (95:5)	C (100)		51897-63-3	3.5	Spectrum similar to that of **19** with the exception that the absorption due to H_3 is lacking and H_2 is seen as an apparent quartet (J = 2–3 Hz)	For $C_9H_{13}OD$: calcd *m/e* 139.1107; found 139.1106
			51897-64-4	69.5	Spectrum similar to that of **21** but with H_3 absorption lacking and the appearance of H_2 as a triplet (J = 3.5 Hz)	For $C_9H_{13}OD$: calcd *m/e* 139.1107; found 139.1106
			38452-10-7	27	3.05 (s, 3), 2.52 (m, 1), 2.39–1.54 (m, 6), and 1.03 (s, 3).	For $C_9H_{13}OD$: calcd *m/e* 139.1107; found 139.1105
16g	A (100)		51371-82-5	66	3.40–3.00 (m, 1), 3.17 (s, 3), 2.08 (br s, 1), 1.85–1.20 (m, 4), 1.49 (s, 3), and 1.13 (br s, 1)	For $C_9H_{13}OD$: calcd *m/e* 139.1107; found 139.1105
			51371-83-6	34	3.62 (d, J = 7 Hz, 1), 3.02 (s, 3), 2.50 (v br d, $J \approx 7$ Hz, 1), 2.3–1.4 (m, 5), and 1.02 (s, 3)	For $C_9H_{13}OD$: calcd *m/e* 139.1107; found 139.1105
16a–17a (97:3)	A (115)	**33**		23	3.30–3.00 (m, 1, H_3), 3.17 (s, 3, $-OCH_3$), 2.50 (apparent quintet, $J \approx 3$ Hz, 1, H_2), 2.37–2.03 (m, 1, H_6), and 1.87–0.98 (m, 6)	For $C_8H_{12}O$: calcd *m/e* 124.0888; found 124.0890
		34		77	3.63 (dd, J = 7.3 and 3.5 Hz, 1, H_2), 3.01 (s, 3, $-OCH_3$), 2.74–2.37 (br d, $J \approx 7$ Hz, 1, H_3), and 2.22–1.17 (m, 7)	Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 76.89; H, 9.70
16b–17b (97:3)	D (62)		51838-75-6	24	3.17 (s, 3), 2.53 (apparent quartet, $J \approx 3$ Hz, 1), 2.37–2.03 (m, 1), 1.56 (apparent t, $J \approx 3$ Hz, 2), and 2.00–0.95 (m, 4)	For $C_8H_{11}DO$: calcd *m/e* 125.0951; found 125.0949
			38452-09-4	76	3.04 (s, 3), 2.57 (br s, 1), and 2.23–1.18 (m, 7)	For $C_8H_{11}DO$: calcd *m/e* 125.0951; found 125.0952
16c–17c (97:3)	D (62)		51897-65-5	21	3.50–3.15 (m, 1, H_3), 3.32 (s, 3, $-OCH_3$), 2.70–2.50 (m, 1), 2.37 (v br s, 1), and 2.05–1.10 (m, 5, H_7 and methylenes)[b]	For $C_8H_{11}DO$: calcd *m/e* 125.0951; found 125.0952
			38452-08-3	79	3.63 (dd, J = 7.0 and 3.7 Hz, 1), 3.03 (s, 3), 2.55 (br d, $J \approx 7$ Hz, 1), and 2.34–1.34 (m, 6)	For $C_8H_{11}DO$: calcd *m/e* 125.0951; found 125.0953

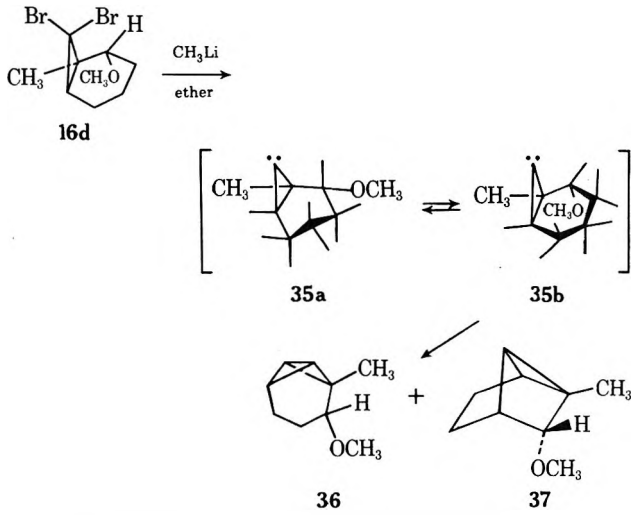
Table II
(Continued)

Starting dibromide	Vpc column employed for separation (°C)[a]	Products	Registry no.	Relative ratio, %	Pmr, δ (C_6D_6, 60 MHz)	Anal. data
16d–17d (95:5)	D (62)	**36**		17	3.20 (s, 3), 3.30–3.00 (m, 1), 2.21 (apparent quintet, 1), 1.75–1.00 (m, 6), and 1.15 (s, 3)	For $C_9H_{14}O$: calcd *m/e* 138.1045; found 138.1046
		37		83	3.45 (d, J = 7.0 Hz, 1), 3.07 (s, 3), 2.56 (br d, $J \approx 7$ Hz, 1), 2.20–1.10 (m, 6), and 1.20 (s, 3)	Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.00; H, 10.36

[a] See ref 37 for identification of the various columns. [b] $CDCl_3$ solvent.

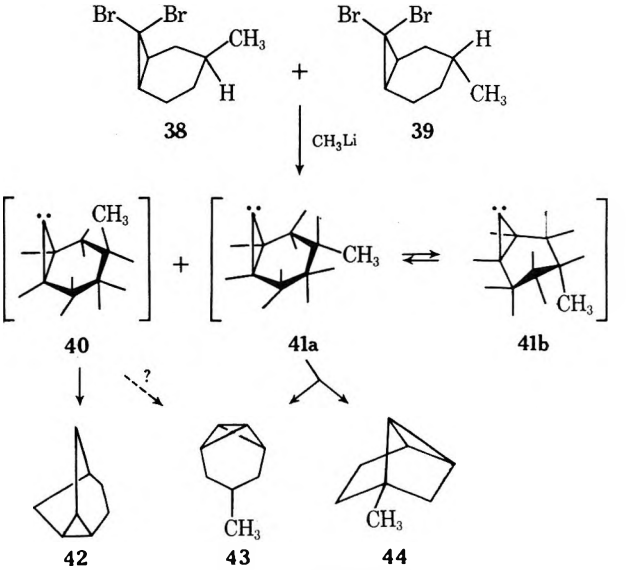
as 3-methoxytricyclo[4.1.0.0^{2,7}]heptane. Further corroboration was derived from the differently deuterium-labeled products obtained by cyclization of **16b–17b** and **16c–17c**, which exhibited spectra suitably modified to accommodate the site of isotopic substitution (Table II). The chemical reactivity of **16a** (the product ratio is not expected to be influenced significantly by the presence of 3% of **17a**) indicates again that C–H bond insertion operates only from that carbenoid conformer (**32b**) in which the methoxyl group is axial. Another interesting aspect of this experiment is that C–H$_\beta$ insertion dominates despite the absence of alkyl substitution at C_3. We therefore needed some basis on which to rationalize this rather low level of H$_\alpha$/H$_\beta$ regioselectivity and also to explain the apparent crossover in preferred C–H insertion which obtains upon placement of a methyl group at C_6 as in **20a**.

With these goals in mind, dibromide **16d** was prepared (95% purity, the remainder being **17d**) and subjected to the action of methyllithium. One might naively expect that positioning of a methyl group at the bridge position adjacent to the methoxyl function might make it less comfortable than usual for the oxygen-bearing substituent to be equatorially disposed and thereby induce a higher proportion of **35b**. At issue was whether increased alkyl substitution of the cyclopropane ring in this fashion would alter the insertion selectivity of the carbenoid. In actual fact, the cyclization of **16d** gave **36** and **37** with the bicyclopentane heavily

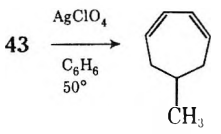


dominating (17:83). The H$_\alpha$/H$_\beta$ selectivity (0.20) observed for **35b** consequently parallels rather closely that exhibited by **32b** (0.30) but is opposite in direction from the reactivity of **20a** (2.4). We infer from these results that the half-chair conformations adopted by **32b** and **35b** are quite similar. The methyl group in **35b** may cause some distortion in a way which moves H_3 toward the C_7 carbenoid center, but the impact of this conformational change is not felt because the methoxyl substituent inhibits competitive insertion into the C_2–H bond. If the same twisting effect operates in **20a**, the C_5 carbon is compressed closer to C_7 and an enhanced selectivity of insertion into the C–H$_\alpha$ bond can be expected to result. We of course do not have a way of assaying this conformational interpretation directly, but note only that dimethyl carbenoid **29b** gives every indication of operating under similar control (H$_\alpha$ insertion only).

Insofar as the reactivity consequences of C_3 substitution are concerned, the behavior of the inseparable mixture of cis and trans dibromides **38** and **39** (57:43)[5e] serves to denote the effect of methyl substitution. When treated with methyllithium, the three hydrocarbons **42** (60%), **43** (28%), and **44** (12%) were obtained. Tricyclo[2.2.2.0^{2,6}]octane(**42**)

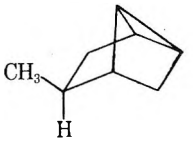


was identified on the basis of its pmr features and the identity of its infrared spectrum and melting point with those of the known compound.[18] Structural assignment to **43** is founded chiefly upon its characteristic pmr spectrum and facile Ag(I)-catalyzed rearrangement[19] to 6-methyl-1,3-cycloheptadiene (**45**). Tricyclic system **44** displays a sharp methyl singlet at δ 1.12 and a multiplicity pattern for the remaining protons very similar to that of **12**.[5e,20] Accordingly, the methyl-substituted carbon must be tertiary, an observation which requires carbenoid insertion into the C–H bond formerly at that site.

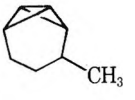


45

An interesting aspect of these product studies is that the major hydrocarbon is derived from intramolecular insertion of the cis carbenoid into its methyl group. Although this process enjoys a threefold statistical advantage over comparable pathways, it requires the intervention of the destabilized conformation **40**. No reaction from that conformational isomer of **40** possessing an equatorially oriented methyl substituent (leading to **46a** or **46b**) was detected.



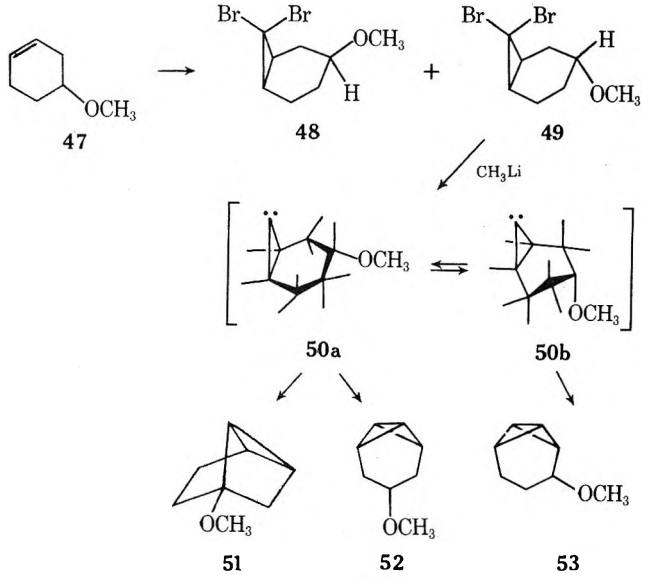
46a



46b

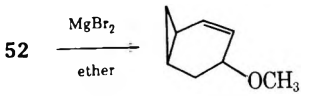
That **40** undergoes no H_α insertion cannot be stated unequivocally. However, mass balance considerations necessitate that if this transformation operates it be quite inefficient. All of the products from trans carbenoid **41** are accounted for in a straightforward way in terms of its more stable conformer **41a**. In marked contrast to the cis series, where the axial methyl conformer commands a large kinetic advantage, **41b** is not a significant product-determining intermediate. Assuming that all of **43** arises directly from **41a**, its H_α/H_β reactivity profile is seen to be 2.3. This result shows that **41a** exhibits, as a result of suitable methyl labeling, a tenfold greater capability for H_β insertion than parent carbenoid **8**. The directing effect of methyl is not, however, as large as that of *tert*-butyl, where H_β insertion now actually predominates (compare **9** for which H_α/H_β = 0.66[5e]).

Reaction of 4-methoxycyclohexene (**47**) with dibromocarbene gave rise to a separable mixture of **48** (37%) and **49**



47 **48** **49** **50a** **50b** **51** **52** **53**

(63%). Exposure of **48** to methyllithium led to consumption of the dibromide without formation of volatile products isomeric with the carbenoid formulation. Under identical conditions, **49** was transformed into a mixture of **51** (71%), **52** (22%), and **53** (7%). Identification of **51** was based on its pmr spectrum, which lacks a >CHO– signal and can otherwise be accommodated only by the indicated tricyclic formulation (see Experimental Section). Ethers **52** and **53** proved inseparable under the many vpc conditions examined. However, treatment of this isomer mixture with a small amount of ethereal magnesium bromide resulted in essentially exclusive rearrangement of **52** to **54**. The recovered unreacted **53** proved identical with an authentic sample.[9b] In agreement with its 2-norcarene structure, **54** exhibits two widely separated olefinic absorptions at δ 6.10–5.90 and 5.75–5.55. The low-field signal due to H_2 is an expected multiplet,[21] but the presence of a methoxyl group at C_4 causes the H_3 absorption to appear as a doublet with J = 10 Hz. The absence of spin–spin interaction between H_3 and H_4 denotes an approximate 90° dihedral angle relationship between these protons. Such geometry could be attained by adoption by the trans isomer of a pseudo-boat conformation, or as a consequence of the cis isomer in a pseudo-chair conformation. Consequently, the stereochemistry of **54** remains a moot question. Notwithstanding, the location of the methoxyl substituent at C_4 in this norcarene requires the precursor tricycloheptane to be **52**. Consequently, intermediate **50a** is characterized by an H_α/H_β reactivity ratio of 0.31 while **50b** cyclizes chiefly with bicyclobutane formation (H_α insertion).



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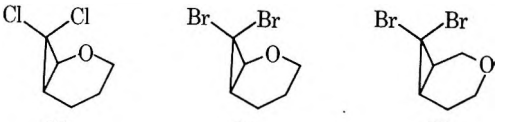
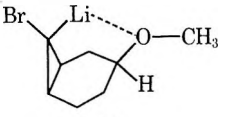
Discussion

In contrast to carbenoid systems of less novel structure, 7-norcaranylidenes are seen to exhibit a richly varied reactivity pattern which is highly sensitive to conformational and substituent effects. As one example, we cite the mandatory requirement for transfer of axial hydrogen such that insertions necessarily occur with retention of configuration. Perhaps the most unique transformation, the conversion of **38** to tricyclic hydrocarbon **42**, establishes that axially oriented 3-methyl groups also are sufficiently proximate to C_7 to allow for ready C–H insertion. Insofar as the inability of the related methoxyl derivative **48** to achieve intramolecular cyclization is concerned, it is recognized that ether oxygen confers a marked stabilizing effect on α-haloalkyllithium compounds. Köbrich[2a,22] and others,[23] for instance, have reported extensively on the chemical properties of tetrahydrofuran-stabilized lithium carbenoids. The fact that the 2-oxabicycloheptyl systems **55** and **56** undergo halogen–metal exchange predominantly at the endo site upon reaction with methyllithium at low temperatures to afford *stable* lithium carbenoids similarly attests to a stabilizing coordinative interaction. The behavior of **57** appears entirely analogous.[24,25] We rationalize on this basis that the cis-oriented methoxyl oxygen in **48** directs the course of the exchange reaction[26] to provide **58**, which because of intramolecular solvation of lithium by neighboring oxygen is deterred from further reaction of the customary type.



55 **56** **57**



58

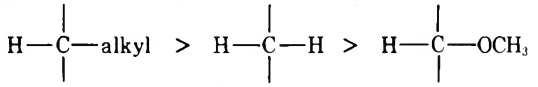
The question now arises as to why the several *trans*-2-methoxyl substituted carbenoids studied, *i.e.*, **20**, **32**, and

35, exhibit the proclivity for C–H insertion only from that conformation in which the group at C_2 is oriented axially.[27] This finding attests to the greater reactivity of the axial conformer, but unfortunately provides no information on the question of which conformer enjoys greater relative stability. Since carbenoids and carbenes are, generally speaking, unstable energetic species and the reactions in which they engage rather strongly exothermic,[2b] the competing transition states for C–H_α and C–H_β insertion might be expected[28] to be somewhat insensitive to product stability and governed to a greater extent by other factors such as proximity considerations, angle distortions, C–H bond nucleophilicities, and the like. However, it need not follow that precisely the same mechanism operates during the course of H_α and H_β insertion. Owing to geometric restrictions, both types of hydrogen must experience intramolecular abstraction by way of triangular transition states[29] rather than *via* theoretically favored linear approach.[30] If the assumption is now made that biradicals subsequently intervene, then the causative factors underlying the prototypical preferential H_β abstraction within **32b** (H_α/H_β = 0.30) to the exclusion of H_α abstraction within **32a** seeks explanation. Dreiding molecular models show that the proximity of C_7 to H_α and H_β in either conformer is rather closely balanced; consequently, to focus attention on steric factors is unwarranted.

The recognized ability of oxygen and other heteroatoms to stabilize an incipient free radical is now universally attributed to delocalization factors which give rise to polar contributions.[31] That such polar effects are important in carbene chemistry has been amply documented, especially for ether oxygen,[32] and is further substantiated in 7-norcaranylidene systems by the behavior of **50a**. Thus, to the

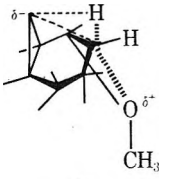
extent that factors which stabilize free radicals also stabilize the transition state in a hydrogen atom transfer reaction,[33] H_α abstraction by **32a** should be favored. However, such reactivity is not encountered.

A possible rationalization is that oxygen resonance stabilization can only fully materialize when the geminal C–H bond is extensively broken. Should H_α abstraction in 7-norcaranylidenes proceed along a reaction coordinate wherein the transition state is reached early *without extensive C–H bond stretching*, C–H bond nucleophilicities would be expected to become the dominant controlling reactivity factor. H_α insertion adjacent to a methoxyl group would thereby be disfavored. On the basis of electronegativity considerations alone, the following H_α reactivity order is expected. The behavior of all 7-norcaranylidenes exam-



ined to date conform to this working hypothesis, the apparent frustration of thermodynamics arising because of the reactant-like nature of the activated complex, where cationic effects are less prevalent than inductive influences.

We can account for the role played by the axial 3-methoxyl group in promoting high levels of H_β insertion by assuming that such transition states arrive later in the reaction profile. Greater C–H bond stretching and a decreased resemblance of the transition state to the reactant now obtain. It is known from studies on the solvolysis of ether oxygen-containing sulfonate esters that the capability of divalent oxygen to function as a neighboring group in carbonium ion reactions operates at a high level.[34] This is particularly so when three-membered cyclic oxonium ions are produced as intermediates. Given that the carbenoid center in 7-norcaranylidenes is electrophilic in character, the act of C–H_β insertion will incur in its transition state a significant quantity of electron deficiency in the carbon atom bearing the hydrogen. The ability of methyl and *tert*-butyl groups to supply electron density to the carbon under siege and thereby modify the normal reactivity order has already been commented upon. Given this electronic state of affairs and the conformation now recognized to be favored for such reactions, it is entirely possible that C–H_β reactivity is enhanced by "backside" assistance provided by the axial methoxyl substituent. As represented in **59**, the develop-



59

ment of epioxonium characteristics by trans diaxial involvement of methoxyl oxygen could reasonably increase the normal levels of C–H_β nucleophilicity. Interestingly, carbenoids in which the methoxyl group is equatorial and unable to participate in this way exhibit little or no propensity for C–H_β insertion. This anchimeric assistance by neighboring methoxyl is reminiscent of the effects encountered in radical-chain halogenations of certain alkyl bromides and chlorides where anomalously high reactivity and product stereochemistry control have been attributed to intervention of bridged free-radical intermediates involving the σ-bonded halogen atom.[35] Finally, the H_α/H_β reactivity order encountered in the cyclization of **50b** is restored to a value greater than unity presumably as a result of assistance by the neighboring axial 4-methoxyl of hydrogen abstraction at both sites (not necessarily to equal extents). The product distribution is commensurate with this analysis.[36]

Experimental Section

All boiling points are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 137 spectrophotometer and proton magnetic resonance spectra were recorded with Varian A-60A and Joelco MH-100 instruments. Apparent splittings are given in all cases. Mass spectra were obtained with a AEI-MS9 instrument at an ionizing potential of 70 eV. Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

Preparation of the 3-Methoxycyclohexenes. Generalized Procedure. A solution of 75.0 g (0.67 mol) of 2-methylcyclohex-1-en-3-ol in 170 ml of anhydrous dimethylformamide was added dropwise under nitrogen to a mechanically stirred suspension of sodium hydride (56.4 g, 1.34 mol) in the same solvent (450 ml). After complete addition, the mixture was stirred for 1.5 hr at 40° and cooled in an ice bath before a solution of methyl iodide (400 g, 2.8 mol) in dimethylformamide (100 ml) was added at a rate such as to keep the temperature below 15°. The resulting slurry was stirred overnight at 25°, water (300 ml) was introduced with ice cooling, and the entire mixture was shaken with pentane (750 ml) and more water (900 ml) after being transferred to a separatory funnel. The separated aqueous layer was extracted with pentane (400 ml) and the combined pentane layers were washed with water (3 × 150 ml) before drying. Solvent was removed by distillation at atmospheric pressure. Distillation of the residue gave 73.0 g (86%) of **15d** as a colorless, fragrant oil, bp 91–100° (92 mm). Preparative vpc (column A,[37] 94°, 60 ml/min He) afforded analytically pure material: pmr δ_{TMS} ($CDCl_3$) 5.70–5.45 (m, 1, olefinic), 3.65–3.45 (m, 1, >CHO–), 3.36 (s, 3, $-OCH_3$), 1.75 (br s, 3, $-CH_3$), and 2.25–1.35 (m, 6, methylenes).

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.06; H, 11.32.

Dibromocarbene Additions. Typical Procedure. A solution

of 56 g (0.5 mol) of 3-methoxy-1-cyclohexene[38] in 100 ml of pentane was added to a mechanically stirred suspension of potassium *tert*-butoxide (60.5 g, 0.54 mol) in pentane (750 ml) which was precooled and maintained at −30° under a nitrogen atmosphere. A solution of bromoform (126.5 g, 0.5 mol) in pentane (100 ml) was then introduced to this suspension during 3 hr while keeping the reaction mixture at −30°. Following complete addition, the mixture was stirred at room temperature for 5 hr and hydrolyzed by the addition of water (250 ml). The separated organic layer was washed with water (250 ml), dried, and concentrated. Short-path vacuum distillation of the residue gave 92 g (65%) of a pale yellow oil, bp 97–107° (0.8 mm). The nmr spectrum of this material indicated that it contained 7% unchanged methoxycyclohexene and **16a–17a** (97:3). Preparative vpc purification (column B, 132°, 70 ml/min He) gave an analytically pure sample (see Table I).

Prototypic Cyclization Procedure. A magnetically stirred solution containing 20 g (0.07 mol) of **16a–17a** (97:3) in 125 ml of anhydrous ether was precooled to −10° and maintained at approximately this temperature under a nitrogen atmosphere during dropwise addition of a solution of methyllithium in ether (50 ml of 1.6 *M*, 0.08 mol) over a 2-hr period. Upon complete addition, the orange reaction mixture was stirred at room temperature for 1 hr before cooling to 5° and cautious addition of water (125 ml). The separated organic layer was washed with saturated aqueous sodium chloride solution (125 ml), dried, and carefully concentrated. Bulb-to-bulb distillation of the residue at 60° (1 mm) gave 4 g (46%) of a colorless liquid, vpc analysis of which (column A,[37] 115°, 60 ml/min He) indicated it to contain two major components (89% of total multicomponent mixture) in a relative ratio of 77:23. These products were separated and purified by preparative vpc techniques and characterized spectroscopically (Table II).

endo-**1-Methyl-3-methoxynorbornane (23).** A magnetically stirred suspension of 10% Pd on carbon (14 mg) in absolute ethanol (6 ml) was treated with hydrogen (1 atm) until uptake ceased. A solution of **22** (44 mg, 0.3 mmol) in absolute ethanol (4 ml) was injected and rapid uptake of hydrogen was noted. After 30 min, 1.08 equiv of hydrogen was consumed and the mixture was stirred for an additional 1 hr, filtered, diluted with water (6 ml), and then washed four times with 0.75-ml portions of pentane. Preparative vpc isolation of the sole detectable product (column D,[37] 100°, 120 ml/min He) in the combined pentane washings led to collection of 9.5 mg (22%) of **23**: pmr δ_{TMS} (C_6D_6) 3.62 (d of t, $J_{2exo,3exo}$ = 9.5, $J_{2endo,3exo}$ = 4.5, $J_{3exo,4}$ = 4.5 Hz, 1, exo H_2),[39] 3.08 (s, 3, $-OCH_3$), 2.23 (br s, 1, H_4), 2.13–1.00 (m, 8), and 1.02 (s, 3, $-CH_3$).[39]

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.25; H, 11.49.

Hydrogenation of *syn*-3-Methoxy-1-methyltricyclo[4.1.0.0^{2,7}]heptane (21).[40] A 99-mg sample of **21** in absolute ethanol (10 ml) containing 10% Pd on carbon (32 mg) was reduced in essentially the same manner as described above. The consumption of 1.91 equiv of hydrogen was realized in 30 min. Preparative vpc (column D,[37] 100°, 75 ml/min He) led to collection of the four components: A (20 mg), B (5 mg), and a mixture (owing to their proximate retention times) of C and D (5 mg). These were identified as $C_9H_{18}O$ isomers by accurate *m/e* measurements and by pmr data: for A, δ_{TMS} (C_6D_6) 3.21 (s, 3, $-OCH_3$), 2.85–2.30 (m, 1, >CHO–), 2.30–1.85 (m, 1), 1.85–0.80 (m, 7), 1.09 (br s, 3, $-CH_3$), and 0.91 (br s, 3, $-CH_3$); for B, δ_{TMS} (C_6D_6) 3.21 (s, 3, $-OCH_3$), 3.20–2.75 (m, 1, >CHO–), 2.20–0.70 (m, 8), and 0.90–0.70 (m, 6, two $-CH_3$); for C + D, δ_{TMS} (C_6D_6) 3.22 and 3.18 (two s of approximately equal intensity, 3, two $-OCH_3$), 3.45–2.80 (m, 1, >CHO–), 2.20–0.70 (m, 8), and 1.00–0.70 (m, 6, two $-CH_3$).

Cyclization of *cis*- and *trans*-7,7-Dibromo-3-methylnorcarane (38 and 39). Treatment of 10.0 g of a 57:43 mixture of **38** and **39**[5e] dropwise with 25 ml of 1.6 *M* methyllithium in 50 ml of ether at −20° as described above gave a pale yellow liquid, vpc analysis (column A,[37] 80°, 70 ml/min) of which showed three components in the ratio 12:28:60.

The major component was identified as **42**: mp 87–89° (lit.[18] mp 91–92°); major infrared peaks correspond to those reported;[18] nmr δ_{TMS} ($CDCl_3$) 2.00–1.60 (m, 9, including sharp s at 1.60), 1.60–1.20 (m, 2), and 0.80–0.50 (m, 1); for C_8H_{12} calcd *m/e* 108.0938 (found 108.0940).

The middle peak was characterized as **43**: pmr δ_{TMS} ($CDCl_3$) 2.35–2.10 (m, 2), 1.60–1.25 (m, 6), and 1.00–0.65 (m, 4, including d centered at 0.87, J = 7 Hz, 3); ν_{max} (neat) 3100, 3000, 2958, 2920, 2860, 1455, 1150, 1065, 988, and 920 cm^{-1}; for C_8H_{12} calcd *m/e* 108.0938 (found 108.0940).

Anal. Calcd for C_8H_{12}: C, 88.92; H, 11.18. Found: C, 88.90; H, 11.22.

The minor product was formulated as **44**: pmr δ 2.10–1.60 (m, 4), 1.60–1.20 (m, 5), and 1.12 (s, 3); ν_{max} (neat) 3060, 3050, 2950, 2930, 2862, 1455, 1380, 1333, 1285, 1260, 1230, 797, 770, and 730 cm^{-1}; for C_8H_{12} calcd *m/e* 108.0938 (found 108.0940).

Anal. Calcd for C_8H_{12}: C, 88.92; H, 11.18. Found: C, 88.98; H, 11.18.

Ag(I)-Catalyzed Rearrangement of 43. To 50 mg of **43** dissolved in 500 μl of dry benzene was added 500 μl of a 0.1790 *N* silver perchlorate–benzene solution. After this solution was heated to 50° for 12 hr, saturated brine was added and the product was extracted with pentane. Vpc analysis (column A,[37] 70°) revealed essentially total conversion to **45**: λ_{max} (C_2H_5OH) 249 nm; pmr δ_{TMS} ($CDCl_3$) 5.90–5.50 (m, 4), 2.40–1.90 (m, 4), 1.80–1.59 (m, 1), and 1.10–0.85 (m, 3); for C_8H_{12} calcd *m/e* 108.0938 (found 108.0940).

cis- **and** *trans*-**7,7-Dibromo-3-methoxynorcarane (48 and 49).** 4-Methoxycyclohexene (**47**),[41] bp 129°, was prepared in 77% yield by pyrolysis of 4-methoxycyclohexyl acetate at 490°. Reaction of 30.0 g of this alkene and 33 g of potassium *tert*-butoxide in 75 ml of pentane at −20° with 76 g of bromoform in 20 ml of pentane as previously described afforded 40.3 g (53%) of an isomeric mixture, bp 129–131° (3 mm).

Anal. Calcd for $C_8H_{12}Br_2O$: C, 33.83; H, 4.26. Found: C, 33.56; H, 4.25.

The cis and trans isomers were separated on column E[37] (150°, 100 ml/min) and the ratio was seen to be 37:63: for **48**, pmr δ_{TMS} ($CDCl_3$) 3.30 (br, s, 4), 2.20–1.70 (m, 6), and 1.60–1.30 (m, 2), for $C_8H_{12}Br_2O$ calcd *m/e* 281.9256 (found 281.9261); for **49**, δ_{TMS} ($CDCl_3$) 3.28 (br s, 4). 2.20–1.70 (m, 6), and 1.60–1.30 (m, 2), for $C_8H_{12}Br_2O$ calcd *m/e* 281.9256 (found 281.9261).

Cyclization of 48–49. Exposure of a solution composed of 10.0 g of the dibromide mixture in 50 ml of ether with 25 ml of 1.6 *M* methyllithium in ether at −40° for 30 min according to the predescribed method gave a product which could be separated into two components (ratio 71:29) on column D[37] (50°, 60 ml/min). The first component was collected and amounted to 591 mg. Pmr analysis showed the second peak (267 mg) to be comprised of two methyl ethers (ratio *ca.* 3:1). Separation of these isomers could not be achieved on any of the many columns examined.

The more rapidly eluted component was identified as **51**: ν_{max} (neat) 3040, 2940, 2910, 2860, 2825, 1460, 1445, 1320, 1280, 1250, 1050, and 890 cm^{-1}; pmr δ_{TMS} ($CDCl_3$) 3.27 (s, 3), 2.40–2.05 (m, 2), 2.00–1.65 (m, 2), and 1.65–1.30 (m, 5).

Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.47; H, 9.74.

Characterization of the remaining two products was achieved after selective magnesium bromide promoted rearrangement (*vide infra*). When the purified isomeric dibromides **48** and **49** were individually allowed to react with ethereal methyllithium, **48** was not converted to any of the above three products; no volatile substances were seen. In contrast, trans isomer **49** gave rise to **51–53** in the same ratios realized for the mixture.

Reaction of 52–53 with Ethereal Magnesium Bromide. A mixture of **52–53** (32 mg, *ca.* 3:1) was allowed to stand overnight in the presence of 1.5 ml of 0.1 *M* ethereal magnesium bromide. After quenching with water, the organic layer was separated, dried, and carefully concentrated. Vpc analysis on column D[37] (65°, 60 ml/min) revealed that the major component had chiefly undergone isomerization to a substance with longer retention time (ratio 2.5:1). Preparative scale isolation gave pure **53**, the pmr spectrum of which was identical with that of an authentic sample.[9b]

The major peak of longer retention time was characterized as norcarene **54**: ν_{max} (neat) 3030, 2920, 2860, 2820, 1450, 1320, 1100, 800, and 700 cm^{-1}; pmr δ_{TMS} (C_6D_6) 6.10–5.90 (m, 1), 5.75–5.55 (d, J = 10 Hz, 1), 3.60–3.30 (m, 1), 3.16 (s, 3), 2.50–2.20 (m, 1), 1.70–1.30 (m, 1), 1.20–0.80 (m, 2), and 0.80–0.10 (m, 2); for $C_8H_{12}O$ calcd *m/e* 124.0888 (found 124.0890).

Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.00; H, 9.83.

Acknowledgment. This work was supported in part by the National Science Foundation, whom we thank.

Registry No.—**15a,** 2699-13-0; **15b,** 38445-64-6; **15c,** 38445-63-5; **15d,** 38445-61-3; **16a,** 38445-66-8; **16b,** 38445-69-1; **16c,** 38445-68-0; **16d,** 38580-52-8; **16e,** 38445-67-9; **16f,** 38445-70-4; **16g,** 51326-30-8; **17a,** 51897-58-6; **17b,** 51897-59-7; **17c,** 51897-60-0; **17d,** 51838-95-0; **17e,** 51349-28-1; **17f,** 51838-96-1; **19,** 42403-40-7; **21,** 42403-41-8; **22,** 51349-29-2; **23,** 51838-97-2; **33,** 51838-69-8; **34,** 38452-05-0; **36,** 51838-70-1; **37,** 38452-06-1; **38,** 51897-61-1; **39,** 51897-62-2; **42,** 285-43-8; **43,** 51838-71-2; **44,** 51838-72-3; **45,**

38511-91-0; **47**, 15766-93-5; **48**, 51838-98-3; **49**, 51838-99-4; **51**, 51838-73-4; **52**, 51838-74-5; **53**, 51838-69-8; **54**, 38996-47-3; 2-methylcyclohex-1-en-3-ol, 20461-30-7.

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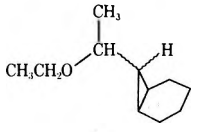

i

(16) This hypothesis is supported qualitatively by the reactivity of the 2-methyl-7,7-dibromobicyclo[4.1.0]heptanes.[5f]

(17) We thank Dr. Tanida for providing us with a copy of the pmr spectrum of **34**. High-resolution pmr analysis revealed that each component of the doublet of doublets due to H_2 is further split ($J \simeq 0.5$ Hz) by long-range coupling.

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(37) The following Al columns were employed herein: A, 12 ft × 0.25 in. 5% OV-11 on 60/80 mesh Chromosorb G; B, 5 ft × 0.25 in. 3% SE-30 on 100/120 mesh Varaport No. 30; C, 12 ft × 0.25 in. 5% Carbowax 20 M on KOH-washed 60/80 mesh Chromosorb P; D, 2 ft × 0.25 in. 12% OV-11 on 80/100 mesh Chromosorb W; E, 6 ft × 0.25 in. 10% UCON 50 HB 2000 Polar on 60/80 mesh Chromosorb G.

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Substituent Effects on Carbon-13 Chemical Shifts in 4-Substituted Biphenyls and Benzenes. A Substituent Effect Transmitted through Eight Covalent Bonds

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Received April 1, 1974

The ^{13}C chemical shifts of 14 monosubstituted benzenes and 14 4-substituted biphenyls have been determined and correlated by various linear free energy relationships. Resonance has been shown to be the dominant factor affecting ^{13}C chemical shifts in these systems. A significant substituent effect through eight covalent bonds has been observed.

Linear free energy relationships of the simple Hammett type

$$\ln \frac{k}{k_0} = \sigma\rho$$

based on the effect of substituents on the ionization of 3- and 4-substituted benzoic acids date back to 1937.[2] Over the ensuing years many other defining reactions have been developed to better represent the transition states of reaction under study.[3] These studies have adequately demonstrated for a very restricted scope of transition states that a particular σ constant will give a good linear free energy plot and a corresponding reaction constant with fairly high correlation. Hammett plots have previously been applied to measurements other than chemical reactions, such as ^{19}F chemical shifts in polynuclear aromatic compounds[4] and as a probe of π delocalization[5] and ^{13}C chemical shifts in monosubstituted benzenes.[6]

Unfortunately, the number of substituent parameters has proliferated without bounds, and recently various attempts have been made to simplify, consolidate, and better understand these multitudinous sets of constants. It is apparent that the major contributions to any substituent effect must be related in some way to the ability of the substituent to alter the electronic structure at the site involved in the molecule under study. Contributions due to simple electrostatic effects arising from electronegativity differences in the substituent are transferred to the reaction site through simple inductive processes, field effects, and resonance or mesomeric phenomena. Attempts have been made to divide substituent effects into these various contributions and thereby find a common basis for the numerous substituent effects derived from a variety of chemical reactions or physical properties. Swain and Lupton[7] have, for example, represented any substituent constant as

$$\sigma = fF + rR \quad (1)$$

using a variable combination of field and resonance parameters (F and R) unique to any substituent weighted by the empirical f and r coefficients. The field contributions in this treatment are based on the ionization constants for 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids. The resonance contribution to any substituent effect is determined by removal of the field effect from the corresponding σ_p (Hammett's original parameter). The per cent resonance character of any substituent constant can thus be determined from the relative magnitude of r and f. For example, Swain and Lupton calculate the per cent resonance for σ_p^+ to be 66% whereas σ_m manifests only a 22% resonance contribution.

Dewar has attempted to relate the effect of a substituent on all positions in a molecule by a combination of three parameters, F, M, and MF (field, mesomeric, and mesomeric field) properly weighted in a given molecule by coefficients which reflect the assumed molecular geometry. In this theory, a given substituent is thus represented by the appropriate admixture of three basic parameters, thus combining into a unified treatment the substituent effect at all points in a molecule. This approach has been applied with success to the pK_a of substituted carboxylic acids and chemical reactions in side chains, but with a marked lack of success in the case of ^{19}F chemical shifts. This led Dewar[8] to conclude that "the effects of substituents on chemical properties and on ^{19}F chemical shifts present entirely different problems and that attempts to combine the two will prove fruitless." A fluorine atom, at the periphery of a molecule and extensively involved in solvent interactions, probably is not a very good probe of a substituent effect, especially when inference is made regarding the nonfluorinated species. On the other hand, all organic molecules are made up of frameworks of carbon atoms, and the fortuitous replacement of a ^{12}C nucleus by a ^{13}C has little effect on the electronic structure of the molecule being studied and thus could be expected to be an excellent probe of substituent effects. The availability of modern techniques (fast Fourier transform pulse nmr, incoherent noise decoupling, large sample sizes, etc.)[9] permits the measurement of the nuclear magnetic resonance of the relatively rare (1.1%) and difficult to detect ^{13}C nucleus in fairly dilute solutions. Two useful spectroscopic results can be anticipated from such studies. First, the correlation with existing parameter sets would demonstrate the terms important in chemical shift theory. Second, once the dependence of a particular ^{13}C shift on substituents is determined, the relationship can be used to predict unknown chemical shifts and aid in the interpretation of complex cmr spectra. For example, a linear free energy relationship was used to good advantage in determining the identity of CIDNP polarizations arising from the induced decomposition of benzoyl peroxide in tetrachloroethylene.[10]

Experimental Section

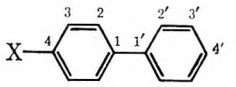
All compounds were commercially available and used as received with the exception of *p*-biphenylcarboxylic acid (Aldrich), which was sublimed and twice recrystallized from glacial acetic acid. The methyl ester was prepared by treatment of the *p*-biphenylcarboxylic acid with ethereal diazomethane,[11] followed by evaporation of ether. Whenever possible cmr measurements were made in 12-mm sample tubes on 10% solutions in acetone containing 10% benzene as internal standard. Acetone was selected simply as the only solvent capable of dissolving the majority of the biphenyls in the 10% concentration range. Samples that were not soluble in this solvent system were run in suitable solvents as noted in Table II. All chemical shifts are expressed in δ units relative to

Table I
Carbon-13 Chemical Shifts of Substituted Benzenes[a]

Substituent	Registry no.	Position 1	2,6	3,5	4	Other
H[d]	71-43-2	0	0	0	0	0
CH_3[e]	108-88-3	−9.36	0.10	−0.65	3.00	107.59
F[c]	462-06-6	−34.61	13.19	−1.94	4.07	
Cl[c]	108-90-7	−5.60	−0.18	−1.74	1.55	
Br[c]	108-86-1	6.17	−3.15	−2.07	1.13	
I[c]	591-50-4	34.47	−9.17	−2.19	0.64	
OH[e]	108-95-2	−29.29	13.00	−1.13	8.90	
OCH_3[e]	100-66-3	−31.59	14.41	−1.09	7.85	73.77
CN[f]	100-47-0	15.98	−3.78	−1.06	−4.63	−44.28
NO_2[b,c]	98-95-3	−19.64	5.19	−0.97	−6.31	
CO_2H[f]	65-85-0	−2.32	−1.39	−0.18	−4.69	−39.16
CO_2CH_3[f]	93-58-3	−2.13	−1.08	−0.19	−4.63	−38.10 76.81
NH_2[c]	62-53-3	−20.08	13.87	−0.65	11.51	
CH_3CO[g]	98-86-2	−9.13	0.14	−0.25	−4.55	−68.70 102.44

[a] δ(^{13}C) relative to internal benzene = 0.00; 10% in acetone unless otherwise noted. [b] Neat, 10% added benzene. [c] H. Spiesecke and W. G. Schneider, *J. Chem. Phys.*, **35**, 731 (1961). [d] P. C. Lauterbur, *J. Amer. Chem. Soc.*, **83**, 1846 (1961). [e] T. D. Alger, D. M. Grant, and E. G. Paul, *ibid.*, **88**, 5397 (1966). [f] A. M. Ihrig and J. L. Marshall, *ibid.*, **94**, 1756 (1972). [g] Assigned by proton decoupling using the values of J. S. Martin and B. P. Dailey, *J. Chem. Phys.*, **39**, 1722 (1963).

Table II
Carbon-13 Chemical Shifts of 4-Substituted Biphenyls[a]



Substituent	Registry no.	1	2	3	4	1'	2'	3'	4'	Other
H	92-52-4	−12.75	1.39	−0.56	0.99	−12.75	1.39	−0.56	0.99	
CH_3	644-08-6	−9.90	1.61	−0.50	−8.63	−12.71	1.55	−0.50	1.30	108.05
F	324-74-3	−9.12	−0.44	12.84	−34.34	−11.71	1.47	−0.60	0.99	
Cl[c]	2051-62-9	−11.34	−0.17	−0.66	−4.70	−11.43	1.48	−0.60	0.60	
Br	92-66-0	−11.39	−0.69	−3.59	7.14	−11.87	1.51	−0.54	0.54	
I	1591-31-7	−11.43	−0.70	−9.64	35.66	−12.34	1.59	−0.70	0.50	
OH	92-69-3	−4.09	0.30	12.55	−29.74	−12.74	1.99	−0.45	1.92	
OCH_3	613-37-6	−5.15	0.37	13.96	−12.46	−12.46	1.85	−0.48	1.68	73.47
CN	2920-38-9	−17.02	0.59	−4.36	17.37	−10.70	1.14	−0.85	−0.37	9.74
NO_2	92-93-3	−19.13	0.44	4.34	−19.03	−10.35	0.94	−0.91	−0.65	
CO_2H	92-92-2	−17.44	1.14	(−1.98)[d]	(0.15)[d]	−11.64	1.33	−0.72	0.06	(−42.47)[d]
CO_2CH_3[b]	720-75-2	−17.14	1.15	−1.68	−4.57	−11.47	1.32	−0.75	0.04	−38.47 76.79
NH_2	92-67-1	−1.15	0.79	13.48	−19.70	−13.16	2.46	−0.37	2.46	
CH_3CO[e]	92-91-1	−17.04	1.28	−0.74	−7.97	−11.55	1.16	−0.58	0.04	−29.57 102.26

[a] 10% in acetone with 10% benzene internal reference. [b] 5% in acetone. [c] 20% in acetone. [d] Saturated in HOAc at 85°. [e] 5% in acetone.

internal benzene and were measured in the FFT mode on a Varian XL-100-15 spectrometer equipped with 620f computer and gyrocode decoupler. Field-frequency lock was obtained utilizing a concentric 4-mm tube of acetone-d_6.

Linear regression analyses were obtained using a plot program on a Hewlett-Packard 9810A (500 program steps, 111 data registers) equipped with 9862A plotter and 11210A mathematics ROM.

Regression analysis of the equation

$$\Delta\delta = aAF^s + bBM^s + cCM_F^s \qquad (2)$$

was accomplished by matrix solution of the following equations.

$$a\Sigma(AF^s)^2 + b\Sigma[(AF^s)(BM^s)] + c\Sigma[(AF^s)(CM_F^s)] = \Sigma[(AF^s)\Delta\delta]$$

$$a\Sigma[(AF^s)(BM^s)] + b\Sigma(BM^s)^2 + c\Sigma[CM_F^s(BM^s)] = \Sigma[(BM^s)\Delta\delta]$$

$$a\Sigma[(AF^s)(cM_F^s)] + b\Sigma[(BM^s)(CM_F^s)] + (CM_F^s)^2 = \Sigma[(CM_F^s)\Delta\delta] \qquad (3)$$

Here $\Delta\delta$ is the chemical shift of the substituted compound relative to the parent; A, B, and C are Dewar's weighting factors; and a, b, and c are the regression parameters which measure the relative importance of Dewar's three terms to the carbon-13 shift.

Results and Discussion

Carbon-13 magnetic resonance FFT measurements were made on the 14 monosubstituted benzenes listed in Table I and the 14 4-substituted biphenyls listed in Table II. The tables summarize the chemical shifts observed for each of the positions in each of the compounds relative to benzene internal standard. The chemical shift region covered by the aromatic region in these compounds is about 55 ppm. The measurements on monosubstituted benzenes are in excellent agreement with earlier assignments made on neat samples by continuous wave cmr.

Our first attempts to correlate and in fact to assign the chemical shifts of the various carbons in each compound consisted of linear regression analyses of the shift and individual position *vs.* various σ parameters available in the literature to determine which gave the best correlation. As expected, the 1 and 2 positions of 1-substituted benzene and the 4 and 3 positions of 4-substituted biphenyls did

Table III
Summary of $\sigma\rho$ Correlations for 12 Substituents (Acetyl Excluded)

Compd	Position	σ_T	ρ_T	r^c
Biphenyl	1	p^+	−9.5887	−0.9926
Biphenyl	2	m	−0.9853	−0.3256
Biphenyl[a]	2	m^+	−1.3720	−0.4657
Biphenyl	2 ep[b]	m	−2.6408	−0.9322
Biphenyl[a]	2 ep	m^+	−2.1611	−0.9537
Biphenyl	2 no ep	m	−1.5603	−0.9656
Biphenyl	2 no ep	m^+	−1.6222	−0.9725
Biphenyl	1′	m	3.3065	0.9471
Biphenyl	2′	p^+	−0.6397	−0.9520
Biphenyl	3′	m	−0.5088	−0.8483
Biphenyl[a]	3′	m^+	−0.5344	−0.8676
Biphenyl	3′	p	−0.3664	−0.9544
Biphenyl	4′	p^+	−1.5712	−0.9909
Biphenyl	4′	p	−2.1823	−0.9972
Benzene	3	m	−1.2306	−0.4409
Benzene[a]	3	m^+	−1.5621	−0.5148
Benzene	3 ep	m	−2.7123	−0.9441
Benzene[a]	3 ep	m^+	−2.2172	−0.9765
Benzene	3 no ep	m	−1.3898	−0.8371
Benzene	3 no ep	m^+	−1.9431	−0.9018
Benzene	4	p^+	−9.8090	−0.9923

[a] OH omitted. [b] ep = electron pairs. [c] Correlation coefficient. Average correlation obtained from σ_p^+ and σ_m (divided) = 0.94 ± 0.02.

not correlate with any of the parameters, being too subject to local and steric effects of the attached substituents. However, the 3 and 4 positions of benzenes and the 1, 2, 1′, 2′, 3′, and 4′ positions of 4-substituted biphenyls did give excellent correlation with appropriate σ constants.

Table III summarizes the results of these linear regression analyses, giving the observed ρ's (slopes) and correlation coefficients. Theoretically the intercepts of these lines, which are plots of $\Delta\delta$ (chemical shift, substituted–unsubstituted) *vs.* the appropriate σ constant should be zero. The intercept, however, was allowed to float in these analyses and used as a further check of the validity of fit. In each case the intercept is less than ±1 ppm and thus give a fairly good check on the reliability of the treatment. The coefficients of correlation for the best fit of each position range between 0.84 and 0.99 providing the correlations with m and m^+ are divided into those substituents with and without free electron pairs. Several points should be made with respect to Table III. First the ρ's (slopes) reported range from *ca.* −10 to +3.

The best fits for the 4 position of benzenes and the 1 position of biphenyls were found for σ_p^+, although σ_p was about as good or even slightly better for 4′-biphenyls. Positions 3 of benzene and 2, 1′, and 3′ of biphenyls correlate well with σ_m although 3, 2, and 1′ are slightly better characterized with σ_m^+ although these correlations are for fewer substituents. An interesting phenomenon is observed in plots of 3-carbons in benzenes and 2-carbons of biphenyls. Figure 1 shows a plot of $\Delta\delta$ *vs.* σ_m^+ for the 2-carbon of biphenyls. As can be seen, the substituents evenly distribute above and below the best least-squares line. However, excellent correlation is obtained when the two natural lines are treated separately. The result is that every substituent on the lower line ($\ddot{N}H_2$, $\ddot{O}H$, $\ddot{O}CH_3$, $\ddot{X}$) contains a free pair of electrons while all those on the upper line (CH_3, COOH, $COOCH_3$, CN, NO_2) have no such free electrons available. Taken together with the fact that correlation is obtained with σ_p^+ (66% resonance)[7] rather than σ_p (53% resonance)[7] this result shows the importance of the contribution of electron pairing to the carbon chemical shift.

Two more points should be made with respect to these correlations. First, if each nonsterically interacting position

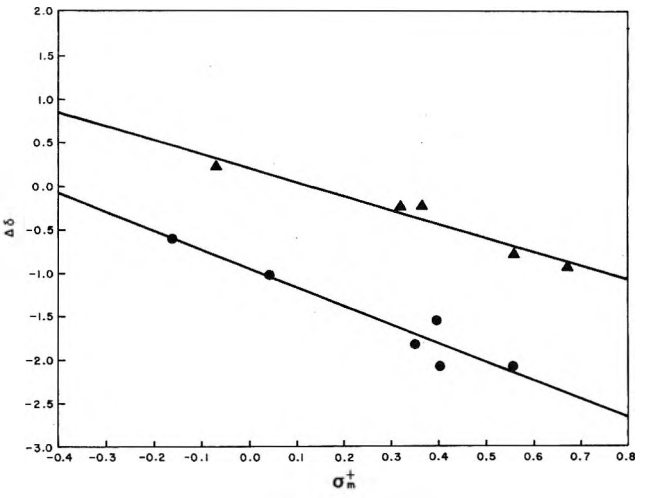


Figure 1. $\Delta\delta$ (ppm) *vs.* σ_m^+ for the 2-carbon of 4-substituted biphenyls: ▲, substituents with unshared electron pairs; ●, substituents without unshared electron pairs.

in monosubstituted benzenes and 4-monosubstituted biphenyls is plotted against the product of the appropriate σ constant (for simplicity either σ_m or σ_p^+) and the ρ corresponding to that position, an excellent straight line is obtained. Such a composite plot should in theory have a slope of 1 and an intercept of 0. Figure 2 shows that the correlation of $\Delta\delta$ with the appropriate $\sigma\rho$ product has a slope of 1.02, intercept of 0.08, and correlation of 0.97. Second, the substituent effect is transmitted (with about 10% efficiency) all the way from the 4-carbon of biphenyls to the 4′-carbon with a correlation of 0.99 (Figure 3). That is to say, we have observed a substituent effect transmitted through eight covalent bonds.

In order to further investigate the classical contributions of field and resonance to the substituent effect we here report, a linear regression was made using Dewar's FMMF treatment.[8] The field, mesomeric, and mesomeric field contributions for each position were taken directly from the literature,[8] while the appropriate geometrical factors were kindly provided by Professor Dewar,[12] and are summarized in Table IV.

Figure 4 shows a plot of $\Delta\delta$ *vs.* Dewar's σ values. As can be seen, the FMMF treatment does not successfully correlate the chemical shifts of monosubstituted benzenes and 4-monosubstituted biphenyls with a single ρ parameter. However, inspection of the points shows independent correlations for each position in a manner similar to that reported above for classical σ plots. The Dewar treatment prescribes an exact mixture of field, mesomeric, and field due to mesomeric effects which correlate with reaction parameters. To explore the importance of an alternative mix in chemical shifts a new regression analysis was undertaken

Table IV[a]
Geometrical Parameters of Dewar Equation for 4-Substituted Biphenyls

$$\sigma = AF^s + BM^s + CM_F{}^s$$

Position	A	B	C
1	0.500	0.129	0.197
2	0.577	0.000	0.360
3	1.000	0.129	0.176
1′	0.333	0.000	0.178
2′	0.277	0.032	0.192
3′	0.218	0.000	0.191
4′	0.200	0.032	0.137

[a] Reference 12.

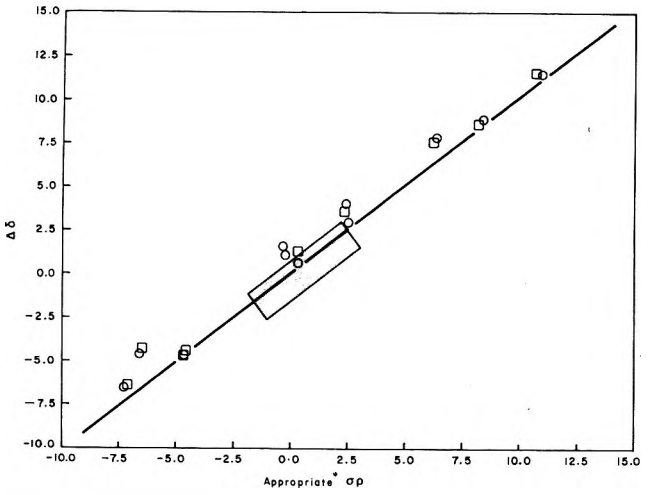


Figure 2. A plot of $\Delta\delta$ *vs.* the appropriate $\sigma\rho$ product for 3 and 4 positions of benzenes and 1, 2, 1′, 2′, 3′, and 4′ positions of biphenyls: ○, 4-C benzenes; □, 1-C biphenyls. The enclosed area comprises the region of extreme overlap of all other positions.

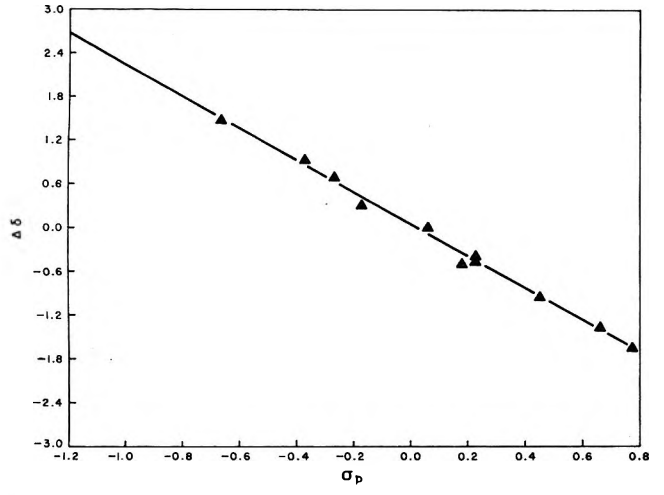


Figure 3. $\Delta\delta$ (ppm) *vs.* σ_p for the 4′-C of biphenyls.

using eq 2. The success of this fit can be seen from Figure 5, which is quite similar to that presented in Figure 2 for a combined classical $\sigma\rho$ treatment. The coefficients found are $a = -0.4833$, $b = -19.8484$, and $c = +1.9520$ with a correlation coefficient of 0.93, only slightly less than that found for the combined $\sigma\rho$ treatment (0.97) which of course contained many more degrees of freedom. These results show that if the field effect is taken as 1.0, the mesomeric effect is 41 times greater, and the mesomeric field effects are 4 times greater and of opposite sign in their effect on chemical shift.

This analysis when taken along with the effect of free electron pairs on the substituent noted in the meta position (in Figure 1) and the correlation of para positions with σ_p^+ (66% resonance) shows the import of resonance as compared with field effects on the carbon chemical shift. As it has been exhibited that chemical shifts will reflect primarily the charge distributions in aromatic systems,[6b,13] we must conclude that electronic reorganization in these molecules through resonance structures is of greater significance than that due to electrostatic field effects. It appears from this study that field effects will alter the carbon-13 shifts in only a minimal way, and to the extent that these contribute to σ values which characterize chemical reactions, one might expect a failure in correlating chemical shifts. In Figure 1 there is reasonable correlation of $\Delta\delta$ for each of the two classes of substituents, but as σ_m and σ_m^+ minimize the

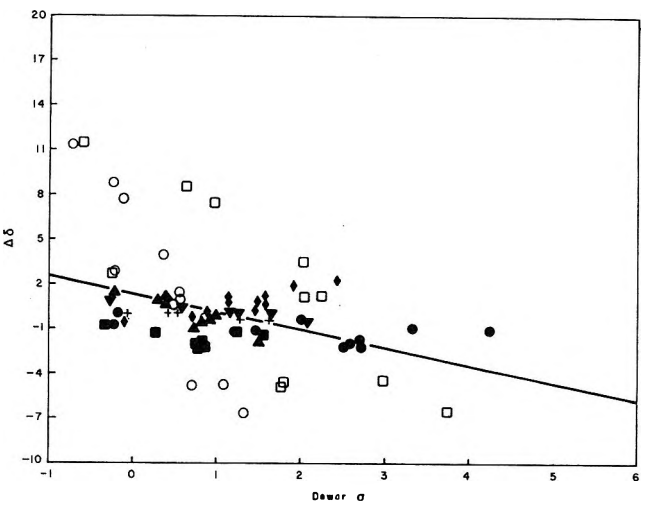


Figure 4. $\Delta\delta$ (ppm) *vs.* Dewar's calculated σ for 3 and 4 positions of benzenes and 1, 2, 1′, 2′, 3′, and 4′ positions of biphenyls. In areas of extreme overlap, representative points have been chosen to demonstrate the data with minimum confusion. The line represents the least-squares "best fit" of the scattered data: ●, biphenyl 2-C; □, biphenyl 1-C; ♦, biphenyl 1′-C; ▼, biphenyl 2′-C; +, biphenyl 3′-C; ▲, biphenyl 4′-C; ■, benzene 3-C; ○, benzene 4-C.

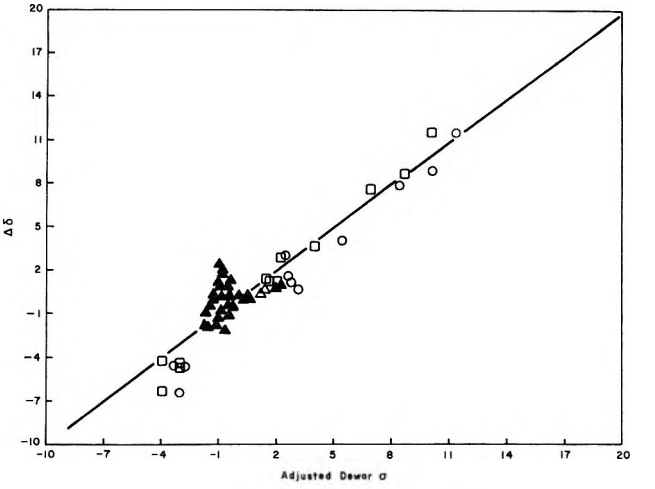


Figure 5. $\Delta\delta$ (ppm) *vs.* adjusted Dewar σ. The shifts are the same as in Figure 4. In areas of extreme overlap only representative points are shown: ○, benzene 4-C; □, biphenyl 1-C; ▲, all other positions.

resonance feature so important in carbon shifts, the plot breaks into those substituents with widely different resonance features. Likewise for the other positions and other σ parameters good chemical shift correlations were always obtained whenever a parameter sensitive to resonance effects was employed.

In chemical shift theory, the magnetic field mixes small amounts of intrinsic angular momentum possessed by p electrons into the ground-state description of the molecules. This, to a first approximation, depends on the electronic charge in the immediate vicinity of the carbon nucleus and is less affected by long-range field effects resulting from remote substituents. On the other hand, σ parameters obtained from reaction rates are determined by the electronic structure of the activated complex, where electrons are loosely held and considerably more delocalized. In this condition the electrons would be more polarizable and therefore more sensitive to electrostatic field effects. It is understandable, therefore, that simultaneous correlation of both shifts and reaction rates with a given σ parameter would be fortuitous unless the appropriate dissection of the contributing components is first achieved. It is to be noted,

however, that carbon shift data can be used to characterize the important resonance feature and thereby aid in the separation of these various effects in reaction rate or related equilibrium data. Thus, instead of the σ's for shifts and other chemical properties being totally unrelated, the information from the two sources is complementary and can be combined to characterize the relative importance of the component parts which affect the various σ's to differing degrees.

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Aromatic Substitution. XXVI.[1] Kinetics of Nucleophilic Substitution of Some Bromopyridines and -picolines with Methoxide, Thiomethoxide, Phenoxide, and Thiophenoxide Ions

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Received March 15, 1974

The rates and activation of parameters were determined for the reactions of KSMe in methanol with 2-bromo-, 2-bromo-3-methyl-, 2-bromo-5-methyl-, 2,3-dibromo-, and 2,5-dibromopyridine, and of KOMe, KOPh, KSMe, and KSPh with 2-bromo-, 2-bromo-3-methyl-, and 2-bromo-5-methylpyridine in hexamethylphosphoramide. The results confirm the previous conclusion that a 3-methyl substituent activates the 2 position in the case of attack by thiophenoxide ion (but not with the other three nucleophiles) because of a combination of ion–dipole and dispersion attractive forces between the 3 substituent and the PhS^-, and not because of a heavy (sulfur) nucleophile effect.

Quantitative studies[2] of the nucleophilic aromatic substitution of a hydride ion equivalent in the pyridine series by phenyllithium have established that a 3-methyl or a 3-ethyl group *activates* the 2 position of the pyridine nucleus toward this nucleophilic attack, methyl activating it more than ethyl. On the other hand, the 6 position was *deactivated* normally, as expected on the basis of the electron-donating effect of the alkyl group. In the reactions of 3-picoline with methyllithium[3] and with sodamide (Tschitschibabin reaction),[4] however, the 3-methyl substituent did not activate C-2, although attack still occurred predominantly at the 2 rather than at the 6 position. An ion–dipole attractive interaction between the 3-methyl group and the approaching methyllithium[3] or amide anion could account for these observations.[5] Steric acceleration of substitution at C-2 by the 3 substituent was considered but had to be rejected on the basis that a 3-methyl group was found to activate C-2 more than did a 3-ethyl group.[2] The normal deactivation of C-6, but the much lesser deactivation, or even net activation, of C-2 is not explained, contrary to what is stated,[6] by simple Hückel calculations of localization energies which do not take into account ortho effects by the substituent at C-3. Two possibilities were discussed to account for the results obtained in the phenyllithium reactions. (a) London dispersion forces[7] acting between the 3-alkyl substituent and the polarizable attacking nucleophile could lower the activation energy for attack at C-2 but not at C-6. (b) The formation of an electron-deficient type bond[8] between the 3-alkyl group and the organolithium compound would facilitate attack at C-2.

In order to decide between these alternatives, kinetic studies on two model systems were carried out. The reaction of 2-bromo-, 2-bromo-3-methyl-, and 2-bromo-5-methylpyridine with methoxide ion was studied under a variety of conditions.[9] The rates were in the order 2-bromo- > 2-bromo-3-methyl- > 2-bromo-5-methylpyridine and were dependent upon E_a. This order of reactivity parallels that found in the methyllithium and Tschitschibabin reactions but not in the phenyllithium reaction. The lesser deactivation of the ortho than the para position by a 3-methyl group was attributed[9] to an ion–dipole attraction[10] between the methoxide ion approaching the 2 position and the methyl group which more than compensates for the greater inductive effect of the substituent at the ortho than at the para position, and any steric hindrance by the 3 substituent[11] to approach.

In order to find a system that would provide a model for the relative reactivities observed with phenyllithium, the kinetics of the reaction of 2-bromopyridines (1) with phenoxide ion in methanol to give 2 were studied, in the hope that the highly polarizable thiophenoxide would lead to the London attractive forces[7] discussed above. Indeed, the sought-for order of reactivities was observed: 2-bromo-3-methyl- > 2-bromo- > 2-bromo-5-methylpyridine.[12] The

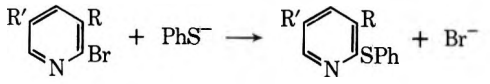
Table I
Kinetic Data for the Reaction of 2-Bromopyridines Derivatives with Potassium Thiomethoxide in Methanol

Pyridine	Registry no.	$10^4 k_2$, l. mol^{-1} sec^{-1} (temp, °C)					
2-Bromo-	109-04-6	2.29 (102.2)	3.74 (108)	6.65 (115)	10.0 (120)	14.5 (125)	22.2 (130)
2-Bromo-3-methyl-	3430-17-9	1.16 (100)	2.21 (108)	3.94 (115)	5.88 (120)	8.91 (125)	12.8 (130)
2-Bromo-5-methyl-	3510-66-5	0.274 (100)	0.594 (108)	1.07 (115)	1.70 (120)	2.53 (125)	3.85 (130)
2,3-Dibromo-	13534-89-9	7.52 (70)	18.6 (80.6)	40.9 (90.7)	83.6 (100.1)		
2,5-Dibromo-	624-28-2	3.11 (70)	7.54 (80)	16.9 (90)	24.9 (94.8)	39.4 (100.6)	

Table II
Activation Parameters for the Reaction of 2-Bromopyridine Derivatives with Potassium Thiomethoxide in Methanol[a]

Pyridine	$10^4 k_2$, l. mol^{-1} sec^{-1} (at 100°)	E_a,[b] kcal/mol	ΔS^*, eu	ΔF^*, kcal mol^{-1} (at 100°)
2-Bromo-	4.43 [0.944]	24.3 [26.8]	−12.9 [−9.2]	28.3
2-Bromo-3-methyl-	2.69 [0.24]	24.1 [27.8]	−14.5 [−9.5]	28.7
2-Bromo-5-methyl-	0.70 [0.15]	26.2 [29.0]	−11.6 [−7.4]	29.8
2,3-Dibromo-	168 [15.5]	20.3 [23.6]	−15.9 [−12.3]	25.5
2,5-Dibromo-	76.7 [15.2]	21.1 [24.7]	−15.5 [−9.4]	26.1

[a] Values in brackets are the corresponding values for MeO^-.[9] These have been recalculated using the same computer program as was used here for the thiomethoxide data. [b] Experimental errors are ±0.2 kcal in E_a and ±0.4 eu in ΔS^*.



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ortho effect arose from a decrease in the energy of activation (ΔE_a = 2 kcal/mol). To decide between the dispersion forces and ion–dipole attractive interaction possibilities the kinetics of the reaction of 2,3- and 2,5-dibromopyridine with thiophenoxide ion in methanol were studied.[12] It was expected if only London dispersion forces were at work that a larger ortho:para ratio would be observed with the more polarizable β-bromo substituent than with methyl. If only ion–dipole interactions[10,13] were involved then $k_{o\text{-Br}}$ would be predicted to be smaller than $k_{p\text{-Br}}$ since the polarity of the $\overrightarrow{C\text{–}Br}$ bond is the reverse of that of the $\overleftarrow{C\text{–}CH_3}$ bond. In fact, the ortho:para ratio was not smaller than unity *nor* was it larger than that for a β-methyl substituent, and it was concluded that a combination of *both* polarizability effects *and* ion–dipole interactions had to be taken into account to explain the observed results.

In order to determine if the activation of C-2 by a 3-methyl group toward attack by thiophenoxide ion is due to a specific sulfur (heavy) nucleophile effect[14] or if the overall polarizability of the nucleophile[12,15] determined the magnitude of the attractive interactions with an ortho substituent, attention was turned to the reactions of 2-bromopyridine derivatives (1) with potassium thiomethoxide and with potassium phenoxide in methanol. The results of the kinetics of the reaction of 1 with KSMe are summarized in Tables I and II.

The data show that a 3-Me group does not activate C-2 toward attack by MeS^- in methanol. Indeed, the behavior observed is similar to that of methoxide ion in methanol and to the Tschitschibabin and methyllithium reactions, with the order of reactivities 2-bromo- > 2-bromo-3-methyl- > 2-bromo-5-methylpyridine. In this case, E_a values for 2-bromo- and 2-bromo-3-methylpyridine are essentially the same (as opposed to the case with MeO^-) and the slightly lower rate of reaction of 2-bromo-3-methylpyridine is due to a somewhat lower entropy of activation. The absence of activation of C-2 toward attack by MeS^- indicates that more than just a sulfur nucleophile effect is important in causing activation. It seems reasonable to suggest that the overall polarizability of the nucleophile plays the dominant role in determining whether or not a β-methyl group activates C-2; *e.g.*, phenyllithium is more polarizable than methyllithium.

Table III
Calculated Rate Ratios for the Reactions of 3-R- or 5-R-2-Bromopyridines with Potassium Methoxide and Potassium Thiomethoxide in Methanol at 110°

R	$k_{o\text{-R}}:k_{p\text{-R}}$	$k_{(MeS^-:MeO^-)R}/(k_{MeS^-}:k_{MeO^-})_H$	$(k_{MeS^-}:k_{MeO^-})_{o\text{-R}}/(k_{MeS^-}:k_{MeO^-})_{p\text{-R}}$
CH_3	3.9 (MeS^-) 1.6 (MeO^-)	2.4 (*o*-Me), 0.96 (*p*-Me)	2.4
Br	2.2 (MeS^-) 1.0 (MeO^-)	2.3 (*o*-Br), 1.1 (*p*-Br)	2.2

The greater reactivity of 2-bromo-3-methyl- than of 2-bromo-5-methylpyridine with thiomethoxide ion is due to a lower energy of activation with the former (ΔE_a = 2.1 kcal/mol). This lesser deactivation of C-2 than C-6 could again be due either to London dispersion forces or to ion–dipole attraction, and to try to distinguish between these two possibilities the reactions of 2,3- and 2,5-dibromopyridine with MeS^- in methanol were studied, the rationale being as above for MeO^-. The ortho:para ratios were calculated directly as well as by the methods of Reinheimer and Bunnett[7] and of Sisti and Lowell,[16] the latter two approaches being used to cancel out nucleophilicity differences between the reagents MeS^- and MeO^-. These ratios are given in Table III.

Regardless of which rate ratios are considered, the data are not consistent with the involvement of either purely ion–dipole interactions, since the ortho:para ratio for a β-bromo substituent is not <1, or of purely polarizability effects, since the *o*-Br:*p*-Br ratio is not greater than the *o*-Me:*p*-Me ratio. A combination of these two factors[12] would

Table IV
Rate Ratios for the Reacton of 2-Bromo, 2,3-Dibromo-, and 2,5-Dibromopyridine with Methoxide, Thiomethoxide, and Thiophenoxide Ions at 110°

Nucleophile	2,3-Br_2:2-Br	2,5-Br_2:2-Br
$^-OCH_3$	16	16
$^-SCH_3$	38	17
^-SPh	50	20

Table V
Differences in Arrhenius Parameters

	Substituent in 2-bromopyridine				
	H	3-Me	5-Me	3-Br	5-Br
$\Delta E_a(E_{MeO^-} - E_{MeS^-})$	2.5	3.7	2.8	3.3	3.6
$\Delta\Delta S^*(MeO^- - MeS^-)$	3.7	5.0	4.2	3.6	6.1
$\Delta E_a(E_{MeO^-} - E_{PhS^-})$	1.2	3.0	2.6	2.4	1.3
$\Delta\Delta S^*(MeO^- - PhS^-)$	6.4	7.2	8.7	6.9	5.9

Table VI
Kinetic Data for the Reaction of 2-Bromopyridines with Methoxide, Thiomethoxide, Phenoxide, and Thiophenoxide Ions in HMPA

Pyridine	Nucleophile	$10^3 k_2$, l. mol^{-1} sec^{-1} (temp, °C)	$10^3 k_2$ (110°) calcd
2-Br	CH_3O^-	1.98 (30), 7.7 (48), 16.1 (58)	339
2-Br-3-CH_3	CH_3O^-	1.08 (30), 4.53 (48), 9.18 (58)	219
2-Br-5-CH_3	CH_3O^-	0.53 (30), 2.32 (48), 5.0 (58)	135
2-Br	PhO^-	0.72 (88.7), 3.4 (110.8), 6.83 (120.9)	3.13
2-Br-3-CH_3	PhO^-	0.42 (90), 2.26 (110.8), 4.33 (120.6)	2.1
2-Br-5-CH_3	PhO^-	0.094 (90), 0.457 (110.8), 1.0 (120.4)	0.42
2-Br	CH_3S^-	12.66 (28), 32.6 (42), 82.2 (55)	1740
2-Br-3-CH_3	CH_3S^-	5.76 (28), 15.7 (42), 38.8 (55)	742
2-Br-5-CH_3	CH_3S^-	1.33 (30), 4.16 (42), 14.1 (55)	389
2-Br	PhS^-	2.34 (80), 9.96 (100.2), 20.4 (110.2)	20.2
2-Br-3-CH_3	PhS^-	3.4 (80), 12.8 (100.2), 28.6 (110.2)	28.3
2-Br-5-CH_3	PhS^-	0.77 (90), 3.82 (110), 7.94 (120)	3.8

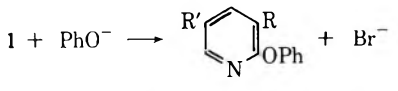
best account for the results. A comparison of the rate ratios given in Table IV shows that as the polarizability of the nucleophile increases from MeO^- through MeS^- to PhS^- the activating influence of a 3-bromo substituent increases, while a 5-bromo substituent exerts an activating ($-I > +M$) effect independent of the polarizability of the attacking nucleophile.

Another way of looking at this "ortho effect" which does take into account the differences in nucleophilicities between the reagents is to consider the differences in Arrhenius parameters of these reactions as a function of the nature and position of the substituent. These data are given in Table V along with the corresponding data for thiophenoxide ion.[16] For a 3-methyl substituent the ΔE_a value is larger than that for a 5-methyl substituent ($\Delta\Delta E_a = 0.9$ for MeO^- compared with MeS^-, $\Delta\Delta E_a = 0.4$ for MeO^- compared with PhS^-). If the polarizability of the sulfur atom were not taken into account, an unfavorable steric effect with the sulfur nucleophile should have resulted in a trend in ΔE_a in the opposite direction. When MeO^- and PhS^- are compared, ΔE_a for 3-Br is larger than ΔE_a for 5-Br ($\Delta\Delta E_a = 1.3$), and this difference is larger than that (0.4) for the β-methyl groups. This suggests that for PhS^- the polarizability factor is more important than the Coulombic interaction. On the other hand, when MeO^- is compared with MeS^-, ΔE_a for 3-Br (3.3) is not as large as ΔE_a for 5-Br (3.6), which suggests that polarizability is not as important with thiomethoxide as it is with thiophenoxide.

To complete the comparison between thiophenoxide as a nucleophile and the oxygen analogs it was necessary to study the kinetics of the reaction of phenoxide ion with bromopyridines. Preliminary runs of the reaction of potassium phenoxide with 2-bromopyridine in methanol were carried out with equivalent amounts of potassium methoxide and phenol in methanol. With 2-bromopyridine at 100° for 102 hr it gave an almost quantitative yield of 2-methoxypyridine (ratio of 2-methoxy-:2-phenoxypyridine 49:1 by gas chromatography), which is not unexpected, for though the equilibrium $MeOH + PhO^- \rightleftharpoons MeO^- + PhOH$ lies largely to the left, methoxide is a much stronger nucleophile than is phenoxide. In many of the studies involving phenoxide ion in alcoholic solvents an excess of free phenol was employed to control the alkoxide ion concentration.[17-20] In the present study, 18 equiv of PhOH was required to suppress almost completely competition from MeO^- (2-methoxy-:2-phenoxypyridine 1:99). The usefulness of having an excess of free phenol vanished, however, when it was found that 2-bromopyridine reacted with phenol in the absence of base at 120° for 120 hr to give 2-phenoxypyridine in 76% yield, probably *via* the bromopyridinium ion.

In order to bypass the difficulties encountered with phenoxide ion in a protic solvent attention was turned to the use of a dipolar aprotic solvent in which competition from the solvent would be eliminated. Hexamethylphosphoramide (HMPA) was selected as the medium for kinetic studies with phenoxide ion, since it is stable to nucleophiles[21] and is not hydrolyzed in alkaline media. In addition, it is of interest that no nucleophilic substitutions have so far been reported as far as we know for pyridine derivatives in HMPA.

To determine the potential usefulness of such studies preliminary measurements were made of the relative reactivities in HMPA using the competitive technique in which equimolar mixtures of 2-bromo- and 2-bromo-3-methyl-, or 2-bromo- and 2-bromo-5-methylpyridine were allowed to react with a small amount of potassium phenoxide. The reaction products were analyzed by gas chromatography and the total rate ratios were calculated. Authentic samples of the 2-phenoxypyridines were prepared for comparison



with the reaction products. The order of reactivities was found to be 2-bromo- > 2-bromo-3-methyl- > 2-bromo-5-methylpyridine; $^{o\text{-Me}}K_H = 0.47$ and $^{p\text{-Me}}K_H = 0.099$; ortho:para ratio (at 80° in HMPA) 4.8. This order of reactivity parallels those found in the Tschitschibabin and methyllithium reactions.

In order to compare the reactivity of PhO^- with those of MeO^-, MeS^-, and PhS^- it was necessary to carry out kinetic measurements of the reactions of the bromopyridines with these nucleophiles in HMPA. The specific rate constants so obtained are summarized in Table VI. These reveal that a 3-methyl group does not activate C-2 in 2-bro-

Table VII
Comparison of Rate Constants for Reactions of Bromopyridines in MeOH, HMPA, and DMSO at a Common Temperature

Pyridine	Nucleophile	$10^3 k_2$ (110°) in HMPA	$10^3 k_2$ (110°) in MeOH	$10^3 k_2$ (110°) in DMSO (1% MeOH)
2-Br	CH_3O^-	339	0.0944[a]	309[b]
2-Br-3-CH_3	CH_3O^-	219	0.0239[a]	170[b]
2-Br-5-CH_3	CH_3O^-	135	0.0154[a]	117[b]
2-Br	PhS^-	20.2	0.0214[a]	2.3[b]
2-Br-3-CH_3	PhS^-	28.3	0.0300[a]	
2-Br-5-CH_3	PhS^-	3.8	0.0061[a]	
2-Br	CH_3S^-	1740	0.443	
2-Br-3-CH_3	CH_3S^-	742	0.269	
2-Br-5-CH_3	CH_3S^-	389	0.097	

[a] See ref 12. [b] See ref 9.

Table VIII
Arrhenius Parameters for the Reactions of 2-Bromopyridine Derivatives with OCH_3^-, PhO^-, CH_3S^-, and PhS^- Ions in HMPA and MeOH

Pyridine	Nucleophile	E_a (HMPA)[a]	E_a (MeOH)	ΔS^*(HMPA)	ΔS^*(MeOH)
2-Br	CH_3O^-	14.8 [17.9][d]	26.8[b]	−24.0 [−18.1][d]	−9.2
2-Br-3-CH_3		15.2 [18.7]	27.8[b]	−23.9 [−16.9]	−9.5
2-Br-5-CH_3		16.0 [19.5]	29.0[b]	−22.8 [−16.2]	−7.4
2-Br	PhO^-	19.8		−20.7	
2-Br-3-CH_3		21.9		−16.3	
2-Br-5-CH_3		21.8		−19.3	
2-Br	PhS^-	19.2 [22.3][d]	25.6[b]	−18.5 [−13.0][d]	−15.6[b]
2-Br-3-CH_3		17.4	24.8[b]	−22.8	−16.7[b]
2-Br-5-CH_3		22.1	26.4[b]	−14.3	−16.1[b]
2-Br	CH_3S^-	13.6	24.3[c]	−24.1	−12.9[c]
2-Br-3-CH_3		13.7	24.1[c]	−25.2	−14.5[c]
2-Br-5-CH_3		18.1	26.2[c]	−14.0	−11.6[c]

[a] Experimental errors are ±0.4 kcal in E_a and ±0.8 eu in ΔS^*. [b] See ref 9, 12, and 16. Experimental errors are ±0.3 kcal in E_a and ±1 eu in ΔS^*. [c] See Table II. Experimental errors are ±0.2 kcal in E_a and ±0.4 eu in ΔS^*. [d] Values in brackets are corresponding values in DMSO; see ref 9 and 12.

mopyridine toward attack by the MeO^-, PhO^-, and MeS^- ions, but does in the case of PhS^- anion in HMPA. This is similar to the behavior in methanol. Thus, phenoxide is not polarizable enough to lead to overall activation so that, in that sense, the sulfur atom is essential. These results are in keeping with the suggestion that the overall polarizability of the nucleophile plays the dominant role in determining whether or not a β-methyl group activates C-2. In all cases except for PhS^- the order of reactivities was 2-bromo- > 2-bromo-3-methyl- > 2-bromo-5-methylpyridine.

The reactions in HMPA were faster (by *ca.* 10^3) than those in methanol (Table VII), and slightly more so than those in DMSO (1% MeOH).[12] The Arrhenius parameters for the reactions in HMPA are summarized in Table VIII, in which the corresponding data for the reactions in methanol and DMSO are included for ease of comparison. The increased rates in HMPA are due to a reduction of 5–13 kcal/mol in E_a, somewhat counterbalanced by lower ΔS^* values ($\Delta\Delta S^* = \Delta S^*_{MeOH} - \Delta S^*_{HMPA}$ = 4–15 eu, except for the reaction of 2-bromo-5-methylpyridine with MeS^- and PhS^-). These ΔS^* values in HMPA reflect the expected[12,19] decrease in solvation of the anionic nucleophiles in the ground state, since HMPA is expected to solvate cations best.[21] HMPA forms a solvation shell around the smaller anions MeO^- and MeS^- less readily ($\Delta\Delta S^* = \Delta S^*_{MeOH} - \Delta S^*_{HMPA}$ = *ca.* 12 eu) than around the larger thiophenoxide ion ($\Delta\Delta S^*$ = *ca.* 5 eu). Again, a comparison of ΔS^* for MeO^- *vs.* PhO^-, as well as MeS^- *vs.* PhS^- (Table VIII), shows that the smaller nucleophiles give rise to the lower value of ΔS^*. In the case of the sulfur nucleophiles the order $\Delta S^*_{MeS^-} < \Delta S^*_{PhS^-}$ in HMPA is the reverse of the order in methanol, in which differences in ion solvation are less pronounced and the full effect of the steric interactions for the larger PhS^- emerge. Comparison of $^-OCH_3$ with another relatively small nucleophile, $^-SCH_3$, in HMPA shows little difference between the ΔS^* values; this similarity is what is predicted if solvation effects influence the magnitude of ΔS^* to a greater extent than heavy nucleophile steric interactions between entering and leaving groups. The choice of a solvent, methanol or HMPA, appears to have little effect, however, upon the relative magnitudes of ΔS^* within a group of three bromopyridines for each nucleophile. For methoxide ion in methanol these differences in entropies of activation, though small, have been accounted for[9] on the basis of differences in solvation of the ground states and the transition states. In the present cases, other factors need to be taken into account also, such as adverse steric interactions at a nonbonding level below that at which there are substantial increases in ΔH^* (*e.g.* steric effect by a 3-CH_3 group upon the rotational degrees of freedom of the bulky sulfur nucleophile in the transition state for attack at C-2),[22] steric interactions between the sulfur nucleophile and the departing bromine atom, and differences in the degrees of solvation of the transitions states in HMPA for the various substituted pyridines. This is discussed in detail elsewhere.[23]

Experimental Section

Materials. HMPA (Dow Chemical Co.) was fractionally distilled, the fraction of bp 65–66° (1 mm) being used. The purification of methanol, 2-bromo-, 2-bromo-3-methyl-, and 2-bromo-5-methylpyridine was as previously reported.[9] 2,5-Dibromopyridine was recrystallized from ethanol and had mp 94° (lit.[24] mp 94°). The preparation of 2,3-dibromopyridine was reported previously.[12]

Solutions of potassium thiomethoxide in methanol were prepared by dissolving solid potassium thiomethoxide in pure methanol and storing the solutions under nitrogen. These solutions were standardized by direct titration with hydrochloric acid. Potassium thiomethoxide was prepared[25] by adding an excess of methyl mercaptan to a methanolic solution of potassium methoxide (200 ml, 0.5 *M*). To this solution toluene (200 ml) was added, and the resulting mixture was distilled until the boiling point of toluene (110°) was reached. The potassium thiomethoxide precipitated as a fine crystalline mass and was dried at 100° (1 mm) for 12 hr.

Solutions of potassium phenoxide in methanol were prepared by adding an equivalent amount of potassium methoxide in methanol to a weighed amount of phenol.

Solutions of potassium methoxide, potassium thiomethoxide, potassium phenoxide, and potassium thiophenoxide in HMPA were prepared by dissolving the corresponding salt in pure HMPA.

The solutions were standardized by potentiometric titration with standard hydrochloric acid (0.00232 *M*). Potassium methoxide was prepared by the addition of pure potassium metal (4 g) in small portions to dry methanol (250 ml) under a nitrogen atmosphere. The methanol was removed on a film evaporator and the resulting white solid was dried at 60° (1 mm) for 12 hr. Potassium phenoxide was prepared from phenol by the procedure of Kornblum and Lurie.[26] Solid potassium thiophenoxide was prepared by the procedure previously reported.[12]

Reaction Products. These were obtained by a preparative reaction of the appropriate 2-bromopyridine with potassium thiomethoxide in methanol and with potassium methoxide, thiomethoxide, phenoxide, and thiophenoxide in HMPA under the conditions of the kinetic runs. 2-Methoxypyridine had bp 138–140° (755 mm) [lit.[9] bp 140–142° (740 mm)]. 2-Methoxy-3-methylpyridine had bp 157–159° (750 mm) [lit.[9] bp 38° (6 mm)]. 2-Methoxy-5-methylpyridine had bp 39–40° (2 mm) [lit.[9] bp 52° (6 mm)]. 2-Thiophenoxypyridine had bp 123–124° (1 mm) [lit.[27] bp 160–162° (8 mm)]. 3-Methyl-2-thiophenoxypyridine had bp 132–133° (1 mm) [lit.[12] bp 142–144° (2 mm)]. 5-Methyl-2-thiophenoxypyridine had bp 139–140° (1 mm) [lit.[12] bp 148–150° (2 mm)]. 2-Phenoxypyridine (from light petroleum) had mp 41–42° (lit.[28] mp 42–44°). 2-Thiomethoxypyridine had bp 54–55° (3 mm) [lit.[29] bp 197° (760 mm)].

3-Methyl-2-thiomethoxypyridine had bp 61–62° (2.6 mm) (61%). The picrate (from methanol) had mp 119–120°.

Anal. Calcd for $C_7H_9NS,C_6H_3N_3O_7$: C, 42.39; H, 3.26. Found: C, 42.49; H, 3.34.

Nmr (CCl_4) of free base: δ 8.17 (1 H, q, $J_{5,6}$ = 4.6, $J_{4,6}$ = 1.8 Hz, H-6), 7.14 (1 H, q, $J_{4,5}$ = 7.9 Hz, H-4), 6.74 (1 H, q, H-5), 2.48 (3 H, s, CH_3S), 2.19 (3 H, s, CH_3).

5-Methyl-2-thiomethoxypyridine had bp 70–71° (2.6 mm) (53%).

Anal. Calcd for C_7H_9NS: C, 60.39; H, 6.52. Found: C, 60.46; H, 6.75.

The picrate (from methanol) had mp 181–182°.

3-Bromo-2-thiomethoxypyridine had bp 71–72° (2 mm) (56%).

Anal. Calcd for C_6H_6BrNS: C, 35.31; H, 2.96. Found: C, 35.37; H, 2.98.

5-Bromo-2-thiomethoxypyridine (from ethanol) had mp 40–41° (83%), nmr (CCl_4) δ 8.43 (1 H, d, $J_{4,6}$ = 1.3 Hz, H-6), 7.48 (1 H, q, $J_{3,4}$ = 4.5 Hz, H-4), 7.00 (1 H, d, H-3), 2.50 (3 H, s, CH_3).

Anal. Calcd for C_6H_6BrNS: C, 35,31; H, 2.96. Found: C, 35.47; H, 2.99.

3-Methyl-2-phenoxypyridinehad bp 101–102° (1 mm) (81%), nmr (CCl_4) δ 7.80 (1 H, q, H-6), 7.12 (6 H, m, H-4 and C_6H_5), 2.67 (3 H, s, CH_3).

The picrate (from methanol) had mp 145–146°.

Anal. Calcd for $C_{12}H_{11}NO$, $C_6H_3N_3O_7$: C, 52.17; H, 3.38. Found: C, 52.12; H, 3.48.

5-Methyl-2-phenoxypyridinehad bp 81° (0.1 mm) (78%), nmr (CCl_4) δ 7.80 (1 H, d, H-6), 7.16 (6 H, m, H-4 and C_6H_5), 6.70 (1 H, d, $J_{4,5}$ = 4 Hz, H-5), 2.20 (3 H, s, CH_3).

Anal. Calcd for $C_{12}H_{11}NO$: c, 77.81; H, 5.99. Found: C, 77.83; H, 6.06.

Kinetic Procedures. A. Potassium Thiomethoxide in Methanol. The runs were carried out in sealed tubes under nitrogen using 5-ml portions of solutions containing equimolar (*ca.* 0.0095 *M*) proportions of potassium thiomethoxide and the 2-bromopyridine. Aliquots were quenched in ice. The time at which the first tube was removed from the oil bath was taken as zero time. The kinetics were followed by estimating unreacted thiomethoxide ion by potentiometric titration with dilute hydrochloric acid [time in minutes, titer for thiomethoxide determination *vs.* 0.0244 *M* HCl (a = 18.00 ml)]: 0, 17.71; 30, 15.80; 60, 14.43; 90, 13.06; 115, 12.21; 150, 11.13; 180, 10.43; $k_2 = 1.00 \times 10^{-3}$ l. mol^{-1} sec^{-1}.

B. Potassium Thiophenoxide in HMPA. Equimolar amounts of the 2-bromopyridine and potassium thiophenoxide in HMPA (*ca.* 4.0 mequiv in 3.95 ml) were sealed in glass tubes under nitrogen. Tubes were submerged in a thermostat and allowed 10 min to attain thermal equilibrium. Aliquots were quenched at regular intervals by addition to dilute hydrochloric acid (40 ml, 0.00757 *M*). The kinetics were followed by measuring unreacted thiophenoxide by back titration with barium hydroxide solution (0.0090 *M*).

C. Potassium Methoxide and Thiomethoxide in HMPA. Equimolar amounts of the 2-bromopyridine and potassium methoxide (or thiomethoxide) were combined in a flask under nitrogen. The flask was immersed in a thermostat and allowed 5 min for thermal equilibration. Aliquots (2.0 ml) were quenched in hydrochloric acid (30 ml. 0.00757 *N*) and the excess acid was back-titrated with barium hydroxide solution (*ca.* 0.005 *N*).

D. Potassium Phenoxide in HMPA. The runs were carried out in sealed tubes under nitrogen using 1.97-ml portions of a solution containing equimolar (0.0033 mol) proportions of the 2-bromopyridine and potassium phenoxide. Aliquots were quenched in halide-free nitric acid (*ca.* 30 ml, 0.1 *M*), and liberated bromide ion was titrated against silver nitrate (0.0010 *M*) potentiometrically using a calomel reference cell and a bromide-specific electrode (Orion).

Competitive Reactions of 2-Bromopyridine and 2-Bromomethylpyridines with Potassium Phenoxide in HMPA. 2-Bromopyridine (1.3144 g, 0.0083 mol), 2-bromo-3-methylpyridine (1.4311 g, 0.0083 mol), and potassium phenoxide (0.3689 g, 0.00279 mol) were dissolved in HMPA (12 g) in a dry Pyrex tube. The tube was sealed under nitrogen and suspended in a thermostat at 80°. After 142 hr biphenyl (0.1105 g) was added as internal standard and also water (75 ml). The aqueous layer was extracted with ether (5 × 75 ml), and the combined ethereal extracts were washed with water (2 × 75 ml), dried, concentrated to 10 ml, and analyzed by glc on a 6 ft × 0.25 in. column packed with SE-52 (10%) on Chromosorb W (60–100 mesh) at 160° and a 60 ml/min He flow rate. The total rate ratio was calculated using the Ingold–Shaw equation[30] and found to be $^{o\text{-Me}}K_H = 0.47 \pm 0.005$. When 2-bromo-5-methylpyridine was used $^{p\text{-Me}}K_H = 0.099 \pm 0.002$.

Acknowledgments. We wish to thank the University of Alabama Research Grant Committee for support of this work, which was carried out during the tenure (by A. J. N.) of an NDEA fellowship (1968–1970). We also wish to thank Reilly Tar & Chemical Corp. for the gift of some starting pyridines.

Registry No.—Potassium methoxide, 865-33-8; potassium thiomethoxide, 26385-24-0; potassium phenoxide, 100-67-4; potassium thiophenoxide, 3111-52-2; 3-methyl-2-thiomethoxypyridine, 51933-73-4; 3-methyl-2-thiomethoxypyridine picrate, 51933-74-5; 5-methyl-2-thiomethoxypyridine, 51933-75-6; 5-methyl-2-thiomethoxypyridine picrate, 51933-76-7; 3-bromo-2-thiomethoxypyridine, 51933-77-8; 5-bromo-2-thiomethoxypyridine, 51933-78-9; 3-methyl-2-phenoxypyridine, 51933-79-0; 3-methyl-2-phenoxypyridinepicrate, 51933-80-3; 5-methyl-2-phenoxypyridine, 51933-81-4.

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Products and Mechanisms in the Anodic Oxidation of *N,N*-Dimethylbenzylamine in Methanol

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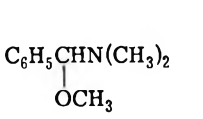
Received April 18, 1974

The anodic oxidation of *N,N*-dimethylbenzylamine has been studied in methanol–tetra-*n*-butylammonium fluoroborate and in methanol–potassium hydroxide. The major oxidation mechanism is of the ECE type and initiated by electron transfer from the amine substrate. The initially formed cation radical loses a proton and transfers an electron in subsequent steps to give cations, which react with available nucleophiles to yield the final products. The relative amount of attack on the methyl and benzyl positions is determined by the nature of the base participating in the proton transfer. When the base is the amine substrate, attack on methyl is strongly favored. When a strong base, *e.g.*, hydroxide ion or methoxide ion, is involved, the direction of attack is very nearly in accord with statistical expectations.

The anodic methoxylation of *N,N*-dimethylbenzylamine in methanol–potassium hydroxide affords two substitution products, α-methoxy-*N,N*-dimethylbenzylamine (I) and *N*-methoxymethyl-*N*-methylbenzylamine (II), in the ratio



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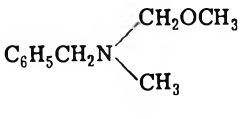


II

of 1:4.[1] Weinberg and Brown[1] proposed that this oxidation was initiated by electron transfer from the amine, but Smith and Mann[2] suggested that the oxidation resulted from the attack on the substrate of anodically generated methoxyl radicals. In later work[3] Weinberg supported his proposal by demonstrating that significant methoxylation occurs only at potentials greater than the half-wave potential for *N,N*-dimethylbenzylamine oxidation (0.92 V *vs.* sce at a rotating platinum microelectrode in acetonitrile containing 0.5 *M* lithium perchlorate).

The preference for substitution of the methyl group was contrary to *a priori* expectation and was even more pronounced in the anodic cyanation of *N,N*-dimethylbenzylamine, where substitution occurred exclusively on the methyl group.[4] Both Weinberg[3] and Andreades[4] have invoked adsorbed intermediates, in which the methyl group of the adsorbed species is more accessible to chemical attack, to account for the observed direction of substitution.

However, many homogeneous, chemical oxidations of *N,N*-dimethylbenzylamine, all initiated by an electron transfer from the amine to form an aminium cation radical, show preferential attack on the methyl group. Some examples are the oxidation by chlorine dioxide in aqueous solution,[5] the oxidation by potassium hexacyanoferrate(III) in 2 *M* potassium hydroxide,[6] and the photochemical oxidation by 4-benzoylbenzoic acid in 2:1 *tert*-butyl alcohol–water.[7] It is, therefore, possible that the observed preferential attack on the methyl group is a, as yet incompletely understood, characteristic reaction of the amine cation radical and does not involve the intervention of the electrode surface. To explore this possibility we have carried out a more detailed study of the anodic oxidation of *N,N*-dimethylbenzylamine.

Cyclic Voltammetry. Fleischmann and Pletcher[8] have reported that the solvent decomposition potential, defined as the potential above which the current is greater than 10 mA/cm^2, for the acetonitrile–0.14 *M* tetraethylammonium fluoroborate electrolyte exceeds 3 V *vs.* Ag/Ag$^+$ 10^{-2} *M*. On cyclic voltammetry of dimethylbenzylamine in acetonitrile–0.1 *M* tetra-*n*-butylammonium fluoroborate, the peak current varied linearly with the amine concentrations, and the peak potential occurred at 0.86 V *vs.* sce, a value in reasonable agreement with the polarographic half-wave potential reported by Weinberg.[3]

Figure 1 shows a cyclic voltammogram for 0.6 *M* dimethylbenzylamine in methanol–0.5 *M* potassium hydroxide at a scan speed of 200 mV/sec. The concentrations are those used in the preparative experiments to be described later. Curve A is for the electrolyte alone and curve B is with added amine. Below 1.1 V *vs.* sce the observed currents are actually depressed by the addition of the amine, and this is in qualitative agreement with a similar observation, based on Tafel plots, made by Weinberg.[3] Above 1.1 V the currents are higher with the amine present. Both dimethylbenzylamine and methoxide ion are being oxidized simultaneously, and the waves for the two oxidations are not fully separable.

The solvent decomposition potential for methanol–0.4 *M* tetra-*n*-butylammonium fluoroborate is approximately 1.3 V *vs.* sce. In this electrolyte methoxide ion is absent, and the current increase above 1.3 V is due to oxidation of methanol. The cyclic voltammogram at a scan speed of 200 mV/sec for 0.6 *M* dimethylbenzylamine in this electrolyte is shown in Figure 2. The concentrations used are again those of preparative experiments. In this system the wave for the amine oxidation is clearly separable from the background, and the peak potential is 0.94 V *vs.* sce.

More detailed cyclic voltammetry studies in both acetonitrile and methanol, with 2.96×10^{-2} amine and 0.1 *M* tetra-*n*-butylammonium fluoroborate, satisfy the theoretical criteria, developed by Nicholson and Shain,[9] for an

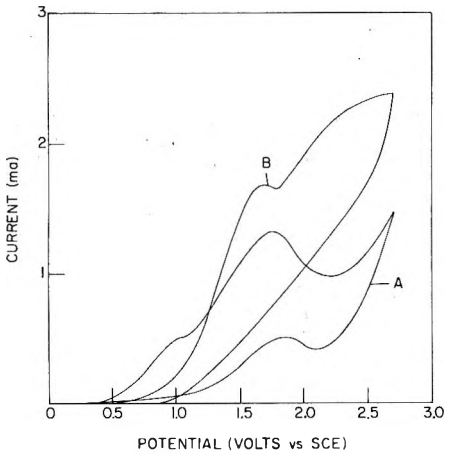


Figure 1. Cyclic voltammogram for 0.6 *M* *N,N*-dimethylbenzylamine in methanol–0.5 *M* potassium hydroxide at a scan speed of 200 mV/sec: A, background; B, amine.

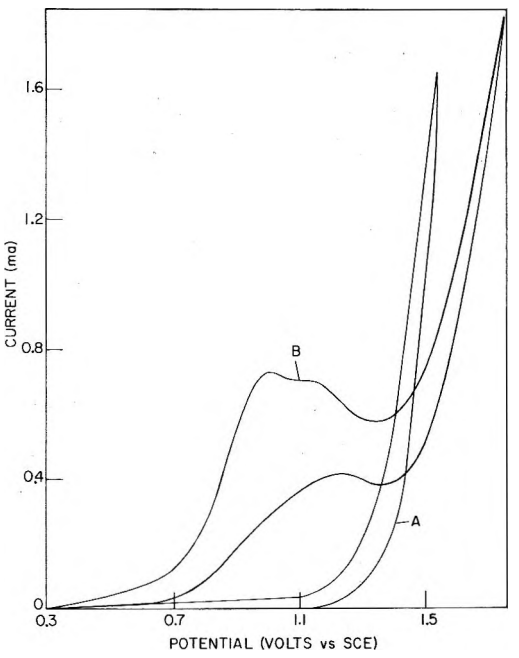


Figure 2. Cyclic voltammogram for 0.6 *M* *N,N*-dimethylbenzylamine in methanol–0.4 *M* tetra-*n*-butylammonium fluoroborate at a scan speed of 200 mV/sec: A, background; B, amine.

ECE mechanism and eliminate the possibility of an EC mechanism, involving disproportionation of the initially formed cation radical.[10] No detectable cathodic current was observed at scan rates as high as 50 V/sec. The number of electrons transferred in the reaction was found to be greater than one and very probably two.

Product Studies. A typical reaction mixture after electrolysis contains eight or more components. Our primary concern, in this study, was the relative amounts of attack on the methyl and benzyl positions of the starting substrate. We have, therefore, chosen to simplify the analytical problem by hydrolyzing the product mixture prior to analysis. After hydrolysis the reaction mixture contains the starting amine, benzaldehyde, resulting from attack on the benzyl position, and *N*-methylbenzylamine and benzyl-

Table I
Products Obtained after Anodic Oxidation of 0.1 Mol of Dimethylbenzylamine in Methanol, Passing 0.149 F of Charge at Constant Current, and Hydrolysis of the Reaction Mixture

Current, A	Recovered $C_6H_5CH_2N(CH_3)_2$, %	Products C_6H_5CHO, %	Products $C_6H_5CH_2NHCH_3$, %	Products $C_6H_5CH_2NH_2$, %	% starting materials accounted for	Ratio attack on methyl/attack on benzyl
A. With 0.36 *M* Tetra-*n*-butylammonium Fluoroborate as Supporting Electrolyte						
2.0	73	8	7	2	90	1.4
1.0[a]	57	10	20	4	91	2.8
0.5	35	7	48	4	94	8.0
0.1[b]	29	7	58	2	94	8.9
B. With 0.47 *M* Potassium Hydroxide as Supporting Electrolyte						
2.0	43	15	34	2	94	2.5
1.0[b]	42	15	36	3	96	2.8
0.1[b]	40	10	35	1	86	3.7

[a] Average of three experiments. [b] Average of two experiments.

Table II
Products Obtained after Anodic Oxidation of 0.0296 Mol of Dimethylbenzylamine in Methanol at Constant Potential and Hydrolysis of the Reaction Mixture

Potential, V *vs.* sce	Charge passed, F	Recovered $C_6H_5CH_2N(CH_3)_2$, %	Products C_6H_5CHO, %	Products $C_6H_5CH_2NHCH_3$, %	Products $C_6H_5NH_2$, %	% starting materials accounted for	Ratio attack on methyl attack on benzyl
A. With 0.40 *M* Tetra-*n*-butylammonium Fluoroborate as Supporting Electrolyte							
+1.05	0.0296	44	4	40		88	10.1
+1.60	0.0296	48	5	35		88	7.0
+1.90	0.0296	59	5	23	3	90	5.8
+2.30	0.0296	63	5	22	3	93	5.6
B. With 0.47 *M* Potassium Hydroxide as Supporting Electrolyte							
+1.0	0.0122	73	4	8		85	2.0
+1.1	0.0300	62	9	21		92	2.3
+2.3	0.0750	16	24	42	6	88	2.3

amine, products from attack on the methyl positions. The justification for this simplifying procedure is given in the Experimental Section.

The results of experiments on the anodic oxidation of *N,N*-dimethylbenzylamine in methanol containing 0.36 *M* tetra-*n*-butylammonium fluoroborate as supporting electrolyte and in methanol containing 0.47 *M* potassium hydroxide as supporting electrolyte are shown in Tables I and II. Table I reports the results at constant current, and Table II gives the results at constant potential. The percentages shown in these tables indicate the amounts of starting material converted to a given product rather than coulombic yields. The last column of the two tables, headed, Ratio, attack on methyl/attack on benzyl, is obtained by adding the percentage yield of *N*-methylbenzylamine and two times the percentage yield of benzylamine and dividing the sum by the percentage yield of benzaldehyde. The factor of 2 for the benzylamine is necessary, since its formation results from two stages of oxidation, one on each methyl group, and an overall four-electron change.

In the experiments in the methanol–potassium hydroxide electrolyte the observed ratios of attack on the methyl position to attack on the benzyl position were essentially constant at the average value of 2.2 at constant anodic potentials of 1.0, 1.1, and 2.3 V, all *vs.* sce. In the constant-current experiments the ratios were 2.5 at 2.0 A, 2.8 at 1.0 A, and 3.7 at 0.1 A. From purely statistical considerations one would expect a ratio of 3. The present results, therefore, do not indicate any preference for attack on the methyl group in this electrolyte system.

In the methanol–fluoroborate electrolyte a very different situation is observed. At the lowest constant potential, 1.05 V *vs.* sce, the preference for attack on methyl is strong, and the observed ratio is 10. At 1.60 V there is a sharp drop to a ratio of 7.0, and then as the potential increases there is a further decrease in the ratio to values of 5.8 at 1.9 V and 5.6 at 2.3 V.

In all of the constant-potential experiments attack on the methyl group is, therefore, strongly favored. The experiments at constant current exhibit a similar trend. The highest ratio, 8.9, is observed at the lowest current, 0.1 A. At 0.5 A the ratio drops to 8 and at 1.0 A to 2.8. At the smaller currents, 0.1 and 0.5 A, there is still a preference for methyl group attack, but at 2.0 A the ratio drops to 1.4, where it is now attack on the benzyl group that is favored.

Experimental Section

Materials. Baker and Adamson, electronic grade, acetone-free methanol was used without further purification. DPI acetonitrile containing less than 0.1% water was purified as described by Mann[11] and distilled from phosphorus pentoxide directly into the electrochemical cells. DPI *N,N*-dimethylbenzylamine was distilled from calcium hydride, bp 55° (9 mm). Tetra-*n*-butylammonium fluoroborate was prepared and purified as previously described.[12]

***N*-Benzyl-*N*-methylformamide** was prepared by heating *N*-methylbenzylamine (24.2 g, 0.2 mol) with formamide (10 g, 0.22 mol) at 100° until ammonia evolution ceased. Distillation at 1 mm yielded 24.8 g (83.2%) of the amide, bp 104°.

Cyclic Voltammetry. These studies were performed with a PAR 170 Electrochemistry unit. A single-compartment cell, fitted with a Pt button working electrode, a Pt sheet auxiliary electrode, and a saturated calomel reference electrode, was used. The supporting electrolyte was 0.1 *M* tetra-*n*-butylammonium fluoroborate. For current function studies a Tektronix Type 564 storage oscilloscope was used.

Justification of Analytical Method. In a screening experiment a solution containing 0.1 mol of dimethylbenzylamine and 0.05 mol of tetra-*n*-butylammonium fluoroborate in 140 ml of methanol was electrolyzed at a constant current of 1 A until 0.152 F of charge had been passed. Analysis of the solution by vpc indicated that 64% of the starting amine was unreacted. The products found included 2.0% benzaldehyde, 2.1% *N*-methylbenzylamine, and 1.7% *N*-methyl-*N*-benzylformamide. This accounts for 69.8% of the starting amine. In addition the vpc tracing showed the presence, in lesser quantities, of four compounds, probably methoxy-substituted dimethylbenzylamines, with retention times shorter than that of *N*-methyl-*N*-benzylformamide, and one, possibly the amino ether III, reported by Weinberg,[3] which had a much longer retention time than the amide..

$$(C_6H_5CH_2NCH_2)_2O$$

III

After acid hydrolysis the above reaction mixture afforded 61% recovered amine, 11% benzaldehyde, 12% *N*-methylbenzylamine, and 3.6% benzylamine. These products account for 87.6% of the starting *N,N*-dimethylbenzylamine. The formation of *N*-methyl-*N*-benzylformamide, found prior to hydrolysis, requires a four-electron oxidation and represents two stages of oxidation on a methyl group. Therefore, to the extent that some of the *N*-methylbenzylamine results from hydrolysis of the amide, the ratios reported in the last column of Tables I and II are slightly low. In the experiment described above 1.7% of amide was present prior to hydrolysis and 12% of *N*-methylbenzylamine was found after hydrolysis. The amide, therefore, accounts for only 14% of the *N*-methylbenzylamine found.

Constant-Potential Electrolyses. The PAR instrument with ir compensation was used. The electrolysis cell was a single compartment, water-jacketed cell, cooled by a continuous flow of tap water. A Teflon cap, which held two Pt sheet electrodes (5.5 × 2.5 cm) 2.5 cm apart, was fitted to the top of the cell, and the sce reference electrode was placed in close proximity to the anode through a hole in the cap. The electrolysis solution was stirred with a magnetic stirring bar.

In a typical experiment a solution of *N,N*-dimethylbenzylamine (4.0 g, 0.0296 mol) and tetra-*n*-butylammonium fluoroborate (6.6 g, 0.02 mol) in methanol (50 ml) was electrolyzed under the conditions indicated in Table II. After completion of the electrolysis the solution was transferred to a round-bottomed flask with the aid of additional methanol (20 ml). Water (10 ml) and concentrated hydrochloric acid (10 ml) were added, and the solution was refluxed overnight. The methanol was separated by distillation at atmospheric pressure through a Vigreux column, and this methanol distillate was analyzed by vpc for any products that codistilled.

The addition of ether to the above distillation residue precipitated the fluoroborate salt. Both the salt and the solution were extracted copiously with ether. The ether extracts were combined, dried over magnesium sulfate, and concentrated to a volume of 25 ml for vpc analysis.

The aqueous residue from the above extractions was made basic by the addition of a concentrated solution of sodium hydroxide. This was then again extracted with ether, and the ether extracts were dried and concentrated to a volume of 25 ml for vpc analysis.

For the experiments with the methanol–potassium hydroxide electrolyte the procedure was as shown above except that the hydrolysis was carried out after the addition of 75 ml of water and 20 ml of concentrated hydrochloric acid.

Constant-Current Electrolyses. These were carried out using the cell and electrode configuration previously described.[12] The work-up procedure was essentially the same as that described above for the constant-potential electrolyses except that proportionately larger volumes of reagents were used to take care of the larger scale on which the constant current electrolyses were run.

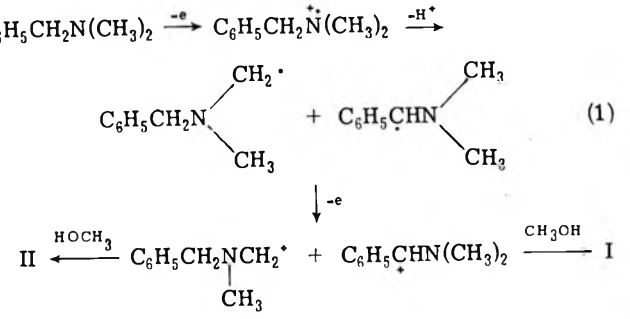
Vpc Analyses. These were done under isothermal conditions on an F & M Model 72 dual column gas chromatograph using thermal conductivity detection and a helium carrier gas. Using a 6-ft column packed with 10% SE-30 on 60-80 Diataport S, benzylamine was determined at 100°, benzaldehyde at 120°, and *N*-methyl-*N*-benzylformamide at 160°. Using a 6-ft column packed with 10% polyphenyl ether (six ring) on Diataport S, benzaldehyde, *N*-methylbenzylamine, and *N,N*-dimethylbenzylamine were determined simultaneously at 140°. The unknown solutions were compared with standards prepared from the identified components.

Discussion

An adequate mechanism for the anodic oxidation of *N,N*-dimethylbenzylamine in methanol must account, at one and the same time, for both the observed electrochemical parameters and the very large difference in the direction of attack when the supporting electrolyte is changed

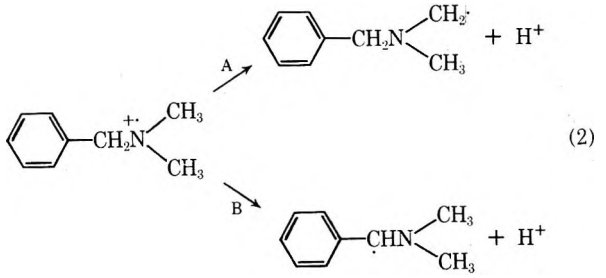
from potassium hydroxide to tetra-*n*-butylammonium fluoroborate. In the methanol–potassium hydroxide electrolyte the divergence from statistical expectations is small. In the methanol–fluoroborate electrolyte the preference for attack on the methyl group is very large at 1.05 V *vs.* sce, where cyclic voltammetry indicates that electron transfer is occurring only from the amine, but decreases significantly at potentials greater than 1.3 V, where cyclic voltammetry indicates that the amine and the methanol solvent are being oxidized simultaneously.

In the synthetic experiment at a constant anodic potential of 1.05 V with methanol–fluoroborate electrolyte (Table II), the oxidation mechanism is unambiguous. At this potential electron transfer can occur only from the amine, and cyclic voltammetry is consistent with an ECE mechanism. The only possible formulation is that shown in eq 1. Yet it is in this very experiment that we found the



(1)

greatest preference for attack on methyl, the observed ratio for methyl attack/benzyl attack being 10. If, in fact, eq 1 is a correct representation of the reaction mechanism, it follows that in the proton transfer step (eq 2) the rate con-

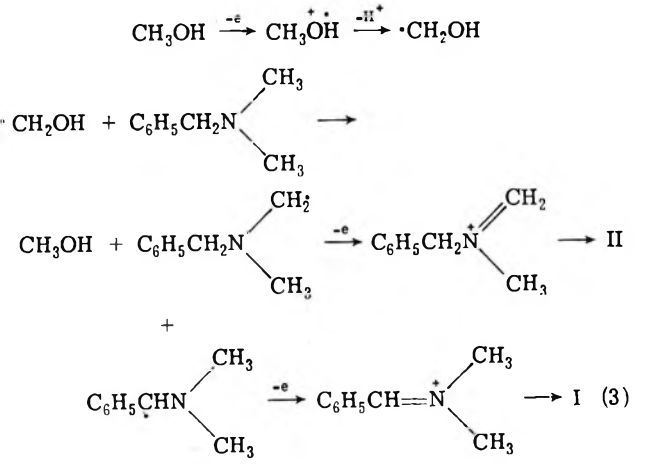


(2)

stant for path A is approximately 3.5 times larger than the rate constant for path B.

It is an obvious corollary of the above that, contrary to all *a priori* expectations, the methyl hydrogens in the *N,N*-dimethylbenzylamine cation radical are much more reactive than the methylene hydrogens, or, stated alternatively, that the positive charge density is greater on the methyl hydrogens of the cation radical than on the methylene hydrogens. It is fortuitous that INDO calculations have been carried out on this cation radical by Lars Cedheim at the University of Lund in Sweden, and we are very much indebted to Professor Lennart Eberson, who conveyed the results to us. These calculations assign positive charge densities to all of the methyl and methylene hydrogens. If one assumes a transition state for the proton abstraction reaction that is close to the cation radical, these results indicate that the methyl hydrogens should be roughly twice as reactive as the methylene hydrogens. Taking the statistical factor into account one would expect a reactivity ratio of 6:1 for attack on methyl and methylene hydrogens, respectively. These results afford us some confidence in the validity of our observations and in the correctness of our interpretation.

Still to be explained is the drop in the observed ratios at anodic potentials of 1.5 V and higher. At these potentials electron transfer is occurring simultaneously from both the amine and the methanol solvent, and we would suggest that a second oxidation mechanism becomes possible and competes at these higher potentials. This mechanism, shown in eq 3, is ECE overall, but involves a hydrogen atom abstrac-



(3)

tion, not by the methoxyl radical, but rather by the hydroxymethyl radical. Since the hydrogen atom abstraction occurs on the amine molecule rather than the cation radical, we can be confident that abstraction from the secondary methylene position will be preferred.

The synthetic experiments at constant current are in qualitative agreement with the foregoing. At the lowest current (lowest potential) the ratio is highest and decreases regularly with increasing constant current. At the highest constant current used, 2.0 A, the observed ratio, 1.4, actually indicates a preference for attack on the methylene position. This is possible, if, under this condition, eq 3 represents the predominant oxidation mechanism.

It is the presently prevailing view that, in the methanol–potassium hydroxide electrolyte, amine oxidation products result only from the reaction sequence shown in eq 1, where the initiating electron transfer is from the amine substrate. This is based on Weinberg's finding that amine oxidation products are formed only at high enough potentials to permit electron transfer from the amine. This implies that at lower potentials methoxide ion may be oxidized to methoxyl radical, but the radical so formed does not abstract a hydrogen from the substrate amine. We have confirmed this view in a qualitative sense at least. In addition to the experiments shown in Table II, we have done a preparative experiment at a constant anode potential of 0.80 V *vs.* sce. At this potential there is presumably no direct oxidation of amine, and the currents observed (10–15 mA) must be attributed to methoxide ion oxidation. In this experiment there was, in fact, some oxidation of the amine, but the coulombic efficiency (~1%) was almost negligible, and the only oxidation product found was benzaldehyde. This is exactly what might be expected if, in this experiment, the only amine oxidation mechanism available was a counterpart of eq 3 with methoxyl radical as the abstracting species and if the methoxyl radical was extremely inefficient in the abstracting process.

These results pose an apparent contradiction. In both electrolyte systems the predominant oxidation mechanism is that shown in eq 1, yet in methanol–fluoroborate this results in a strong preference for attack on the methyl group, but in methanol–potassium hydroxide the direction of attack approaches statistical expectations. The difficulty is readily overcome if one takes due cognizance of the proton-accepting base in the two experiments. In the methanol–

fluoroborate electrolyte the only available base is the amine substrate, but in the methanol–potassium hydroxide electrolyte the much stronger bases, hydroxide ion and/or methoxide ion, are present at a combined concentration of 0.47 *M*. It is reasonable that the weaker base should attack the positions of higher positive charge density in a discriminating fashion and that the much stronger base should attack more randomly in a nondiscriminating reaction.

Support for this point of view can be mustered from other oxidation studies of *N,N*-dimethylbenzylamine. In both the oxidation with chlorine dioxide[5] at pH 8 and in the oxidation with potassium hexacyanoferrate (III) in 2 *M* potassium hydroxide[6] there is exhibited only a modest preference for attack at the methyl position. We have repeated the latter oxidation. The oxidation products obtained were benzaldehyde, *N*-methylbenzylamine, and *N*-benzyl-*N*-methylformamideand the ratio of methyl attack to benzyl attack was 2.8. The electrochemical dealkylation of *N,N*-dimethylbenzylamine at pH 12 at a glassy carbon electrode involves a mechanism similar to that shown in eq 1, and again there is no special preference for removal of the methyl group.[13] All of the above reactions are in the presence of a strong base where the proton transfer step would be expected to be nondiscriminating. By contrast, the photochemical oxidation of dimethylbenzylamine, where the strongest base present is the amine substrate, shows a very strong, albeit not quantitatively determined, preference for attack on the methyl group.[7]

Registry No.—*N*-Benzyl-*N*-methylformamide, 17105-71-4; *N*-methylbenzylamine, 103-67-3; formamide, 75-12-7; *N,N*-dimethylbenzylamine, 103-83-3.

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Peroxodisulfate Oxidation of Guanosine and Deoxyguanosine in Alkaline Aqueous Solution[1]

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Received April 2, 1974

The peroxodisulfate oxidation of the common nucleosides has been investigated. Only guanine nucleosides show appreciable reaction with peroxodisulfate in 1 *M* Na_2CO_3 solution at 40°. Rate *vs.* pH plots suggest that the guanosine anion is the kinetically significant reactant. No reaction between guanosine and peroxodisulfate was observed under neutral or mildly acidic conditions at 40°. Radical traps have no effect on either the rate or extent of peroxodisulfate disappearance or on the rate or extent of product formation. Products identified as a result of peroxodisulfate oxidation of guanosine were guanidine, urea, ribose, ribosylurea, and ribonic acid. Those products identified for deoxyguanosine oxidation were guanidine, urea, and deoxyribosylurea. Alkaline peroxodisulfate oxidation shows promise as a selective chemical method for the modification of polynucleotides at the site of guanine residues.

Our studies on the peroxodisulfate oxidation of the common nucleic acid bases[2] have shown that guanine reacts much more rapidly under all conditions than any other base. The relative rates of oxidation in 1 *N* KOH at 40° are as follows: adenine, 1; thymine, 5.5; uracil, 5.2; cytosine, 8.6; guanine, 338. We have further shown that the rates of these oxidations are dependent upon pH, since it is only the dianions of thymine and uracil and the monoanions of adenine and cytosine which react at a significant rate with peroxodisulfate ions. In contrast, both the mono- and dianions of guanine are reactive. It appeared probable, therefore, that of the nucleosides, only guanosine would be oxidized. We present evidence in this paper to substantiate this supposition. This suggests that peroxodisulfate ions can be used to modify polynucleotides, particularly polydeoxyribonucleotides, in a highly selective way.

Materials and Methods

Adenosine, uridine, thymidine, cytidine, guanosine, and deoxyguanosine were purchased from P & L Biochemicals Inc., Milwaukee, Wis. Guanidine hydrochloride was obtained from Heico, Inc., Delaware Water Gap, Pa. D-Ribose was purchased from Pfanstiehl Laboratories, Waukegan, Ill. Ribonolactone was obtained from the Sigma Chemical Co., St. Louis, Mo. 2-Deoxy-D-ribose and 8-hydroxyguanine were purchased from the Aldrich Chemical Company, Milwaukee, Wis. Potassium peroxodisulfate was a Baker Analyzed reagent, Phillipsburg, N. J., and was recrystallized from water for use in kinetic experiments. All other inorganic chemicals were Baker Analyzed reagents and were used without further purification. Ribosylurea was synthesized by the method of Benn and Jones[3] but was not isolated. Deoxyribosylurea was prepared by permanganate oxidation of deoxyguanosine by the method of Jones and Walker.[4] Ribonic acid was prepared by hydrolysis of ribonolactone in aqueous sodium hydroxide solution.

Ultraviolet absorption spectra were measured using a Perkin-Elmer Model 202 spectrophotometer. Colorimetric measurements were carried out on a Klett-Summerson colorimeter.

Table I
Peroxodisulfate Oxidation of Guanosine and Deoxyguanosine. Nucleoside and Temperature Dependencies

Substrate	Concn,[a] M	Conditions	k_2', M^{-1} min^{-1} [b]	No. of expts
Guanosine[c]	0.01–0.05	1 N KOH, 25°	0.161 ± 0.015	11
Guanosine	0.01–0.05	1 M Na_2CO_3, 40°	0.630 ± 0.04	14
Guanosine	0.05	1 M Na_2CO_3, 50°	1.27	1
Deoxyguanosine[c]	0.05	1 M Na_2CO_3, 30°	0.330	1
Deoxyguanosine	0.03–0.05	1 M Na_2CO_3, 40°	0.678 ± 0.00	2
Deoxyguanosine	0.05	1 M Na_2CO_3, 50°	1.24	1

[a] [Substrate]/[$K_2S_2O_8$] = 10. [b] $k_2' = k\psi$/[substrate]. [c] Activation parameters: guanosine and deoxyguanosine E_a = 13.1 ± 0.4 kcal mol^{-1}, ΔS^* = −28 ± 2 cal mol^{-1} deg^{-1}.

Partition chromatography on paper was performed on Whatman 3 MM paper in the machine cut direction at 25° using an ascending technique. The solvent systems utilized were solvent I, 2-propanol–ammonium hydroxide (58%)–water (7:1:2 v/v); solvent II, ethyl acetate–formic acid (88%)/water (7:2:1 v/v); solvent III, 2-propanol–water (7:3 v/v). Dried chromatograms were sprayed with Ehrlich's reagent[5] for the detection of urea derivatives. Ribose and ribonic acid were visualized with a benzidine–periodate spray.[6] Guanidine, urea, urea derivatives, ribose, and ribonic acid were revealed using the nitroprusside–ferricyanide–hydroxide spray.[7] Ultraviolet-absorbing components were located on paper chromatograms illuminated with an ultraviolet light source.

The concentration of D-ribose was estimated using the colorimetric method of Nelson[8] with the modification that twice the recommended copper concentration was employed in each assay.

Acid-hydrolyzable ribose was determined as follows. An aliquot (5.0 ml) of alkaline guanosine (0.01 M)–peroxodisulfate (0.06 M) reaction mixture was withdrawn, neutralized with dilute hydrochloric acid, and diluted to a final volume of 10.0 ml. The resulting solution was placed in a 125-ml erlenmeyer flask containing 1 g of anion exchange resin (Bio-Rad AG1-X8, 200–400 mesh, chloride form). The mixture was agitated for 20 min at room temperature. After centrifugation of the resin, a 2.0-ml aliquot was withdrawn and mixed with 1 ml of 1.0 N HCl. The resulting solution was heated on a boiling water bath for 25 min, cooled to room temperature, mixed with 1 ml of 1.0 N KOH solution, and diluted to a final volume of 10.0 ml. An aliquot (1.0 ml) of the resulting solution was withdrawn, mixed with 1.0 ml of the modified Nelson's reagent, and developed as described.[8]

Guanidine was determined by the method of Marston[9] as presented by Snell and Snell.[10] Urea was determined by the method of Coulombe and Favreau.[11] In both cases, batchwise pretreatment of neutralized reaction aliquots with excess anion-exchange resin (Bio-Rad AG1-X8, 200–400 mesh, chloride form) to remove unreacted peroxodisulfate was required, since peroxodisulfate interfered with both determinations.

Peroxodisulfate was determined by a modification of the iodometric method of Kolthoff and Carr.[12,13] Kinetic data were collected as described.[2]

Results

Kinetics: Peroxodisulfate Disappearance. The kinetics of peroxodisulfate disappearance in reaction with guanosine were measured under pseudo-first-order conditions in 1.0 N KOH at 25° and in 1 M Na_2CO_3 solution at 40°. Those for deoxyguanosine were measured in 1 M Na_2CO_3 at 40°. Under all conditions, semilog plots of the disappearance of peroxodisulfate with time showed good linearity for at least 2 half-times, suggesting first-order decomposition of peroxodisulfate. Neither EDTA (1×10^{-4} M) nor acrylamide (5×10^{-4} M)[2,14,15] had any effect on the rate of peroxodisulfate disappearance in reactions run in 1 M Na_2CO_3 at 40°.

Control experiments showed no more than 4% decomposition of peroxodisulfate over a 24-hr period in 1 M Na_2CO_3 at 40°. The extent of peroxodisulfate decomposition in the presence of adenosine, cytidine, uridine, or thymidine under the same reaction conditions never exceeded that observed for the maximum peroxodisulfate blank.

A first-order rate constant of 1.6×10^{-5} min^{-1} for the thermal decomposition of peroxodisulfate in aqueous solution at 40° was calculated using the data of Hakoila.[16] The first-order rate constant calculated for 4% decomposition of peroxodisulfate in 1 M Na_2CO_3 at 40° after 24 hr is 2.9×10^{-5} min^{-1}. If the difference between the calculated and our observed-first-order rate constant were attributable to reaction between the nonreactive nucleosides and peroxodisulfate, then the maximum calculated-second-order rate constant for reaction with nucleosides other than guanosine or deoxyguanosine is 1.2×10^{-3} M^{-1} min^{-1} under the conditions employed here. Values for the apparent-second-order rate constants (k_2') for guanosine and deoxyguanosine (Table I) are at least 500 times this value.

Nucleoside Dependence. Table I shows that values for the apparent-second-order rate constants (k_2') for guanosine oxidation in 1 N KOH at 25° and 1 M Na_2CO_3 at 40° are reasonably constant over the fivefold range of nucleoside concentration employed. Thus, the rate law which describes guanosine and deoxyguanosine oxidation is given by $-d[S_2O_8^{2-}]/dt = k_2'[\text{nucleoside}]_{tot}[S_2O_8^{2-}]$. The rate law held for a minimum of 2 half-times for both nucleosides. Second-order rate constants for guanosine and deoxyguanosine oxidation in 1 M Na_2CO_3 at 40° are virtually identical. The observed variation in k_2' with temperature together with the calculated activation parameters are also presented in Table I.

pH Dependence. Values for the apparent-second-order rate constant (k_2') for guanosine (0.01 M) oxidation at 25° showed no significant variation over the range of hydroxide ion concentrations 0.025–1.0 N at constant ionic strength (μ = 1.0, KCl).

Figure 1 shows the effect of varying pH on the apparent-second-order rate constant for the peroxodisulfate oxidation of guanosine at lower pH values, 40°, μ = 1.21. That point on the plot at which the value of k_2' is half-maximal corresponds to a pH of 9, in reasonable agreement with a pK_a for guanosine of 9.1 at 40° calculated from the heat of ionization presented by Izatt and Christensen.[17] These data indicate that it is only the guanosine anion which undergoes reaction with peroxodisulfate. The dianion of guanine is about 30 times more reactive with peroxodisulfate than the monoanion of guanosine.[2]

Ionic Strength Dependence. The peroxodisulfate oxidation of guanosine is subject to a positive salt effect consistent with a bimolecular reaction between ionic species of similar charge. Measurements at two ionic strengths

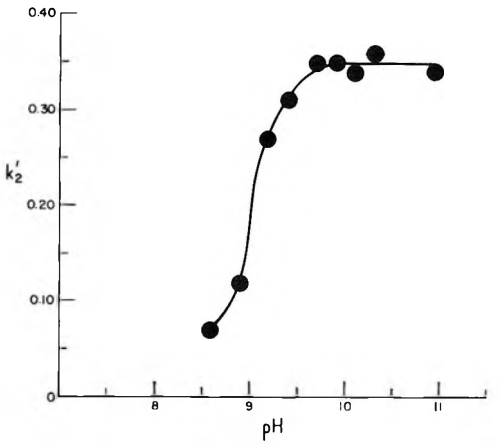

Figure 1. The peroxodisulfate oxidation of guanosine at 40°: pH dependence, [guanosine] 0.010 *M*, [$K_2S_2O_8$] 0.001 *M*, sodium carbonate–sodium bicarbonate buffer, μ = 1.21.

showed the following results: μ = 1.21, k_2' = 0.35; μ = 3.0, k_2' = 0.64 (pH 11, 40°).

Identification of Products. Products characterized in the peroxodisulfate oxidation of guanosine in 1 *M* Na_2CO_3 at 40° were guanidine, urea, ribose, ribosylurea, and ribonic acid. Those for deoxyguanosine were guanidine, urea, and deoxyribosylurea. Guanidine was identified by its chromatographic mobility (R_f's solvents I, II, III: 0.52, 0.57, 0.62), its color development with the nitroprusside–ferricyanide–hydroxide spray,[7] and isolation as its crystalline picrate.[4] Urea was identified by its chromatographic mobility (R_f's solvents I, II, III: 0.58, 0.73, 0.63) and color development with Ehrlich's reagent.[5] Ribose was characterized by its chromatographic mobility (R_f's solvents I, II, III: 0.58, 0.30, 0.67) and by its color development with the benzidine–periodate and nitroprusside–ferricyanide–hydroxide spray (white on yellow background after 5 hr). Ribonic acid (sodium salt) was confirmed by its chromatographic mobility (R_f's solvents I, III: 0.29, 0.38) and color development with the benzidine–periodate spray. Ribosylurea was detected by its chromatographic mobility (R_f's solvents I, II, III: 0.41, 0.24, 0.48) and color development with Ehrlich's reagent and the benzidine–periodate spray. Deoxyribosylurea was confirmed by its chromatographic mobility (R_f solvent III: 0.48) and color development with Ehrlich's reagent.

In addition to the products mentioned, the oxidation of guanosine by excess peroxodisulfate in 1 *M* Na_2CO_3 solution at 40° produces a compound which is detectable chromatographically as a dark spot when dried chromatograms are viewed with an ultraviolet light source. A similar but not identical material is formed in the oxidation of deoxyguanosine. Both the ultraviolet-absorbing component produced as a result of guanosine oxidation (R_f's solvents I, II, III: 0.10, 0.07, 0.24) and that produced as a result of deoxyguanosine oxidation (R_f solvent III: 0.27) can be detected as pink spots when dried chromatograms are sprayed with the nitroprusside–ferricyanide–hydroxide spray.

The ultraviolet-absorption spectrum for both materials was measured following elution from paper chromatograms. The spectra for both materials were identical at three pH values: λ_{max} (pH 1) 210, λ_{max} (pH 6.8) 230 (shoulder), λ_{max} (pH 14) 230.

The oxidation of 8-hydroxyguanine by 2 equiv of peroxodisulfate in 1 *M* Na_2CO_3 at 40° produces a material (R_f solvent III: 0.17) with the same ultraviolet-absorption maxima at the same pH values which also develops a pink coloration with the nitroprusside–ferricyanide–hydroxide spray.

Kinetics of Ribose Liberation from Guanosine. Figure 2 shows the change in free ribose concentration with time as a result of peroxodisulfate oxidation of guanosine in 1 *M* Na_2CO_3 solution at 40°. Data on the change of ribose concentration as a function of increasing initial peroxodisulfate:guanosine ratios are included.

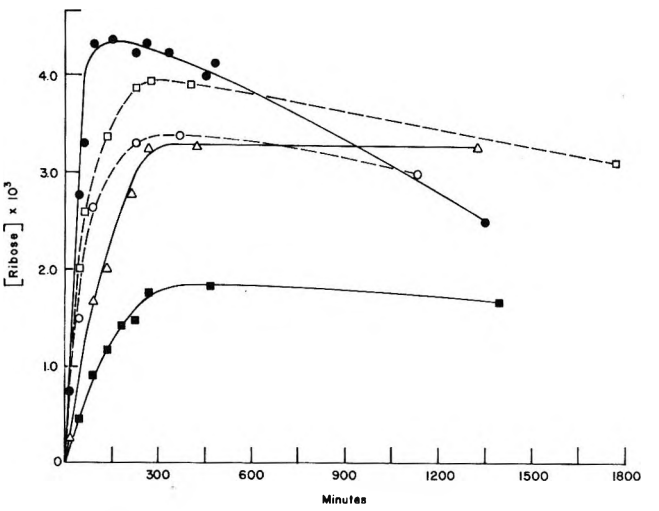

Figure 2. Ribose liberation during the oxidation of guanosine, [guanosine] 0.010 *M*, 1 *M* Na_2CO_3, 40°. Molar ratios peroxodisulfate:guanosine: ■, 1:1; △, 2:1; ○, 3:1; □, 4:1; ●, 6:1.

The data of Figure 2 show that the concentration of ribose initially increases with time during the peroxodisulfate oxidation of guanosine. The initial rate of ribose liberation is directly proportional to the initial peroxodisulfate:guanosine ratio. Ribose concentration approaches a maximum value and remains relatively constant over the time periods investigated when the initial peroxodisulfate:guanosine ratio is less than 4. At an initial peroxodisulfate:guanosine ratio of 6, the concentration of ribose declines from its maximum value. The maximum observed ribose concentration in these experiments was generally in the range of 0.35×10^{-2} to 0.45×10^{-2} *M* or approximately 40% of theoretical.

Kinetics of Peroxodisulfate Oxidation of D-Ribose and 2-Deoxy-D-ribose. The oxidations of D-ribose and 2-deoxy-D-ribose under these conditions are complex and cannot be fully described here. The rate of peroxodisulfate disappearance increases with time following an "induction period" of variable length. The rate of peroxodisulfate disappearance approaches first-order dependence on peroxodisulfate concentration following the observed lag. Neither EDTA nor acrylamide had any significant effect on the duration of the observed lag or on the rate of peroxodisulfate disappearance following the lag. The lag in peroxodisulfate disappearance in the reaction with D-ribose could be eliminated by allowing solutions of D-ribose in 1 *M* Na_2CO_3 to incubate at 40° for 20–30 min prior to the introduction of peroxodisulfate. Values for the apparent-second-order rate constants (k_2') for the oxidation of both sugars increased with decreasing sugar concentration in 1 *M* Na_2CO_3 at 40°. All k_2' values were calculated from linear regions of semilog plots of peroxodisulfate concentration *vs.* time. The variation in values of the apparent-second-order rate constant with decreasing sugar concentration is illustrated by the following data: [D-ribose] 0.100, k_2' = 0.42 ± 0.04 M^{-1} min^{-1}; [D-ribose] 0.0500, k_2' = 0.59 ± 0.04 M^{-1} min^{-1}; [D-ribose] 0.0100, k_2' = 1.1 ± 0.02 M^{-1} min^{-1}; [2-deoxy-D-ribose] 0.100, k_2' = 0.14 ± 0.02 M^{-1} min^{-1}; [2-deoxy-D-ribose] 0.0500, k_2' = 0.362 M^{-1} min^{-1}; [2-deoxy-D-ribose] 0.0050, k_2' = 1.2 M^{-1} min^{-1}. Ribose was oxidized more rapidly than deoxyribose under identical experimental conditions.

Table II
Products and Observed Stoichiometry[a]

Time, hr	[EDTA]	[Acrylamide]	Mol $S_2O_8^{2-}$/mol substrate	Mol ribose/mol substrate	Total mol urea/mol substrate	Mol guanidine/mol substrate	Mol acid-hydrolyzable ribose/mol substrate
			Guanosine				
3			1.9	0.4			
3	10^{-4}		1.9				
3	10^{-4}	0.005	2.0				
24			4.0	0.22	<0.1	0.96	0.13
24	10^{-4}		4.0	0.23	<0.1	0.96	0.08
24	10^{-4}	0.005	3.9	0.23	<0.1	0.94	0.10
			Deoxyguanosine				
3			1.9				
24			3.4		<0.1	0.87	

[a] General conditions: [nucleoside] 0.010 *M*, [$S_2O_8^{2-}$] 0.060 *M*, 1 *M* Na_2CO_3, 40°.

Stoichiometry of Ribose Oxidation. D-Ribose (0.0050 *M*) oxidation in the presence of excess peroxodisulfate (0.010 *M*) was monitored both by measurement of the disappearance of peroxodisulfate and D-ribose with time over 20-hr period. The results showed that 1.8 mol of peroxodisulfate was consumed per mole of ribose. The concentration of reducing sugar at the end of this same period was 0.075×10^{-2} *M* or 15% of the original. Paper chromatography of 1% ribose solutions in 1 *M* Na_2CO_3 in the presence of 2 equiv of $K_2S_2O_8$ showed the presence of ribonic acid and unchanged ribose after 20-hr incubation at 40°. The possible formation of products of the uronic or saccharic acid type was not investigated. Vasudeva, *et al.*,[18] report the formation of both gluconic and glucuronic acids as well as some formaldehyde and formic acid by the peroxodisulfate oxidation of glucose at higher temperatures where free-radical pathways probably predominate.

Stoichiometry of Deoxyribose Oxidation. The measurement of peroxodisulfate (0.010 *M*) disappearance in the reaction with 2-deoxy-D-ribose (0.0050 *M*) showed that 1.2 equiv of peroxodisulfate were consumed per mole of deoxyribose over a 24-hr period. One equivalent of $K_2S_2O_8$ was consumed during the first 9-hr incubation in 1 *M* Na_2CO_3 at 40°.

Stoichiometry of Guanosine and Deoxyguanosine Oxidation with Excess Peroxodisulfate. Table II presents a summary of the quantitative determinations of products for guanosine and deoxyguanosine oxidations in 1 *M* Na_2CO_3 at 40°. The effect of EDTA and acrylamide is included. The conditions for these determinations were adjusted to permit exhaustive oxidation of the nucleosides over a 24-hr period. Peroxodisulfate was present in sixfold molar excess.

The data indicate that 2 equiv of peroxodisulfate is consumed by both guanosine and deoxyguanosine during the first 3 hr of reaction in 1 *M* Na_2CO_3 at 40°. Four equivalents of peroxodisulfate is consumed over a 24-hr period in reaction with guanosine while 3.4 equiv is consumed in reaction with deoxyguanosine under the same conditions. Neither EDTA nor acrylamide had any effect on the initial rate of peroxodisulfate consumption or on the overall consumption of peroxodisulfate over the time period investigated.

Following a 24-hr oxidation under these conditions, the unoxidized carbohydrates are distributed as follows: free ribose, 20%; acid-hydrolyzable ribose (presumably a glycoside), 10%.

The molar ratio of urea produced per mole of substrate oxidized is less than 0.1 for both guanosine and deoxyguanosine. This value represents total urea in both cases and as such is a measure of both the free urea and the ureidoglycosides described as products of these reactions. No additional urea formation was observed following acid hydrolysis of the reaction products by the method employed for the detection of acid-hydrolyzable ribose. Since the total urea concentration is less than the acid-hydrolyzable ribose concentration, the amount of acid-hydrolyzable ribose cannot be an accurate measure of the ribosylurea content of the product mixtures using these analytical methods.

The molar ratio of guanidine produced per mole of both guanosine and deoxyguanosine oxidized approaches 1 over a 24-hr period.

EDTA and acrylamide had no effect on the extent of product formation in the peroxodisulfate oxidation of guanosine under these reaction conditions. The effect of EDTA and acrylamide on the peroxodisulfate oxidation of deoxyguanosine was not investigated.

Discussion

The kinetic dependencies, the lack of effect of radical traps, and the magnitude of the activation parameters all suggest that the peroxodisulfate oxidations described here, like those of the free bases,[2] do not involve any significant free-radical contribution.

A number of reactions of nucleic acid purines and pyrimidines which lead to ring opening have been investigated from the point of view of selectivity. Kochetkov and Budovskii[19] should be consulted for a general review of the chemistry involved and Shapiro[20] for the case of guanine. Potassium permanganate[21] and osmium tetroxide[22] are reasonably specific for thymine residues. *m*-Chloroperoxybenzoic acid,[23] while yielding *N*-oxides of cytosine and adenine in weakly acidic solution, gives ring cleavage of guanine, uracil, and thymine in the alkaline range. Hydrogen peroxide in alkaline solution selectively attacks uracil residues[24] as does hydrazine.[25] Hydroxylamine reacts selectively with cytosine residues at pH 6 and with uracil residues at pH 10.[26] The dye-sensitized photooxidation of guanine also results in a significant reaction with thymine.[27] Oxidation by peroxodisulfate appears to be among the most specific of these reactions. The results of our investigations on the peroxodisulfate oxidation of the common nucleosides in 1 *M* sodium carbonate solution show that guanosine and deoxyguanosine are at least 500 times more reactive than any other nucleoside. This specificity suggests that peroxodisulfate ions could be a useful reagent for the selective alteration of polynucleotides. For example, peroxodisulfate removal of guanine residues followed by base- or amine-catalyzed β-elimination[28] should lead to chain cleavage at guanine sites in a highly selective way.

Since polyribonucleotides are susceptible to base-catalyzed hydrolysis of the phosphodiester bonds, one might suppose that the peroxodisulfate oxidation would be chiefly useful for polydeoxyribonucleotides. However, the hydrolysis is quite slow at pH values suitable for the oxidation. For example, using the data of Bock,[29] one can calculate an approximate half-time of 850 hr for the hydrolysis of RNA at pH 9, 40°.

Acknowledgment. R. C. M. was a Frasch Foundation Fellow and a National Science Foundation Trainee. This work was also supported in part by an NSF Grant, GB-21267.

Registry No.—Guanosine, 118-00-3; deoxyguanosine, 961-07-9; peroxodisulfate ($K_2S_2O_8$), 7721-21-1.

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Sceletium Alkaloids. VI. Minor Alkaloids of *S. namaquense* and *S. strictum*

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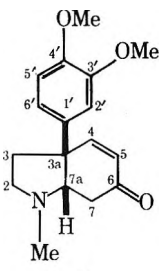
Received April 23, 1974

The structures of five new alkaloids are reported. *Sceletium* alkaloid A_4 (3) is a new type of *Sceletium* alkaloid containing a tetracyclic ring system and *N*-formyltortuosamine (8) is a ring C seco derivative of 3. Three additional members of the 3a-aryloctahydroindole class are described by the structures of the phenolic base, 4′-*O*-demethylmesembrenone (12), Δ^7-mesembrenone (7), and sceletenone (15). The latter constitutes the prototype of a monooxyaryl member of this class. A unified biogenetic scheme which accounts for the origins of the various ring systems of the different classes of *Sceletium* alkaloids is presented.

Previous studies of various *Sceletium* species of the family *Aizoaceae* have provided a number of alkaloids. Most of the bases that have been characterized belong to a single group which are elaborated on the 3-aryl-*cis*-octahydroindoleskeleton as exemplified by mesembrenone (1).[2] A recent report has described the structures of three new *Sceletium* alkaloids based upon a different skeleton which is typified by the structure of joubertiamine (2).[3] The close structural similarity between the mesembrine and joubertiamine types suggests that they originate through a common biosynthetic pathway. While extensive studies[4] have been devoted to elucidating the biosynthetic route to the octahydroindole alkaloids of the mesembrine series, no clear understanding of the pathway by which these alkaloids are formed has yet emerged. In cognizance of this fact we have undertaken a study of the minor alkaloids of *S. strictum* and *S. namaquense* with the view that characterization of new structural types may prove helpful in revealing previously unsuspected biosynthetic relationships in this series. In this paper we describe two alkaloids which are representatives of new skeletal types and three additional examples of alkaloids based upon the 3-aryl-*cis*-octahydroindolenucleus.

Sceletium **Alkaloid A_4.** Popelak and coworkers in an earlier investigation of *S. tortuosum* had reported on the isolation of a crystalline alkaloid, sceletium A_4. Aside from a description of the physical properties, the data given were limited to an assignment of the molecular formula of the alkaloid as $C_{20}H_{24}N_2O_2$ and the suggestion that the alkaloid contained two methoxyl groups, probably in a veratryl chromophore, and an *N*-methyl group.[2] The occurrence of two nitrogen atoms in the molecular formula of sceletium A_4 led these authors to suggest that this alkaloid had to be placed in a different structural class from the other mesembrine alkaloids of known structure, which at the time of this observation consisted of three members of the 3-aryl-*cis*-octahydroindolegroup.

An investigation of the structure of sceletium A_4 was made possible when this alkaloid was encountered during a study of the nonphenolic alkaloid fraction of *S. namaquense*. After the removal of mesembrine and mesembrenone from this fraction, sceletium A_4 was obtained together with two other new alkaloids. The former was obtained as an optically active, crystalline base, mp 153–154°, $[\alpha]_D$ +131° (C_2H_5OH), which was assigned the molecular formula $C_{20}H_{24}N_2O_2$ from an accurate mass measurement of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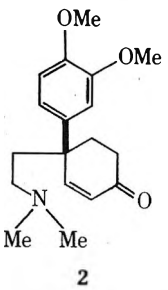
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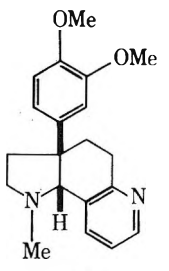
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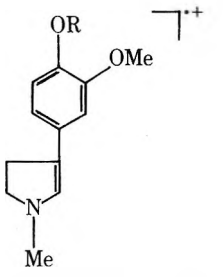
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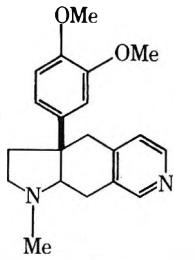
13, R = H (*m/e* 205)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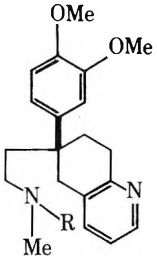
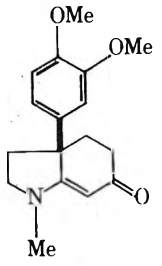
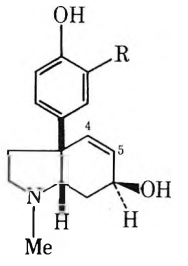
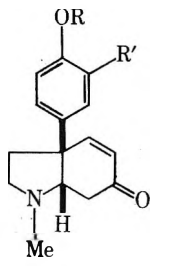

6, R = H
8, R = CHO


7


10, R = OMe (no 4,5 unsaturation)
11, R = OMe


12, R = H, R′ = OMe
15, R = R′ = H
16, R = Me, R′ = H

the molecular ion in the mass spectrum. The suspected identity of this compound with *Sceletium* alkaloid A_4 was confirmed by direct comparison with a sample provided by Dr. Popelak. Comprehensive spectral studies reported below led to the elucidation of its structure as represented in **3**.

The ^1H nmr spectrum of sceletium A_4 at 100 MHz exhibited a well-defined aromatic region consisting of an AMX pattern at δ 8.48 (J = 5.0 and 2.0 Hz), 7.56 (J = 7.8 and 2.0 Hz), and 7.15 (J = 7.8 and 5.0 Hz) and a typical three-proton pattern characteristic of the 3,4-dimethoxyphenyl group of the octahydroindole members of the mesembrine alkaloids. The only other assignable resonances in this spectrum were two *O*-methyl signals at δ 3.71 and 3.78, and an *N*-methyl signal at δ 2.34.

Some further clarification of the ^1H spectrum became apparent in the 220-MHz spectrum of the alkaloid and these assignments are collected in Table I.

The downfield AMX pattern in the aromatic region was clearly indicative of a heteroaromatic ring and both the chemical shifts and coupling constants provided strong evidence in assigning this pattern to a 2,3-disubstituted pyridine system.[5] The ultraviolet spectrum of the alkaloid, with λ_{max} 225 nm (log ϵ 3.59), 267 (3.39), 273 (3.42) and 285 (3.10), supported the presence of this chromophore and in fact compared well with the uv of the model compound, 2-(3,4-dimethoxybenzyl)pyridine, which showed bands at λ_{max} 231 nm (log ϵ 3.27), 262 (3.23), 268 (3.19), and 282 (2.99). The small bathochromic shift observed in the $\pi \rightarrow \pi^*$ bands at 267 and 273 nm is accounted for by the known auxochromic effect of alkyl substituents on the pyridine nucleus.[6] Additional support for the presence of both benzenoid and pyridine chromophores in the alkaloid was provided by the occurrence of bands attributable to C=C and C=N stretching vibrations at 1508 and 1605 cm^{-1} in the infrared spectrum. Further information on the structure of *Sceletium* alkaloid A_4 was obtained by mass spectral studies. Preliminary examination of the low-resolution spectrum showed that aside from the molecular ion, and M − 1 and M − 15 fragments, ions of high abundance occurred in the high-mass range at *m/e* 296, 281, and 266. The high-resolution spectrum indicated that these ions occurred through the loss of ethylene and the loss of nitrogen containing fragments C_2H_5N and C_3H_8N, respectively. The loss of the latter was complemented by the appearance of C_3H_7N fragment of high abundance in the low-mass end of the spectrum. The occurrence of these fragments suggested that the structure of the alkaloid contained an *N*-methylpyrrolidine ring. The finding of an ion of elemental composition $C_{13}H_{17}NO_2$ at *m/e* 219 proved important. An ion of this composition, which has been assigned structure **4**, occurs in the spectra of all of the simple octahydroindole alkaloids containing a 3,4-dimethoxyphenyl substituent. Convincing evidence that the ion from the sceletium A_4 has the same structure as the isobaric fragment observed in the spectra of mesembrine and its derivatives was obtained from a comparison of the decomposition pathways in the mass spectra of sceletium A_4 and the mesembrine series by the use of metastable defocusing data.[7]

Analysis of the metastable spectrum of ion **4** from mesembrne and its analogs shows that it decomposes by two major pathways to give daughter ions at *m/e* 204 and 191, corresponding to the loss of a methyl radical and ethylene, respectively. Similarly, an identical fragmentation of the *m/e* 219 ion was observed in the metastable spectrum of sceletium A_4. These results when considered in conjunction

Table I
^1H Nmr Shift Assignments for 220-MHz Spectrum of *Sceletium* Alkaloid A_4

δ		Multiplicity	J, Hz	Assignment
1.91	1 H	m	$W_{1/2}$ = 13.0	H-3α
2.27	2 H	m		H-4α, H-3β
2.34	3 H	s		NMe
2.50	3 H	m		H-4β, H-2α, H-2β
2.94	1 H	m	$W_{1/2}$ = 16	H-5β
3.30	2 H	m		H-7a, H-5α
3.71	3 H	s		OMe
3.78	3 H	s		OMe
6.56	1 H	dd	8.0, 2.0	H-6′
6.65	1 H	d	2.0	H-2′
6.70	1 H	d	8.0	H-5′
7.15	1 H	dd	7.8, 5.0	Py H-3
7.56	1 H	dd	7.8, 2.0	Py H-4
8.48	1 H	dd	5.0, 2.0	Py H-2

with the previously cited spectral evidence for sceletium A_4 present a strong case for representing its *m/e* 219 fragment by structure **4**.

Combination of both partial structural units in **4** and the 2,3-disubstituted pyridine system leaves only two methylene groups unaccounted for in the moleculr formula of the alkaloid. Of the several possibilities, two structures, **3** and **5** appeared more likely on biogenetic grounds (*vide infra*). Since the alkaloid was available in very limited quantities, the possibility of a rigorous structure proof by chemical methods was precluded and therefore a single-crystal X-ray crystal structure analysis was undertaken in collaboration with Professor McPhail. The results of this analysis demonstrated that *Sceletium* alkaloid A_4 is correctly represented by structure **3**.[8]

Concurrent with our studies of sceletium A_4, Wiechers and collaborators have isolated partially racemic sceletium A_4 and a second alkaloid, tortuosamine ($C_{20}H_{26}N_2O_2$), from *S. tortuosum*. Since tortuosamine differed from sceletium A_4 by two hydrogens in the respective molecular formulas, a close structural relationship between the two alkaloids was suspected.

With the establishment of the structure of sceletium A_4 the South African workers were able to infer the structure of tortuosamine (**6**) which they confirmed through the conversion of sceletium A_4 to **6** by hydrogenolysis.[9]

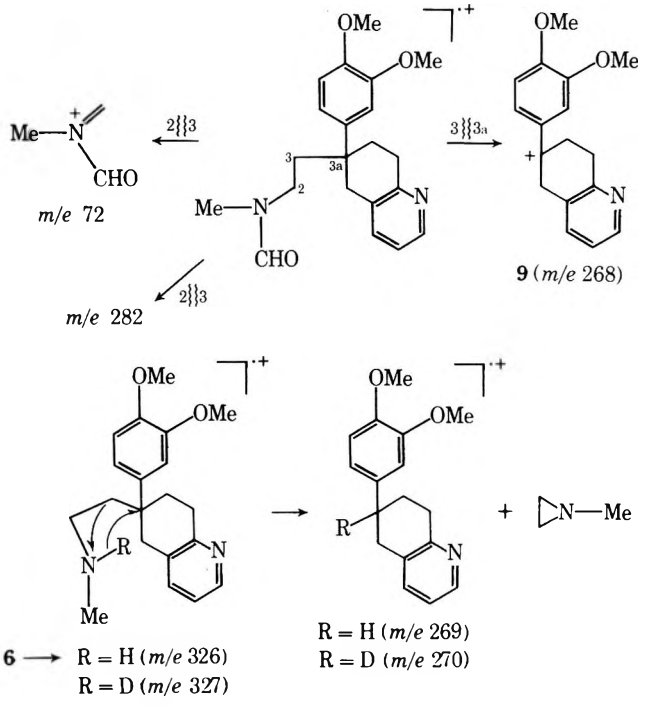
Δ^7-Mesembrenone and *N*-Formyltortuosamine. The late fractions from the column chromatographic separation of the ether-insoluble alkaloid fraction from *S. namaquense* afforded two pure alkaloids.

One of these proved to be a noncrystalline base of molecular formula $C_{17}H_{21}NO_3$. The spectral and chromatographic properties of this compound were identical with those of Δ^7-mesembrenone (**7**), which had previously been obtained by the reaction of mesembrine with diethyl azodicarboxylate.[10]

The second alkaloid from the late fractions was an optically active, noncrystalline base which was shown to have the molecular formula $C_{21}H_{26}N_2O_3$ by high-resolution mass spectrometry. The 250-MHz ^1H spectrum of the alkaloid exhibited a three-proton aromatic pattern centered at δ 6.83 and three low-field multiplets at 7.05, 7.42, and 8.32. The latter signals were shown to be mutually coupled by double-resonance studies and this information served to establish the presence of a 2,3-disubstituted pyridine ring. A strong carbonyl absorption at 1660 cm^{-1} in te infrared spectrum indicative of an amide carbonyl was supported by doubling of the signals associated with both an *N*-methyl (δ 2.66 and 2.70) and two aromatic *O*-methyl groups (δ 3.74, 3.75, 3.77, and 3.78). The temperature dependence of the 100-MHz spectrum showed not only the expected coalescence of the *N*-methyl and *O*-methyl signals at 82° but also resulted in the collapse of two lines centered at δ 7.86. The position and temperature-dependent behavior of the latter signal implied that the amide was present as an *N*-formyl group.

The foregoing spectral data suggested that the new alkaloid was represented by structure **8**. Further support for this proposal was obtained from the mass spectral fragmentation pattern, in which the key features were the observation of ions derived from the sequential loss of fragments of the *N*-formylethamine side chain giving rise to abundant ions at *m/e* 282 and 268 and a complementary ion *m/e* 72 at low mass. In relation to the *m/e* 268 fragment, to which we attribute structure **9**, it was of interest that the mass spectrum of tortuosamine[9] afforded a major fragment ion at *m/e* 269. This suggested that the genesis of the latter involved a hydrogen transfer process from the secondary nitrogen to the charge-bearing fragment. Proof of this pathway was obtained from the observation that tortuosamine *N*-d_1 exhibited a mass shift in this daughter ion fragment to *m/e* 270. The foregoing fragmentation pathways of tortuosamine and its *N*-formyl derivative are summarized in Scheme I.

Scheme I
Principal Mass Spectral Fragmentation Pathways of Tortuosamine (6), Tortuosamine-*N*-d_1, and *N*-Formyltortuosamine (8)



The structure of **8** was confirmed by its derivation from *Sceletium* alkaloid A_4, through hydrogenolysis to tortuosamine, and *N*-formylation of the latter in formic–acetic anhydride to give a product which was identical in its spectral and chromatographic properties with the natural base. A comparison of the CD spectra of the alkaloid and the synthetic product gave identical curves exhibiting a positive Cotton effect at 282 nm and a negative maximum at 266 nm; this served to identify *N*-formyltortuosamine and *Sceletium* alkaloid A_4 as belonging to the same chiral series. Whether the chirality of these alkaloids corresponds to that of the octahydroindroindole bases of the mesembrine series remains to be established.

4′-*O*-Demethylmesembrenone and Sceletenone. Previous investigation of the phenolic alkaloid fraction of *S. strictum* led to the isolation and characterization of the alkaloids 4′-*O*-demethylmesembranol (**10**) and 4′-*O*-demethylmesembrenol (**11**).[11] The presence of a third alkaloid, 4′-*O*-demethylmesembrenone (**12**) was detected initially from a radioscan of a tlc plate of the total phenolic alkaloids derived from a biosynthetic feeding experiment in which [*S*-methyl-^{14}C]methionine had been administered to live *S. strictum* plants. It was subsequently isolated by preparative tlc of the phenolic bases from *S. strictum* and also by a more extensive isolation procedure (*vide infra*) from the phenolic alkaloid fraction of *S. namaquense*.

4′-*O*-Demethylmesembrenone, $C_{16}H_{19}NO_3$, an optically inactive, oily base, exhibited bands at 3540 and 1668 cm^{-1} indicative of the presence of a phenolic hydroxyl and an α,β-unsaturated ketone group. Its mass spectrum displayed a fragmentation behavior analogous to that found for the alkaloids **10** and **11**, the most distinctive feature being the

Table II
^{13}C Nmr Shift Assignments of Membrenone (1) and Sceletenone (15)

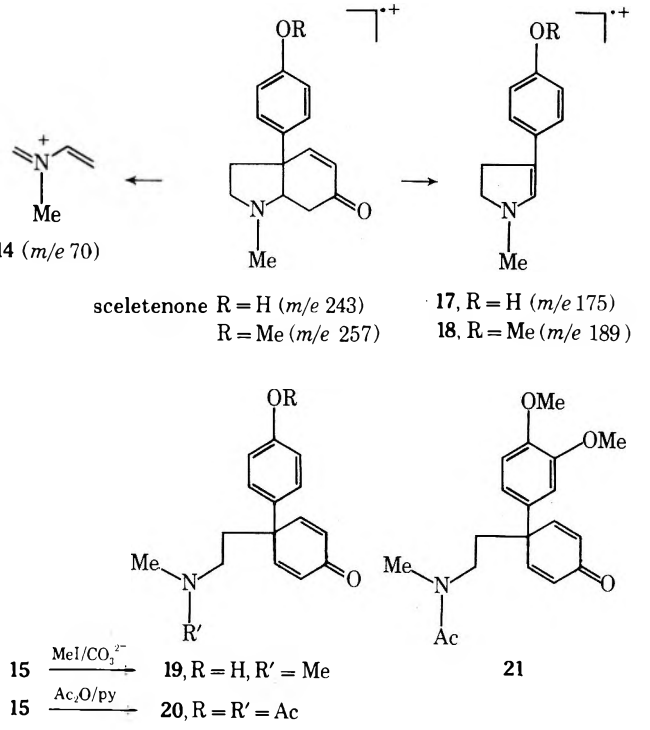
Compd	^{13}C shift, ppm															
	1′	2′	3′	4′	5′	6′	2	3a	3	4	5	6	7	7a	NMe	OMe
Mesembrenone (1)	135.2	110.9	148.6	147.7	110.0	118.8	56.2	50.9	38.3	153.3	126.2	196.9	38.6	73.8	40.1	55.8, 55.9
Sceletenone (15)	133.6	126.8	115.5	154.3	115.5	126.8	55.8	50.6	35.9	155.4	125.9	197.8	38.4	73.4	40.0	

occurrence of fragmentation pathways leading to the ions 13 (*m/e* 205) and 14 (*m/e* 70). The ^1H nmr spectrum of 12 resembled very closely that of mesembrenone and its relationship to this alkaloid was established by methylation to mesembrenone with diazomethane. These data reduce the structural possibilities to two, structure 12 and an isomer in which the position of the phenolic hydroxyl and *O*-methyl group in 12 are reversed.

A distinction between these two possible structures was made by a variation of the radiolabeling procedure which we had previously employed[11] in deducing the structures of 10 and 11. On this occasion advantage was taken of the availability of biosynthetically labeled 4′-*O*-demethylmesembrenone containing ^{14}C labels in the *O*- and *N*-methyl groups. Methylation of the radiolabeled alkaloid afforded mesembrenone, which was oxidized to veratric acid, and the latter was selectively demethylated to isovanillic acid as previously described. A loss of 95% of the radiolabel occurred in the conversion of veratric acid to isovanillic acid and thereby established the aromatic substitution pattern of the alkaloid as depicted in structure 12.

Examination of the phenolic alkaloid fraction of *S. namaquense* has revealed that is consists of a highly complex multicomponent mixture. Column chromatrography of the mixture over silica gel in chloroform–methanol afforded 240 fractions (see Experimental Section). Combination of fractions 148–164 followed by preparative tlc afforded (±)-4′-*O*-demethylmesembrenone and a new phenolic base, sceletenone (15), in impure form. High-pressure chromatography of the impure sceletenone over silica gel gave a sample which, although slightly contaminated, was used in the chemical studies described below. An analytically pure sample of sceletenone was obtained by further purification using high-pressure chromatography on phenyl–Corasil in water–acetonitrile (9:1). With the exception of the ^{13}C nmr spectrum, all of the crucial spectral data were obtained with this sample.

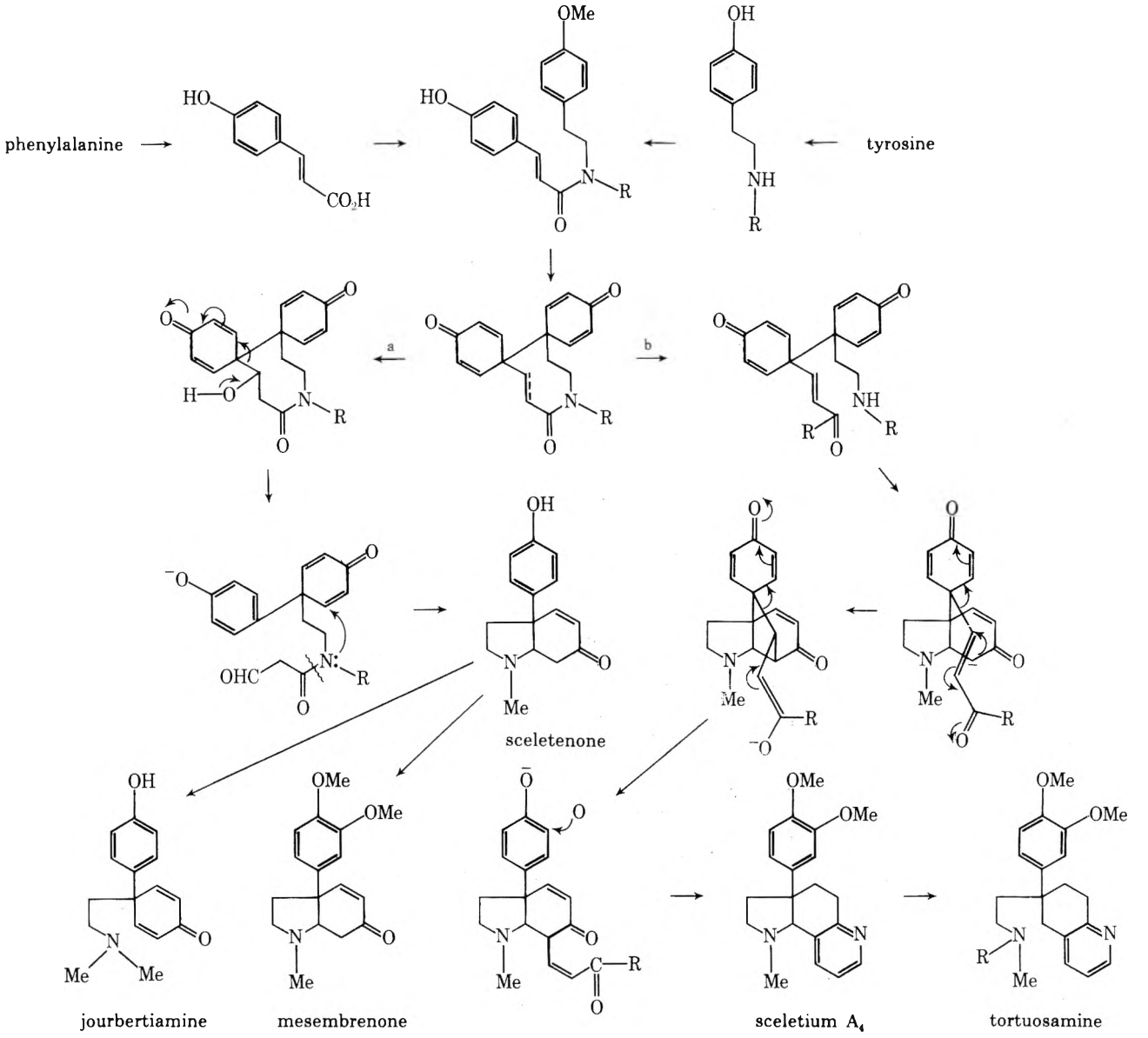
Sceletenone, $C_{15}H_{17}NO_2$, contained absorptions at 3592, 3300, and 1678 cm^{-1} indicative of a phenolic hydroxyl and an α,β-unsaturated ketone. The presence of a phenolic hydroxyl was confirmed by the methylation with diazomethane to give an *O*-methyl derivative 16. The ^1H nmr spectra of both sceletenone and its *O*-methyl derivative contained an aromatic AA′BB′ pattern, two deshielded olefinic signals mutually coupled (J = 10.0 Hz), and also showed the typical small long-range coupling of the β hydrogen characteristic of the C-4 hydrogen in 6-keto-4-ene compounds in the mesembrine series. An *N*-methyl signal was also observed at δ 2.32. A further indication that sceletenone was based upon the octahydroindole skeleton was provided by the appearance of a C_4H_8N fragment (*m/e* 70) as the base peak in the mass-spectra of the alkaloid and its *O*-methyl derivative. The C_4H_8N fragment (14) occurs in high abundance in the mass spectra of all octahydroindole alkaloids of the mesembrine series and may be considered diagnostic for this class of alkaloids provided that it is accompanied by the appropriate 3-aryl-*N*-methylpyrrolidinium ion (*cf.* 4 or 13) for the dioxyaryl members. Since sceletenone obviously possesses only a single aromatic oxygen function, the comparable ion, 17, if present, would be expected at *m/e* 175. Indeed, this ion is found in the mass spectrum of sceletenone and its structure assignment is supported by the observation of a mass shift Δm = 14 in the comparable ion 18 in the mass spectrum of *O*-methylsceletenone.



Compelling evidence for the structure of sceletenone was obtained by comparison of its ^{13}C nmr spectra with that of mesembrenone. The assignments of the carbon resonances (Table II) for the latter were made after a detailed examination of the ^{13}C spectra of a series of octahydroindole alkaloids of the mesembrine class. A comparison of the carbon shifts of the two alkaloids shows a very close correspondence in all signals with the exception of aromatic carbon resonances. The latter reflect the different aromatic substitution patterns and the values observed in each case are in fact found to be in good agreement with the calculated shifts derived from the substituent parameters of Levy and coworkers.[12] We have found that ^{13}C shifts are a very sensitive indicator of structural change in this series and therefore the close correspondence in chemical shifts of the nonaromatic carbons constitutes firm evidence for the proposed structure of sceletenone as 15.

Some additional evidence supporting the proposed structure has been obtained from reactions of sceletenone involving a Hofmann degradation and its behavior upon acetylation. In the case of the former reaction, the methiodide of 15 underwent a facile elimination on basification with aqueous sodium carbonate solution. The ease of this elimination is in keeping with the presence of a β-amino ketone structural fragement and is paralleled by the equally facile Hofmann reaction of the ketones, mesembrine and mesem-

Scheme II
A Unified Scheme for the Biogenesis of the Various Classes of *Sceletium* Alkaloids



brenone. The structure of the product as the dienone **19** is supported by its spectral properties, with bands in the ultraviolet spectrum at 232 (log ϵ 4.24) and 272 nm (3.25) and a low-frequency carbonyl at 1655 cm^{-1} in the infrared spectrum. The mass spectrum of the Hofmann product exhibited ions at *m/e* 58 and 72, characteristic for an *N,N*-dimethylaminoethyl side chain, and an M − CO fragment at *m/e* 215 providing strong support for the proposed structure of this compound.

Acetylation of sceletenone in acetic anhydride–pyridine results in the formation of an *O,N*-diacetate. The assignment of the structure of this product as **20** is in full accord with its spectral properties, which compare well (see Experimental Section) with those obtained for the model compound **21** derived from a similar acetylation of mesembrenone.

The formation of the dienones **19** and **20** is in accord with the known propensity of β-amino ketones to undergo β-elimination under acetylation conditions.

Biogenetic Relationships. Although it is possible that sceletium A_4 and related bases such as tortuosamine and its derivatives are biosynthesized by a process which simply involves heteroannelation of mesembrine, another and more attractive hypothetical pathway is presented in Scheme II. The utilization of phenylalanine and tyrosine in the manner indicated in this scheme is consistent with the results of labeling experiments[4] insofar that they indicate that (1) these two mino acids furnish the aromatic ring and the C_6–C_2–N units in mesembrine, (2) the mode of incorporation of phenylalaninnine probably requires a ring A spirodienone intermediate, and (3) all likely Ar–C_1–N–C_2–Ar (norbelladines) candidates may be excluded from consideration.

The transformation of phenylalanine to hydroxylated cinnamic acids is a well-established metabolic pathway in higher plants[13] and the combination of *p*-hydroxycinnamic acid with a tyrosine Ar–C_2–N unit to provide a cinnamic acid amide has precedent in the biosynthesis of colchicine.[14] The intervention of a similar Ar–C_3–N–C_2–Ar intermediate in the biosynthesis of mesembrine and *Sceletium* alkaloid A_4 can readily account for the genesis of both ring systems by the route depicted in Scheme II. The postulation of the late-stage aromatic oxygenation for the introduction of the second aromatic oxygen function, which is present in the majority of the alkaloids of this family, although arbitrary, has the advantage that it is possible to in-

clude both the monooxyaryl alkaloids of the joubertiamine series and sceletenone in a single unified scheme.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were obtained for solutions in $CHCl_3$ on Perkin-Elmer Models 137, 237, and 621 spectrophotometers. Ultraviolet spectra were measured in 95% ethanol on a Beckman DBG or Cary 14 spectrophotometer. Proton nuclear magnetic resonance (nmr) spectra were recorded at 60 MHz on a Varian A-60, at 90 MHz on a Bruker HFX-90, at 100 MHz on a JEOL MH-100, at 220 MHz on a Varian HR-220, and at 250 MHz on a spectrometer constructed at the Carnegie-Mellon Institute. Carbon-13 spectra were recorded at 22.63 MHz on the Bruker HFX-90. Tetramethylsilane was used as an internal reference in deuteriochloroform as a solvent unless otherwise noted. Low-resolution mass spectra were determined on a Du Pont 21-490 instrument. Radioactive samples were counted on a Beckman LS 150 as previously described.[4] CD spectra were obtained on a Jasco ORD/CD spectropolarmeter. Gas–liquid chromatography (glc) was carried out on a Hewlett-Packard 402 instrument with 8 ft × 0.125 in. glass columns packed with 3% OV-17 or 3% SE-30 on Gas-Chrom Q (100–120 mesh). High-pressure liquid chromatography (hlpc) was performed on a Waters ALC-202 instrument.

Extraction of Alkaloids from *Sceletium namaquense*. Several methods were employed in the extraction of the alkaloid fraction from this species; that described is representative of one of the more satisfactory procedures.

Dried plant material of *S. namaquense* (3.5 kg) was placed in a Soxhlet and extracted with 15 l. of 95% ethanol for 17 hr. The extracted material was transferred in portions to a blender and macerated with a further 10 l. of 95% ethanol. The combined ethanol extracts were concentrated to *ca.* 2.5 l. and acidified with 5% tartaric acid. The aqueous acidic solution was extracted with ether (5 × 300 ml) and the ether extract was discarded. After basification of the aqueous phase with Na_2CO_3 the solution was extracted successively with $CHCl_3$ (10 × 500 ml) and $CHCl_3$–MeOH (4:1) (3 × 100 ml). The $CHCl_3$ extracts were combined, the solvent was concentrated to *ca.* 1.5 l., and the solution was filtered to remove small quantities of insoluble fatty impurities. The $CHCl_3$ filtrate was extracted with 1 *N* NaOH (3 × 100 ml) and washed thoroughly with water. Evaporation of the $CHCl_3$ solution gave 120 g of nonphenolic alkaloids. The phenolic alkaloids (20 g) were recovered from the NaOH solution by adjusting to pH 9 (with CO_2) and extraction into $CHCl_3$ (5 × 100 ml).

Isolation of Nonphenolic Alkaloids. The nonphenolic alkaloid fraction (120 g) was extracted with 3 × 500 ml of boiling ether to remove 60 g of ether-soluble alkaloids containing largely mesembrine and mesembrenone. The ether-insoluble residue was dissolved in 1200 ml of $CHCl_3$–MeOH (3:1) and filtered through a column (4 ft × 3 in.) containing 1400 g of silica gel (170–200 mesh). Evaporation of the total eluate gave 50 g of alkaloidal material. A portion (20 g) of this fraction was dissolved in $CHCl_3$ (100 ml) and chromatographed over neutral alumina (1400 g, activity 4) contained in a 4 ft × 3 in. column. The column was eluted with 3 l. of solvent using a linear gradient of $CHCl_3$–$CHCl_3$/MeOH (4:1) and 15-ml fractions were collected: fractions 1–120, nonalkaloidal material (3.10 g); 121–143, mesembrine (1.63 g); 144–175, mesembrenone (2.0 g); 176–205, mesembrenone and *Sceletium* alkaloid A_4 (0.65 g); 206–215, unidentified alkaloids (1.45 g); 216–225, *N*-formyltortuosamine and unidentified alkaloids (3.115 g); 226–235, Δ^7-mesembrenone and other alkaloids (1.114 g); and four further fractions (236–330) containing mesembranol (2.3 g) and an unresolved mixture of polar components (5.852 g).

Sceletium Alkaloid A_4 (3). Fraction 176–205 (0.65 g) was rechromatographed over neutral alumina (30 g, activity 3) using two successive linear solvent gradients of benzene–benzene/EtAc (1:1) and EtAc/MeOH (1:1)–MeOH. Mesembrenone was eluted in the early fractions and sceletium A_4 in the late fractions. Sceletium A_4 crystallized from EtAc as prisms: mp 153–154.5°; ir 1605 (C=N–) and 1580 cm^{-1} (aromatic ring C=); uv max 225 nm (log ϵ 3.59), 267 (3.39), 273 (3.42, 285 (3.10); CD (95% EtOH) $[\theta]_{278}$ +6310°, $[\theta]_{274}$ +5550°, $[\theta]_{247}$ −1879°; nmr, see Table I; mass spectrum *m/e* (rel intensity) 324 (100, M^+), 323, (78, M − 1), 309 (45, M − CH_3), 296 (30, M − C_2H_4), 281 (17, M − C_2H_5N), 266 (56, M − C_3H_8H), 219 (12, $C_{13}H_{17}NO_2$), 57 (15, C_3H_7N).

Anal. Calcd for $C_{20}H_{24}N_2O_2$: *m/e* 324.1837. Found: *m/e* 324.1832.

***N*-Formyltortuosamine (8).** Fractions 216–225 (3.11 g) were subjected to successive preparative tlc separation on silica gel in $CHCl_3$–MeOH (9:1), alumina in $CHCL_3$–MeOH (97:3), and finally alumina in $CHCl_3$ to give *N*-formyltortuosamine (8), homogeneous by tlc and glc, as an oil: ir 1660 cm^{-1} (amide C=O); uv max 220, 271, and 277 nm; 250-MHz proton nmr δ 2.66 and 2.70 (two s, 3 H, NCH_3 for each conformer), 3.74, 3.75, 2.77, and 3.78 (four s, 6 H, OMe), 6.88 (m, 3 H, aromatics), 7.0 (m, 1 H, pyr-H_3), 7.42 (apparent t, 1 H, pyr-H_4), 7.81 (two s, 1 H, NCHO for each conformer), 8.32 (m, 1 H, pyr-H_2); 100-Mz proton nmr (120°) δ 2.74 (NCH_3), 3.84, 3.86 (two s, 6 H, OMe), 6.90 (m, 3 H, aromatics), 7.00 (dd, 1 H, *J* = 8.0, 5.0 Hz, pyr-H_3), 7.42 (dd, 1 H, *J* = 8.0, 2.0 Hz, pyr-H_4), 7.80 (s, 1 H, NCHO), 8.32 (dd, 1 H, *J* = 5.0, 2.0 Hz, pyr-H_2); CD (95% EtOH) $[\theta]_{282}$ +12,000°, $[\theta]_{266}$ −6380°; mass spectrum *m/e* (rel intensity) 354 (30, M^+), 282 (100, M − C_3H_6NO), 269 (32, M − C_4H_7NO), 268 (57, M − C_4H_8NO), 151 (30, $C_9H_{11}O_2$), 130 (31, C_9H_8N), 118 (30, C_8H_8N), 107 (28, C_7H_9N), 72 (10, C_2H_6NO), 57 (5.4, C_3H_7N), 55 (16, C_3H_5N).

Anal. Calcd for $C_{21}H_{26}N_2O_3$: *m/e* 354.1943. Found: *m/e* 354.1934.

Hydrogenolysis of Sceletium A_4. The alkaloid **3** (94 mg) was dissolved in water (3 ml) containing 50 μl of 12 *N* HCl, and mixed with 10% palladium on carbon catalyst. The mixture was stirred at 55° for 42 hr until the hydrogenolysis was complete. Chromatography on silica gel plates (made up in 5% K_2CO_3 solution) in $CHCl_3$–MeOH (3:2) gave tortuosamine (**6**) as a colorless oil: ir (neat) 3280 (NH), 1600 1580 cm^{-1}; mass spectrum *m/e* (rel intensity) 326 (17, M^+), 269 (100, M − C_3H_7N), 268 (66, M − C_3H_8N), 254 (8, M − $C_4H_{10}N$), 132 (13, $C_9H_{10}N$), 57 (13, C_3H_7H), and 55 (12, C_3H_5N). Tortuosamine-*N*-d_1 showed M^+ 327 and Δ*m* 269 → 270, Δ*m* 268 → 269 (it was necessary to equilibrate the source with D_2O in order to obtain this spectrum); nmr (60 Mz) δ 1.27 (s, 1 H, NH), 2.29 (s, 3 H, NMe), 3.80 and 3.83 (s, 3 H, OCH_3), 6.79 (m, 3 H, phenyl H), 7.06 (dd, 1 H, *J* = 5.0 and 8.0 Hz, pyr-H_3), 7.48 (dd, 1 H, *J* = 8.0, 2.0 Hz, pyr-H_4), 8.40 (dd, 1 H, *J* = 5.0, 2.0 Hz, pyr-H_2). The above spectral data agree well with those reported for tortuosamine.[9]

Anal. Calcd for $C_{20}H_{26}N_2O_2$: *m/e* 326.1994. Found: *m/e* 326.1990.

N-Formylation of Tortuosamine. Tortuosamine (50 mg) was stirred at 0° with 2 ml of acetic–formic anhydride for 6 hr. Basification of the reaction mixture with saturated Na_2CO_3 solution followed by extraction with $CHCl_3$ afforded *N*-formyltortuosamine (40 mg). The chromatographic (tlc and glc) and spectral data (nmr, CD, and ir) were identical with those of the natural base.

Treatment of *N*-formyltortuosamine (10 mg) under reflux with 1 *N* HCl for 2 hr gave tortuosamine as the major product, mass spectrum *m/e* 326 (M^+).

(−)-Δ^7-Mesembrenone (7). Preparative tlc of fractions 226–235 (1.114 g) on silica gel in $CHCl_3$–MeOH (9:1) afforded 240 mg of a component of R_f value 0.35. Rechromatography of this component on alumina (tlc) in $CHCl_3$–MeOH (97:3) gave a band (R_f 0.46, 90 mg) which was further purified by tlc on alumina in $CHCl_3$ to give 40 mg of (−)-Δ^7-mesembrenone (**7**) as an oil. The spectral (mass spectrum, ir, nmr, uv, and CD) and chromatographic data (glc and tlc) of this compound were identical with those of an authentic sample prepared from mesembrine.[10]

Phenolic Alkaloids. Isolation of 4′-*O*-Demethyl[3′-*O*-methyl-^{14}C,*N*-methyl-^{14}C]mesembrenone. The phenolic alkaloid fraction derived from an experiment in which the alkaloids had been obtained from *S. strictum* plants to which [*S*-methyl-^{14}C]methionine had been administered was subjected to preparative tlc on silica gel H. Double development with $CHCl_3$–MeOH (3:1) gave 4′-*O*-demethylmesembrenol (**10**, R_f 0.62) and 4′-*O*-demethylmesembranol (R_f 0.38). A radioscan of the plate showed a single radioactive component at R_f 0.65 which on recovery from the plate gave labeled 4′-*O*-demethylmesembrenone (**12**) as an oil. The same alkaloid was subsequently isolated by preparative tlc of the column fractions 148–164 from the phenolic alkaloid fraction of *S. namaquense*. 4′-*O*-Demethylmesembrenone showed the following spectral properties: ir 3540 (OH), 1678 (O=O), 1612, 1605, 1510 cm^{-1}; nmr (100 MHz) δ 2.10–2.80 (m, 4 H), 2.33 (s, 3 H, NMe), 2.59 (br m, 8 H), 3.01 (t, 1 H, H-7a), 3.33 (m, 1 H, H-2), 3.91 (s, 3 H, OMe), 5.40–5.70 (br s, 1 H, OH), 6.12 (d, 1 H, *J* = 10.0 Hz, H-5), 6.75 (dd, 1 H, *J* = 10.0 and 2.0 Hz, H-4), 6.90 (m, 3 H, phenyl H); uv max 220 nm (log ϵ 4.04), 280 (3.59); uv max (0.1 *N* NaOH) 213 nm (log ϵ 4.04), 244 (4.0), 292 (3.69); mass spectrum *m/e* (rel intensity) 273 (44, M^+), 258 (5.3, M − CH_3), 205 (21), 70 (100, C_4H_8N).

Anal. Calcd for $C_{16}H_{19}NO_3$: *m/e* 273.1365. Found: *m/e* 273.1361.

Methylation of 4′-*O*-Demethyl[3′-*O*-methyl-^{14}C,*N*-methyl-^{14}C]mesembrenone. Radioactive 4′-*O*-demethylmesembrenone 92.5 mg, 2.63 μCi/mmol) was dissolved in 2 ml of MeOH and the

solution was cooled to −78°. An excess of diazomethane was added to the solution and the solution was allowed to stand at 0° for 48 hr. Mesembrenone (97.5 mg) was added to the reaction mixture and the solvent was evaporated. The residue was treated with 2-propanol–ether containing HCl and the mesembrenone hydrochloride was crystallized several times from this solvent to give 52 mg of material of constant activity (4.03×10^{-2} μCi/mmol).

Oxidation of [3′-*O*-methyl-^{14}C,*N*-methyl-^{14}C]Mesembrenone. Radiolabeled mesembrenone hydrochloride (52 mg) from the above experiment was mixed with inactive mesembrenone hydrochloride (58 mg) and added to a solution of $K_3Fe(CN)_6$ (33 g) and KOH (5.8 g) in 35 ml of H_2O. The solution was brought to reflux, and during the course of 72 hr three further additions of the above quantities of $K_3Fe(CN)_6$ and KOH were made. The reaction mixture was filtered and the filtrate was acidified with 50% H_2SO_4 before extracting continuously with Et_2O for 72 hr. The Et_2O extract was washed successively with 1 *N* HCl and water. Extraction of the ether solution with saturated Na_2CO_3 and recovery of the acidic fraction by acidification of the $NaCO_3$ solution followed by reextraction into ether gave 40 mg of [3′-*O*-methyl-^{14}C]veratric acid. Several recrystallizations from H_2O–MeOH (5:1) gave a radiochemically pure sample, mp 180–182° (9.2×10^{-3} μCi/mmol).

Demethylation of [3′-*O*-methyl-^{14}C]Veratric Acid to Isovanillic Acid. A suspension of labeled veratric acid (19.5 mg) and carrier (19.5 mg) in 1.0 ml of 48% HBr was dissolved by gently refluxing the solution. Immediately after a copious precipitate had formed, the reaction mixture was quickly cooled and filtered. Examination of the precipitate by tlc showed some veratric acid remaining; so the mixture was methylated with CH_2N_2 and extracted with 2% NaOH. Upon acidification and extraction with $CHCl_3$, tlc examination of the $CHCl_3$ extract showed partial hydrolysis; so the ester was hydrolyzed with 10% NaOH on a steam bath for 30 min. After acidification and extraction with $CHCl_3$, a pink solid was obtained which was crystallized from EtOH–H_2O to give isovanillic acid, mp 248–249.5°. Counting of this sample showed that it contained only 8% of the activity (4.08×10^{-4} μCi/mmol) of the veratric acid from which it was derived.

Isolation of Sceletenone (15) from *S. namaquense.* The crude phenolic fraction from *S. namaquense* was chromatographed over silica gel (1200 g) using a linear gradient of $CHCl_3$–MeOH (20:1, 2 l.) against $CHCl_3$–MeOH (3:1, 2 l.) followed by $CHCl_3$–MeOH (3:1, 1 l.) against $CHCl_3$–MeOH (1:1, 1 l.). A total of 260 25-ml fractions was collected to give a total of 4.90 g.

Preparative tlc of fractions 148–164 (1.86 g) on silica gel in $CHCl_3$–MeOH (9:1) gave 450 mg of a component, R_f 0.3. Further purification of this material by high-pressure liquid chromatography on a 6 ft × 0.375 in. column of silica gel H in $CHCl_3$–MeOH (20:1) at 300 psi gave 277 mg of sceletenone (**15**) containing <5% of a higher molecular weight impurity (by mass spectral analysis). A sample (20 mg) of this material was further purified by high-pressure liquid chromatography on a 6 ft × 0.125 in. column of phenylcorasil in H_2O–CH_3CN (9:1), giving 12 mg of an oil: ir 3592, 3300 (OH, ratio of intensity of the former to the latter peak increased on dilution), and 1678 cm^{-1} (–C=O); uv max ~230 nm (ε 7570) and 279 (1240); uv max (NaOH–EtOH) ~230, ~240, and 285 nm; 100-MHz proton nmr δ 2.0–2.7 (m, 6 H), 2.32 (s, 3 H, NMe), 3.30 (m, 1 H), 6.09 (d, 1 H, *J* = 10.0 Hz, H-5), 6.74 (dd, 1 H, *J* = 10.0 and 2.0 Hz, H-4), 7.02 (center of AA′BB′ pattern, 4 H, aromatic hydrogens); carbon-13 nmr ($CHCl_3$) 35.9, 38.4, 40.0, 50.6, 55.8, 73.4, 115.3, 115.5, 125.0, 127.4, 154.3, 155.4, and 197.8 ppm (see Table II for assignments); mass spectrum *m/e* (rel intensity) 243 (53, M$^+$), 215 (7, M − CO), 175 (13, $C_{11}H_{13}NO$), 70 (100, C_4H_8N).

Anal. Calcd for $C_{15}H_{17}NO_2$: *m/e* 243.1259. Found: *m/e* 243.1255.

Hofmann Degradation of Sceletenone. Sceletenone (25 mg) was dissolved in 0.5 ml of acetone and CH_3I (0.5 ml) was added. The reaction mixture was allowed to stand overnight. The solid residue obtained on evaporation of the solvent was dissolved in 5 ml of H_2O, basified with saturated Na_2CO_3 solution, dried over $MgSO_4$, filtered, and evaporated *in vacuo*, leaving a light yellow oil. The oil was chromatographed on silica gel with 15% MeOH in $CHCl_3$, giving 6 mg of sceletenone and 5 mg of the dienone **19** as a light yellow oil: ir 3590 (OH), 1655, and 1611 cm^{-1} (dienone); uv max (MeOH) 232 nm (ε 17,500) and 272 (1770); mass spectrum *m/e* (rel intensity) 257 (56, M$^+$). 72 (69, $C_4H_{10}N$), 58 (100, C_3H_8N).

Anal. Calcd for $C_{16}H_{19}NO_2$: *m/e* 257.1416. Found: *m/e* 257.1415.

Acetylation of Sceletenone. A 10-mg sample of sceletenone was dissolved in 1.5 ml of pyridine. Five drops of acetic anhydride was added, and the reaction was stirred overnight at room temperature under a N_2 atmosphere. The excess pyridine and acetic anhydride were removed by vacuum distillation, giving a yellow oil: ir no OH, 1750 (ester), 1660 (dieone + amide), 1627 cm^{-1} (dienone); uv 225 nm (ε 14,800), 277 (4300); 90-MHz proton nmr δ 2.2–2.4 (m, 2 H, H-3), 3.15–3.4 (m, 2 H, H-2), 2.06 (s, 3 H, NAc), 2.31 (s, 3 H, OAc), 2.98 (s, 3 H, NMe), 6.66 (center of AA′BB′ pattern, 4 H, dienone protons), 7.05 (center of AA′BB′ pattern, 4 H, aromatic protons); mass spectrum *m/e* (rel intensity) 327 (27, M$^+$), 285 (11, M − C_2H_2O), 254 (42, M − C_3H_7NO), 212 [96, M − (C_2H_2O + C_3H_7NO)], 199 [18, M − (C_2H_2O + C_4H_8NO)], 185 [46, M − (C_2H_2O + $C_5H_{10}NO$)], 100 (100, $C_5H_{10}NO$), 86 (42, C_4H_8NO).

Anal. Calcd for $C_{19}H_{21}NO_4$: *m/e* 327.1470. Found: *m/e* 327.1464.

Acetylation of Mesembrenone. A 220-mg sample of mesembrenone was dissolved in 25 ml of pyridine under N_2. Acetic anhydride (5 ml) was added, and the solution was stirred for 24 hr. The excess pyridine and acetic anhydride was removed by vacuum distillation. The dark yellow oil was put through a short alumina column (activity II) with $CHCl_3$ and then 2.5% MeOH in $CHCl_3$, resulting in a yellow oil: 230 mg; ir 1658 (dienone + amide), 1640, and 1620 cm^{-1} (dienone); uv (MeOH) 228 nm (ε 13,900), and 278 (3780); 100-MHz proton nmr δ 2.18–2.48 (m, 2 H, H-3), 3.2–3.44 (m, 2 H, H-2), 2.07 and 2.09 (two s, 3 H, NAc for each conformer), 2.98 and 3.03 (two s, 3 H, NMe), 3.92 (s, 6 H, OMe), 6.73 (center of AA′BB′ pattern, 4 H, dienone protons), 6.8–7.05 (m, 3 H, aromatic protons); mass spectrum *m/e* (rel intensity) 329 (30, M$^+$), 256 (30, M − C_3H_7NO), 243 (11, M − C_4H_8NO), 229 (52, M − $C_5H_{10}NO$), 100 (100, $C_5H_{10}NO$), 86 (17, C_4H_8NO).

Anal. Calcd for $C_{19}H_{23}NO_4$: *m/e* 329.1627. Found: *m/e* 329.1632.

***O*-Methyl Derivative of Sceletenone.** An excess of an ethereal solution of diazomethane was added to 25 mg of sceletenone in 5 ml of CH_3OH at 40°. After 48 hr, the solvent was removed *in vacuo* and the oily residue was subjected to tlc on silica gel using $CHCl_3$–MeOH (20:1). The resulting oil was further purified *via* an acid–base extraction to afford a pale yellow oil: 6 mg; ir no OH, 1680 cm^{-1} (C=O); 250-MHz proton nmr δ 2.2–2.7 (m, 6 H), 2.32 (s, 3 H, NMe), 3.25 (m, 1 H), 3.79 (s, 3 H, OMe), 6.10 (d, 1 H, *J* = 10.0 Hz, H-5), 6.70 (dd, 1 H, *J* = 10.0, 1.5 Hz, H-4), 6.88 (center of AA′BB′ pattern, 4 H, aromatic protons); mass spectrum *m/e* (rel intensity) 257 (100, M$^+$), 229 (9, M − CO), 189 (14, $C_{12}H_{15}NO$), 70 (82, C_4H_8N).

Anal. Calcd for $C_{16}H_{19}NO_2$: *m/e* 257.1416. Found: *m/e* 257.1412.

Acknowledgments. We are indebted to Dr. David Rosenthal and Mr. Fred Williams of the Research Triangle Center for Mass Spectrometry, which is supported by the NIH (Grant RR 00330), for the high-resolution mass spectral results. We appreciate the assistance of Dr. W. C. Jankowski of Varian Associates, Palo Alto, Calif., for obtaining the 220-MHz spectrum and Dr. Joseph Breen, Carnegie-Mellon Institute, for recording the 250-MHz spectra.

Registry No. —**1**, 25516-12-5; **3**, 35135-35-4; **6**, 51934-13-5; **7**, 35714-44-4; **8**, 51934-14-6; **12**, 51934-30-6; **15**, 51934-31-7; **16**, 51934-32-8; **19**, 28564-22-9; **20**, 51934-33-9; **21**, 51934-34-0; veratric acid, 93-07-2; isovanillic acid, 645-08-9.

References and Notes

(1) (a) This work was supported through a Career Development Award (GM 42342) and a research grant (GM 19251) from the National Institute of Health. (b) National Science Foundation Undergraduate Research Participant, 1972. (c) James B. Duke Fellow, 1970–1973. (d) National Defense Act Fellow, 1968–1970. Some of these results have been presented in preliminary form: P. W. Jeffs, P. A. Luhan, A. T. McPhail, and N. H. Martin, *Chem. Commun.*, 1466 (1971).
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A Study of the Structures of Some Benzo-1,2,3-triazinium Betaines

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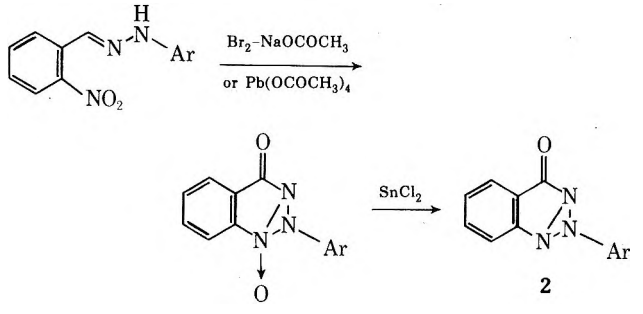
Received March 19, 1974

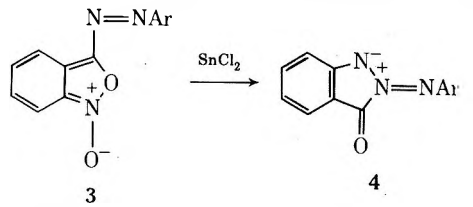
Methylation, phenylation, *p*-bromophenylation, and *p*-methylphenylation of 4(3*H*)-benzo-1,2,3-triazinone with dimethyl sulfate, diphenyl-, di-*p*-bromophenyl-, and di-*p*-tolyliodonium chloride results in formation of the N_2-substituted benzo-1,2,3-triazinium betaines **8** and **6a–c**, respectively. These latter compounds are identical with the products obtained by stannous chloride reduction of the betaines **10** and **5a–c** formed by oxidative cyclization of *o*-nitrobenzaldehyde methyl-, phenyl-, *p*-bromophenyl-, and *p*-tolylhydrazone, respectively, with lead(IV) acetate. Examination of the ir, nmr, uv, and mass spectra of the two classes of betaines **5** and **6** reveals that, while ir and nmr techniques afford little definitive evidence on structure, uv and mass spectroscopy can be used both for confirmation of structure and to distinguish between the two types of betaines.

Mild oxidation of *o*-nitrobenzaldehyde arylhydrazones with either bromine–sodium acetate or lead(IV) acetate results in the overall loss of two hydrogen atoms and production of a class of *N*-aryl heterocycles, the structure of which has been the subject of uncertainty and some controversy for the past 50 years. These oxidation products were first prepared and investigated by Chattaway,[1-6] who described them as "isodiazomethanes" and formulated them as the triaziridine derivatives **1**. Structural assignment was based entirely on evidence from degradation studies; in particular, Chattaway showed that reduction of "**1**" with stannous chloride resulted in the loss of a single oxygen atom and formation of a second class of compounds which he represented as **2**.



1 **2**

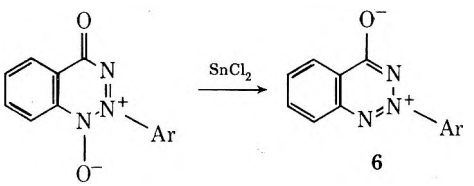
In a later reinvestigation of this work, Gibson,[7] partly on the basis of mechanistic reasoning and partly as a result of spectroscopic (uv, ir) studies, suggested that the initial oxidation products formulated by Chattaway as **1** could be better represented as the isomeric phenylazoanthranil *N*-oxides **3**, and the stannous chloride reduction products as the dipolar species **4**. More recently, however, Kerber[8] has



3 **4**

challenged Gibson's assignments and the evidence on which they were based. Kerber pointed out that Gibson's spectroscopic data were probably not consistent with structure **4**, and that structure **3** was improbable inasmuch as anthranil *N*-oxides are a rare, if not unknown, class of heterocycle, and proposed the triazinium betaine structures **5** and **6** for the oxidation and reduction products, respectively. Kerber's assignments, like those of Gibson, were based partly on mechanistic reasoning and partly on spectroscopic (ir, uv, nmr, mass spectral) evidence.

Heterocyclic betaines have been a subject of interest in this department for some years,[9] and within this context unsuccessful attempts were made some time ago to obtain definitive evidence for the structure of the dipolar species obtained from the oxidation of *o*-nitrobenzaldehyde arylhydrazones.[10] In the present paper we report the results of a further chemical and spectroscopic investigation of these compounds and their derived reduction products which establish not only that the structures **5** and **6** proposed by Kerber for the two classes of heterocycles are correct, but that the two structural types can be clearly differentiated on the bases of their uv and mass spectra.



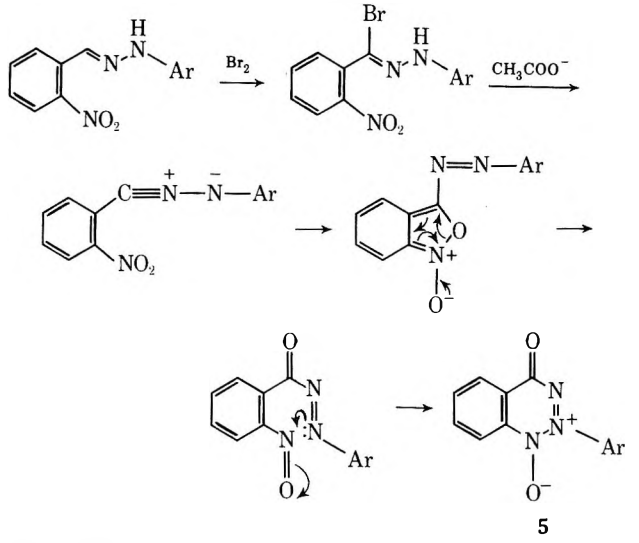
5 **6**

Discussion

At the outset of the present study Kerber's structure **5** for the products of oxidative cyclization of *o*-nitrobenzaldehyde arylhydrazones was assumed to be correct and to be compatible with a plausible mechanism for the overall reaction (Scheme I). Consequently, attention was concentrated on the development of procedures whereby compounds of the type **5** and/or **6** could be synthesized by an alternative route to that used by Chattaway. The simpler of the two series of betaines, *i.e.*, **6**, was investigated initially in the hope that, were an alternative synthesis of these compounds to be devised, it might then prove possible to effect specific N_1-oxidation to give **5**.

In 1968, Wagner and Gentzsch reported[11] that treatment of 4(3*H*)-benzo-1,2,3-triazinone (**7**) with dialkyl sulfates in base gave a mixture of products, namely the O- and N_3-al-

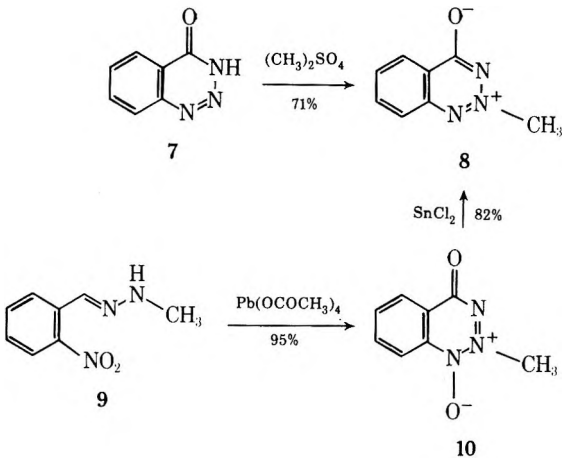
Scheme I



5

kylated derivatives, and a third isomer thought to be either the N_1- or N_2-alkylated compound. We have repeated this reaction and found that by using a slightly modified experimental procedure the latter compound, which is in fact the N_2 isomer, can be prepared readily in good yield. That alkylation occurs at N_2 was demonstrated in the following manner. Oxidation of o-nitrobenzaldehyde methylhydrazone (**9**) with lead(IV) acetate in dichloromethane gave the betaine *N*-oxide **10** (Scheme II); reduction of **10** with stannous chloride proceeded smoothly to give the betaine **8**, which was identical (melting point, mixture melting point, ir, uv, nmr, mass spectrum) with the product obtained by direct methylation of **7**.

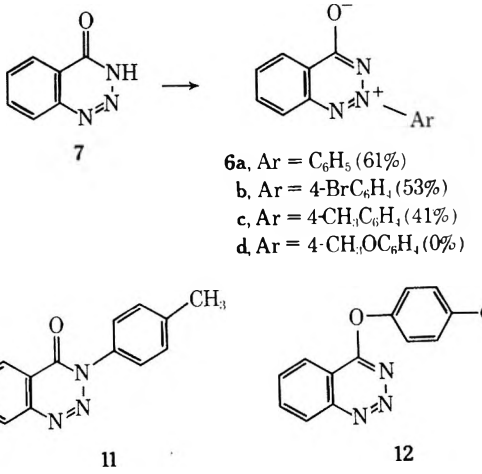
Scheme II



Possible procedures for the direct arylation of **7** were then considered, and it was concluded tha the use of diaryliodonium salts was the most promising approach. Very little work has so far been described on the reactions of these reagents with heterocyclic systems. Makarova and Nesmeyanov have reported that treatment of pyridine with diphenyliodonium fluoroborate results in formation of *N*-phenylpyridinium fluoroborate in 88% yield in an apparently straightforward nucleophilic substitution process;[12] Sandin and Brown, on the other hand, observed free-radical substitution when pyridine was treated with diphenyliodonium chloride in potassium hydroxide solution, and obtained a mixture of the isomeric 2-, 3- and 4-phenylpyridines.[13] Treatment of piperidine[14] and phthalimide[15] with diaryliodonium salts has been reported to lead only to N-arylation; with 2-quinolone, however, no N-substitution occurs, and the products are 3-phenyl-2-quinolone and 2-phenoxyquinoline.[16]

In the present study, direct phenylation of the sodium salt of 4(3*H*)-benzo-1,2,3-triazinone (**7**) proceeded smoothly to give the betaine **6a** in 61% yield (Scheme III). An exactly analogous reaction occurred with di-*p*-bromophenyliodonium chloride, and the betaine **6b** was isolated in 53% yield. In each of these cases substitution occurred solely at N_2, and no N_3- or O-arylated derivatives could be detected in the reaction mixtures. In contrast to the high regioselectivity of arylation in the above experiments, treatment of the sodium salt of **7** with di-*p*-tolyliodonium chloride gave a mixture consisting mainly of the N_2-arylated derivative **6c** together with small amounts of the N_3 (**11**) and O (**12**) isomers. The betaine **6c** was found to be thermally unstable, and after being heated at 120° (0.1 mm) for 1 hr (attempted vacuum sublimation), approximately half of it had rearranged to the *O*-aryl isomer **12**. All attempts to arylate the sodium salt of **7** with di-*p*-anisyliodonium chloride were unsuccessful; starting materials were recovered in virtually quantitative yield from each attempt. The betaines **6a–c** obtained by direct arylation were identical (melting point, mixture melting point, ir, uv, nmr, mass spectrum) with the compounds prepared by oxidative cyclization of the appropriate *o*-nitrobenzaldehyde arylhydrazones and subsequent stannous chloride reduction of the initially formed betaine *N*-oxides.

Scheme III



6a, Ar = C_6H_5 (61%)
b, Ar = 4-BrC_6H_4 (53%)
c, Ar = 4-$CH_3C_6H_4$ (41%)
d, Ar = 4-$CH_3OC_6H_4$ (0%)

The results obtained in the above arylation studies can largely be explained on the basis of nucleophilic substitution of the diaryliodonium salt by the anion of 4(3*H*)-benzo-1,2,3-triazinone. Both diphenyl- and di-*p*-bromophenyliodonium chloride apparently reacted cleanly by such an SNAr mechanism; failure to observe substitution with di-*p*-anisyliodonium chloride is then not unexpected. The results with di-*p*-tolyliodonium chloride possibly indicate a changeover point in mechanism with this reagent.[16]

Independent synthesis of betaines of the types **6** and **8** having been successfully accomplished, attempts were made to N-oxidize some of these to betaines of the type **5**. Attention was concentrated on the *p*-anisyl derivative **6d** (prepared from the appropriate o-nitrobenzaldehyde arylhydrazone), as it was thought that this substrate should undergo N-oxidation most easily (*cf.* **6d** → **13** → **5**, Scheme IV). Compound **6d** was treated with a wide variety of oxidizing agents, *e.g.*, standard hydrogen peroxide and peracetic acid solutions, solutions of 80% hydrogen peroxide in acetic, trifluoroacetic, and concentrated sulfuric acid

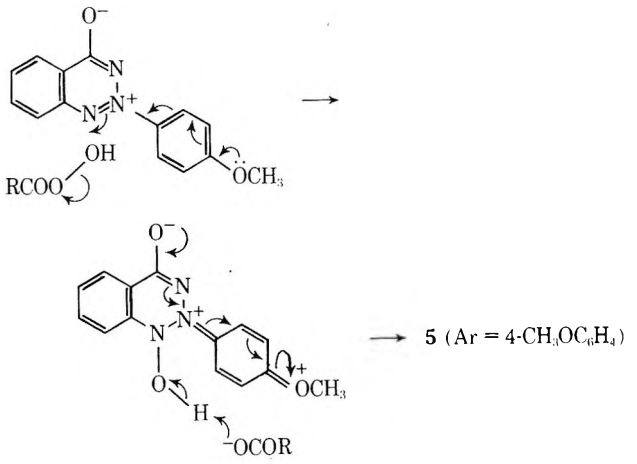
Table I
Yields and Physical Data for 2-Substituted Benzo-1,2,3-Triazinium Betaine 1-Oxides

Compd	Yield, %[a]	Mp, °C[b]	Lit. mp, °C	$\nu_{C=O}$
5a, Ar = C_6H_5	87	147–149	145[c]	1625
5b, Ar = 4-BrC_6H_4	73	144–146	144[d]	1630
5c, Ar = 4-$CH_3C_6H_4$	90	142–143	143[e]	1628
5d, Ar = 4-$CH_3OC_6H_4$	86	141	*f*	1649
5e, Ar = 4-$O_2NC_6H_4$	99	145–146	159[c]	1660
10	95	145–157	*g*	1628

[a] All compounds were prepared by oxidative cyclization of the appropriate *o*-nitrobenzaldehyde alkyl- or arylhydrazone with lead(IV) acetate (see ref c). [b] All compounds decomposed at or near the melting point. [c] W. A. F. Gladstone, J. B. Aylward, and R. O. C. Norman, *J. Chem. Soc. C*, 2587 (1969). [d] Reference 2. [e] Reference 3. [f] *Anal.* Calcd for $C_{14}H_{11}N_3O_3$: C, 62.45; H, 4.12; N, 15.61. Found: C, 62.03; H, 4.34; N, 15.32. [g] *Anal.* Calcd for $C_8H_7N_3O_2$: C, 54.24; H, 3.98; N, 23.72. Found: C, 54.15; H, 4.12; N, 23.87.

mixtures,[17,18] and solutions of *m*-chloroperbenzoic acid in sulfolane. Many reactions were carried out under a wide variety of conditions, but in no instance was any of the expected product **5** (Ar = 4-$CH_3OC_6H_4$) detected by tlc comparison of reaction mixtures with an authentic sample. The starting betaine **6d** was recovered in high yield in each case. Similar results were obtained with **6a–c** and with **8**.

Scheme IV



Spectroscopic Investigation. The results outlined above, in conjunction with the original degradation studies reported by Chattaway, provide conclusive evidence that the structures **5** and **6** proposed by Kerber for the two classes of betaines are correct. Concurrently with the chemical studies, we have carried out a detailed spectroscopic investigation of these betaines, the results of which are also consistent with the assigned structures. Relevant experimental data for the compounds used in this investigation are summarized in Tables I and II.

Examination of the ir and nmr spectra of all of the compounds listed in Tables I and II revealed immediately that neither of these techniques could be used with either accuracy or confidence as a basis for structural assignment with either of the two classes of betaines. The ir spectra were extremely complex and while, like the nmr spectra, they could be interpreted as being consistent with the assigned structures, they do not in our opinion offer any unambiguous proof for them. Moreover, the spectra of neither class of betaine show either significant similarities or meaningful correlations, and it is impossible to distinguish between the two classes of compounds on the basis of ir and nmr spectra.

It is possible, however, to distinguish clearly between the two classes of betaines on the basis of their uv spectra. The spectra of compounds **5a–e** and **10** are remarkably similar with respect to band shape, as are the spectra of compounds **6a–e** and **8**, but the two forms of band shapes are quite different from each other and from those of the comparison compounds **7**, **11**, **12**, and **14**. The spectra of compounds **5c**, **6c**, **11**, and **12**, for example, are shown in Figure 1, and relevant uv data for all of the compounds listed in Tables I and II are summarized in the Experimental Section.

Mass spectroscopy also provided supporting evidence on the structures of the two classes of betaines **5** and **6**, and allowed ready distinction to be made between them. The most notable contrast between the mass spectra of compounds **5a–e** and **6a–e** was the presence of a very intense parent peak for the latter compounds and the almost total absence of a parent peak for the *N*-oxides **5a–e**. All of the compounds **5a–e** underwent fragmentation to give prominent ions at *m/e* values corresponding to P − O, P − N_2 or CO, P − O − N_2 or CO, P − O − N_2 − CO, $RC_6H_4N_3^+O$, $RC_6H_4N_3^+$, $RC_6H_4N_2^+$, $RC_6H_4^+$, and $C_7H_4O^+$ or $C_6H_4N_2^+$.

Table II
Yields and Physical Data for 2-Substituted Benzo-1,2,3-triazinium Betaines and Some Comparison Compounds

Compd	Yield, %[a,b]	Mp, °C	Lit. mp, °C	$\nu_{C=O}$, cm^{-1}
6a	99	116–118.5	*c*	1650
6b	92	199–201	199–200[d]	1675
6c	67	165–167	*e*	1662
6d	88	193–194	*f*	1665
6e, Ar = 4-$O_2NC_6H_4$	78	244–245	*g*	1630
8	82	143–144	144[h]	1630
7	79	217–218	216[i]	1695
14, 3-methyl-4(3*H*)-benzo-1,2,3-triazinone		122–123	123[h]	1675
11, 3-(4-methylphenyl)-4(3*H*)-benzo-1,2,3-triazinone	69	143–144	143[d]	1687
12, 4-(4-methylphenoxy)-benzo-1,2,3-triazine	8	145–147.5	*j*	1667[k]

[a] Compounds **6a–e** and **8** were prepared by stannous chloride reduction of the corresponding betaine 1-oxides (see Table I); compounds **7**, **14**, and **11** were prepared by standard literature procedures; compound **12** was obtained as described in the Experimental Section. [b] Yields refer to isolated material. [c] *Anal.* Calcd for $C_{13}H_9N_3O$: C, 69.95; H, 4.06; N, 18.82. Found: C 70.05; H, 4.14; N, 18.68. [d] Reference 8. [e] *Anal.* Calcd for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.60; H, 4.72; N, 18.10. [f] *Anal.* Calcd for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38, N, 16.59. Found: C, 66.10; H, 4 46; N, 16.97. [g] *Anal.* Calcd for $C_{13}H_8N_4O_3$: C, 58.21; H, 3.01; N, 20.89. Found: C, 57.97; H, 3.21; N, 20.93. [h] Reference 11. [i] H. Finger, *J. Prakt. Chem.*, **37**, 431 (1888). [j] *Anal.* Calcd for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.83; H, 4.75; N, 17.89. [k] $\nu_{C=N}$.

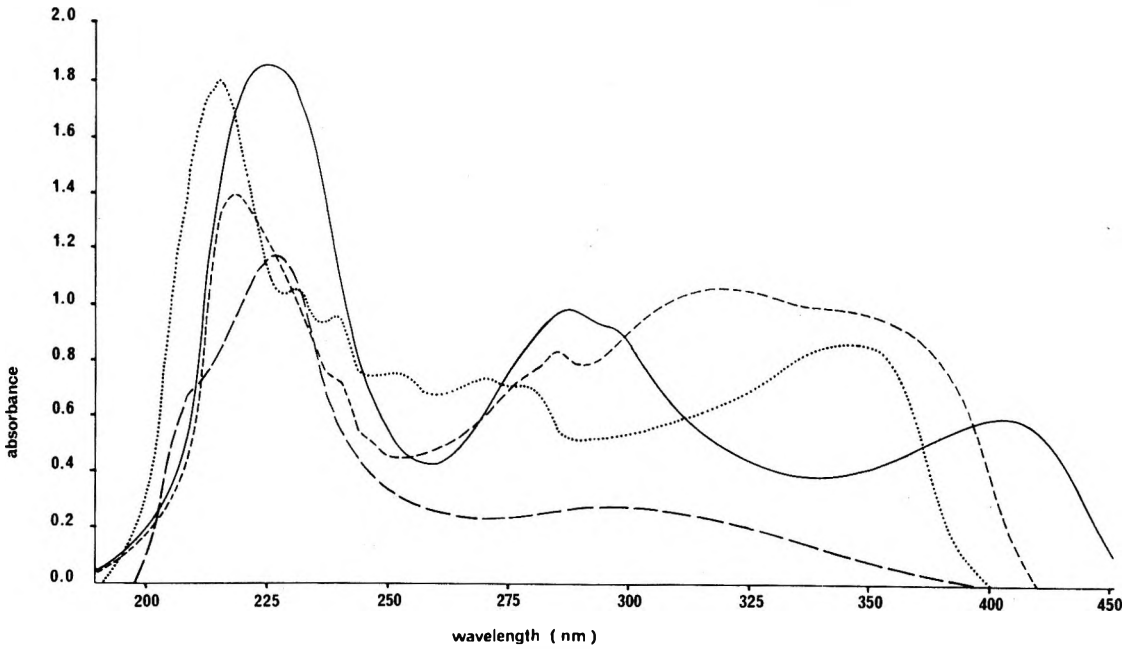


Figure 1. Uv spectra of **5c** (——), **6c** (- - - -), **11** (— — —), and **12** (·····).

In addition to a prominent parent peak, the spectra of compounds **6a–e** showed prominent ions at *m/e* values corresponding to P − N_2 or CO, P − N_2 − CO, $RC_6H_4N_2^+$, $RC_6H_4^+$, $C_7H_4O^+$ or $C_6H_4N_2^+$, and $C_6H_4^+$. The relative intensities of the various prominent ions were reasonably consistent within each group of related compounds, but they differed by a factor of 2–3 between the groups. Distinction between the betaines **10** and **8** and between compounds such as **7, 11, 12,** and **14** could similarly be made by the use of mass spectroscopy (see paragraph at end of paper regarding supplementary material).

From the above spectral investigation it is evident that uv and mass spectroscopic techniques can be utilized for confirmation of structure in the benzo-1,2,3-triazinium betaine field and as a means of distinguishing between the different classes of betaines **5** and **6.** It is equally evident, however, that spectroscopic data alone, as pointed out previously by Kerber,[8] are unreliable criteria on which to base the structure of complex heterocycles.

Experimental Section

Melting points were determined on a Kofler hot-stage microscope apparatus, and are uncorrected. Microanalyses were performed by Mr. A. R. Saunders of the University of East Anglia, and by the Analytical Section of I. C. I. (Pharmaceuticals Division). Infrared spectra were recorded on a Perkin-Elmer Model 257 grating infrared spectrophotometer using the standard Nujol mull technique. Nuclear magnetic resonance spectra were determined on Perkin-Elmer R-12, 60 MHz, and Varian HA-100, 100-MHz spectrometers, using tetramethylsilane as internal standard. Tlc refers to Merck preprepared silica plates, with chloroform as the eluent, unless otherwise stated. All uv spectra were recorded as solutions in ethanol on a Unicam SP-800 spectrophotometer. Solutions were made up immediately prior to recording of the spectra, as it was noticed that the betaines **5** and **6** decomposed fairly rapidly in ethanol when the solutions were exposed to light. Mass spectra were obtained at 70 eV and 300° using a Perkin-Elmer Model RMU-6E mass spectrometer.

Preparation of 2-Methylbenzo-1,2,3-triazinium Betaine 1-Oxide (10) by Oxidative Cyclization of *o*-Nitrobenzaldehyde Methylhydrazone (9). A solution of lead(IV) acetate (16.0 g, 0.036 mol) in dichloromethane (80 ml) was added in one portion to a stirred solution of **9** (6.0 g, 0.034 mol) in dichloromethane (400 ml) at room temperature. An immediate color change from orange to yellow was observed, and lead(II) acetate began to precipitate. The mixture was stirred for 15 min, after which time tlc analysis showed that no starting material remained and that a single product was present. Water (100 ml) was added, and the mixture was stirred for a further 15 min. Precipitated lead(IV) oxide was removed by vacuum filtration through Keiselguhr, and the organic layer separated; this was washed with saturated sodium bicarbonate solution until acid free and then with water (2 × 40 ml) and dried (Na_2SO_4), and the solvent was removed by evaporation under reduced pressure. The residue was recrystallized from a benzene–petroleum ether (bp 60–80°) mixture to give 5.6 g (95%) of **10** as bright yellow, needle-shaped crystals, mp slow over the range 145–157°, with extensive decomposition, softening from 140°.

Preparation of 2-Methylbenzo-1,2,3-triazinium Betaine (8) by Reduction of 2-Methylbenzo-1,2,3-triazinium Betaine 1-Oxide (10). A solution of **10** (2 g, 0.011 mol) in glacial acetic acid (10 ml) was treated with concentrated hydrochloric acid (30 ml) and cooled to 0°, when a small amount of colorless solid precipitated. A solution of stannous chloride dihydrate (2.8 g, 0.0012 mol) in concentrated hydrochloric acid (10 ml) was added dropwise over 10 min to the stirred suspension, and a colorless solid gradually precipitated. The resulting suspension was stirred at 0° for 0.5 hr, and the temperature was then allowed to rise to ambient over a further 0.5 hr. Water (100 ml) was added, the mixture was extracted with dichloromethane (3 × 40 ml), the combined extracts were washed with saturated sodium bicarbonate solution until acid free and then with water (2 × 20 ml) and dried (Na_2SO_4), and the solvent was removed by evaporation under reduced pressure. The residue was recrystallized from a chloroform–petroleum ether mixture to give 1.5 g (82%) of **8** as the hemihydrate, colorless, needle-shaped crystals, mp 122–123 (fast), 143–144° (slow) (lit.[11] mp 139–140°).

Preparation of 2-Methylbenzo-1,2,3-triazinium Betaine (8) by Direct Methylation of 7. Dimethyl sulfate (12.6 g, 0.1 mol) was added dropwise over 5 min at room temperature to a well-stirred solution of 4(3*H*)-benzo-1,2,3-triazinone (14.7 g, 0.1 mol) in sodium hydroxide solution (10% w/v, 40 ml). A transient green color was produced which gradually changed to a pale straw color, and evolution of considerable heat was noted. After being stirred for 15 min the reaction mixture appeared to be homogeneous and was cooled to room temperature in a water bath and then extracted with chloroform (4 × 30 ml). The combined extracts were washed with water (2 × 20 ml) and dried (Na_2SO_4), and the solvent was removed by evaporation under reduced pressure to give a pale tan solid. Recrystallization from a chloroform–petroleum ether mixture gave 12 g (71%) of pure **8** as pale yellow needles, mp 122–123 (fast), 143–145degr (slow) (lit.[11] mp 139–140°).

Preparation of 2-Phenylbenzo-1,2,3-triazinium Betaine (6a) by Direct Phenylation of 7. 4(3*H*)-Benzo-1,2,3-triazinone (2.94 g, 0.02 mol) was added to a solution of sodium (0.5 g, 0.022 mol) in dry, redistilled *tert*-butyl alcohol (120 ml), and the mixture was heated to reflux for 5 min to ensure complete formation of the sodium salt. Diphenyliodonium chloride[19] (6.4 g, 0.02 mol) was added and the mixture was heated to reflux for 1.25 hr. It was then cooled to room temperature, insoluble inorganic salts were re-

moved by vacuum filtration, and the solvent was removed from the filtrate by evaporation under reduced pressure. The oily residue was triturated with warm benzene (100 ml), a further small quantity of inorganic salts was removed by vacuum filtration, and the filtrate was evaporated under reduced pressure. Trituration of the resulting oil with small quantities of petroleum ether resulted in crystallization; the solid was collected by vacuum filtration and recrystallized from a benzene–petroleum ether mixture to give 2.7 g (61%) of pure **6a** as pale yellow needles, mp 116–118°, mmp with the product prepared by the oxidative cyclization of o-nitrobenzaldehyde phenylhydrazone 116–117.5°.

Preparation of 2-*p*-Bromophenylbenzo-1,2,3-triazinium Betaine (6b) by Direct Arylation of 7. 4(3*H*)-Benzo-1,2,3-triazinone (2.94 g, 0.02 mol) was added to a solution of sodium (0.5 g, 0.022 mol) in dry methanol (75 ml), and the mixture was heated gently to effect solution. Di-*p*-bromophenyliodonium chloride[20] (9.5 g, 0.02 mol) was added and the mixture was then heated to reflux for 24 hr. After this time a pale yellow solid had precipitated; anhydrous methanol (40 ml) was added and the mixture was gently warmed to dissolve this precipitate. Small amounts of insoluble inorganic salts were removed by vacuum filtration of the hot reaction mixture, and cooling of the filtrate resulted in precipitation of a pale yellow solid. This was collected by vacuum filtration and identified by tlc analysis as the desired product by comparison of R_f value with that of a genuine sample. Evaporation of the filtrate gave a further crop of a pale yellow solid, extraction of which with hot petroleum ether (2 × 100 ml) removed the petroleum-soluble solid and left a pale yellow residue which was identified as the desired product by tlc comparison with a genuine sample prepared by the oxidative cyclization of o-nitrobenzaldehyde *p*-bromophenylhydrazone. The petroleum-soluble solid, 4.2 g (75%), was identified as *p*-iodobromobenzene.

Recrystallization of **6b** from a dichloromethane–petroleum ether mixture gave 3.2 g (53%) of pure material as pale yellow microneedles, mp 198–201° (lit.[2] mp 197°).

Preparation of 2-*p*-Tolylbenzo-1,2,3-triazinium Betaine (6c) by Direct Arylation of 7. 4(3*H*)-Benzo-1,2,3-triazinone (14.7 g, 0.1 mol) was added to a solution of sodium (2.5 g, 0.11 mol) in dry methanol (100 ml) followed by di-*p*-tolyliodonium chloride[20] (34.5 g, 0.1 mol) and the resultant mixture (pale pink solution) was heated to reflux for 24 hr. The reaction mixture was allowed to cool to room temperature, large amounts of pale brown insoluble inorganic salts were removed by vacuum filtration, and the solvent was removed by evaporation under reduced pressure. Tlc analysis of the residue showed it to consist of small amounts of polar materials, some *p*-iodotoluene, a small amount of N_3-*p*-tolyl-4(3*H*)-benzo-1,2,3-triazinone (by comparison of R_f value with that of a genuine sample[2]), and a major product corresponding in appearance and R_f value to the expected product **6c**, which had been prepared by the oxidative cyclization of o-nitrobenzaldehyde *p*-tolylhydrazone.

Trituration of this oily residue with small amounts of ethanol and cooling to 0° overnight resulted in crystallization of 2.0 g of a pale yellow solid which was collected and assigned structure **12** on the basis of its ir, uv, nmr, and mass spectra. Recrystallization from a chloroform–petroleum ether mixture gave 1.8 g of pure product as pale yellow, light-sensitive platelets, mp 145–7.5°.

Chromatography on silica gel of the residue left after removal of **12** gave, on elution with chloroform and evaporation of the solvent, 14 g of a pale yellow solid the R_f value of which was identical with that of the expected product **6c** which has been prepared independently by the Chattaway procedure. Examination of the nmr spectrum, however, revealed that this material was a mixture of **6c** and **12** in an approximate ratio of 4:1. Recrystallization from a chloroform–petroleum ether mixture gave 9.6 g of almost pure **6c**, mp 143–145°. Complete removal of traces of **12** from this product by either crystallization, chromatography, or sublimation was found to be impossible, and in independent experiments it was shown that when **6c** was heated above about 60° it slowly isomerized to give a 1:1 mixture of **6c** and **12**.

Uv Data. 5a: λ_{max} 227, 285, 404 nm (log ϵ 4.28, 4.06, 3.81). **5b:** λ_{max} 222, 286, 404 nm (log ϵ 4.31, 4.05, 3.80). **5c:** λ_{max} 226, 287, 296 (sh), 404 nm (log ϵ 4.30, 4.03, 3.99, 3.82). **5d:** λ_{max} 230, 286, 300 (sh), 396 nm (log ϵ 4.35, 3.91, 3.85, 3.90). **5e:** λ_{max} 230, 286, 410 nm (log ϵ 4.38, 4.35, 3.91). **10:** λ_{max} 226, 278, 384 nm (log ϵ 4.29, 3.89, 3.76). **6a:** λ_{max} 218, 230 (sh), 238 (sh), 276, 283, 297, 357 nm (log ϵ 4.22, 4.09, 3.94, 4.11, 4.13, 4.07, 3.97). **6b:** λ_{max} 219, 230 (sh), 239 (sh), 278, 284, 310, 358 nm (log ϵ 4.30, 4.17, 4.02, 4.04, 4.09, 4.15, 4.07). **6c:** λ_{max} 218, 233 (sh), 239 (sh), 247 (sh), 275 (sh), 280, 317, 350 nm (log ϵ 4.16, 3.98, 3.88, 3.71, 3.86, 3.93, 4.04, 4.01). **6d:** λ_{max} 217, 230, 250, 276, 284, 364 nm (log ϵ 4.23, 4.12, 3.95, 3.69, 3.69, 4.26). **6e:** λ_{max} 218, 230 (sh), 238 (sh), 277, 284, 370 nm (log ϵ 4.26, 4.17, 4.17, 4.35, 4.34, 4.03). **8:** λ_{max} 212, 231, 238, 250 (sh), 266 (sh), 276 (sh), 335 nm (log ϵ 4.02, 4.01, 4.00, 3.82, 3.55, 3.43, 3.86). **7:** λ_{max} 211, 224, 250, 278, 296, 307 nm (log ϵ 4.15, 4.28, 3.71, 3.80, 3.63, 3.42). **11:** λ_{max} 212, 227, 292 nm (log ϵ 4.30, 4.48, 3.84). **12:** λ_{max} 215, 231, 239, 251, 269, 278, 345 nm (log ϵ 4.29, 4.13, 4.09, 3.98, 3.97, 3.96, 4.05). **14:** λ_{max} 214, 225, 252 (sh), 285, 300 (sh), 316 (sh) nm (log ϵ 4.31, 4.35, 3.69, 3.89, 3.79, 3.61).

Acknowledgments. We should like to thank I. C. I. Pharmaceuticals Division for partial financial sulport of this project. One of us (R. J. K.) acknowledges receipt of a CAPS Studentship.

Registry No.—**5a,** 51932-42-4; **5b,** 51932-43-5; **5c,** 51932-44-6; **5d,** 51932-45-7; **5e,** 51932-46-8; **6a,** 51932-47-9; **6b,** 33986-95-7; **6c,** 51932-48-0; **6d,** 51932-49-1; **6e,** 51932-50-4; **7,** 90-16-4; **8,** 22305-46-0; **9,** 5771-05-1; **10,** 51932-51-5; **11,** 19562-37-9; **12,** 51932-52-6; **14,** 22305-44-8.

Supplementary Material Available. Line diagram mass spectra of the betaines **5a–e, 6a–e, 8,** and **10** will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-2710.

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Cycloaddition Reactions of the 2-Azabicyclo[3.1.0]hex-3-ene Ring System[1]

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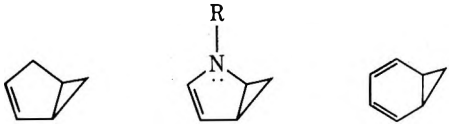
Received April 2, 1974

The 2-azabicyclo[3.1.0]hex-3-ene ring system reacts with dimethyl acetylenedicarboxylate and *N*-phenylmaleimide to give derivatives of the 8-azabicyclo[3.2.1]octene ring system. In contrast, tetracyanoethylene reacts with 2-azabicyclo[3.1.0]hex-3-ene ring system to give derivatives of 2-azatricyclo[4.2.0.0^{3,5}] octane. Stereochemical and kinetic results are discussed with respect to mechanistic possibilities for these cycloadditions.

Few reactions rival cycloadditions in the number of bonds that undergo transformation during the reaction, producing products considerably more complex than the reactants. Cycloaddition reactions have had a tremendous impact on both synthetic[2] and theoretical chemistry.[3] The search continues to discover new cycloaddition reactions.

Some reports have appeared recently dealing with cycloadditions to vinylcyclopropanes[4] and these have prompted us to communicate the results of our studies on the 2-azabicyclo[3.1.0]hex-3-ene ring system.

The 2-azabicyclo[3.1.0]hex-3-ene ring system[5] is sterically analogous to bicyclo[3.1.0]hex-2-ene (**1**). However, the presence of the nitrogen results in a more extensively conjugated π system containing two additional π electrons and electronically it can be considered to be analogous to norcaradiene (**3**), a species that is unstable with respect to its valence isomer, cycloheptatriene.

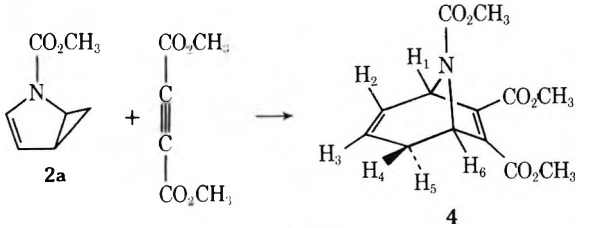


1 **2** **3**

We have observed previously[5] that the presence of the nitrogen can have a profound effect on the thermal rearrangements of the bicyclo[3.1.0]hex-2-ene ring system. Therefore, it was of interest to investigate further the chemical behavior of this heterocycle.

Cycloadditions involving 2-π electron components such as olefins with the carbocycle **1** are, to our knowledge, unknown. In spite of the well-known analogy between a double bond and a cyclopropane,[6] cycloadditions involving a vinylcyclopropane moiety are rare. Cycloadditions of norcaradiene derivatives with olefins or acetylenes usually give Diels–Alder adducts with the diene portion while the cyclopropane function remains intact.[2]

In comparison, we have observed that heating *N*-carbomethoxy-2-azabicyclo[3.1.0]hex-3-ene (**2a**) with dimethyl acetylenedicarboxylate (DMAD) gives a derivative of the 8-azabicyclo[3.2.1]oct-2-ene ring system **4**. The structure of

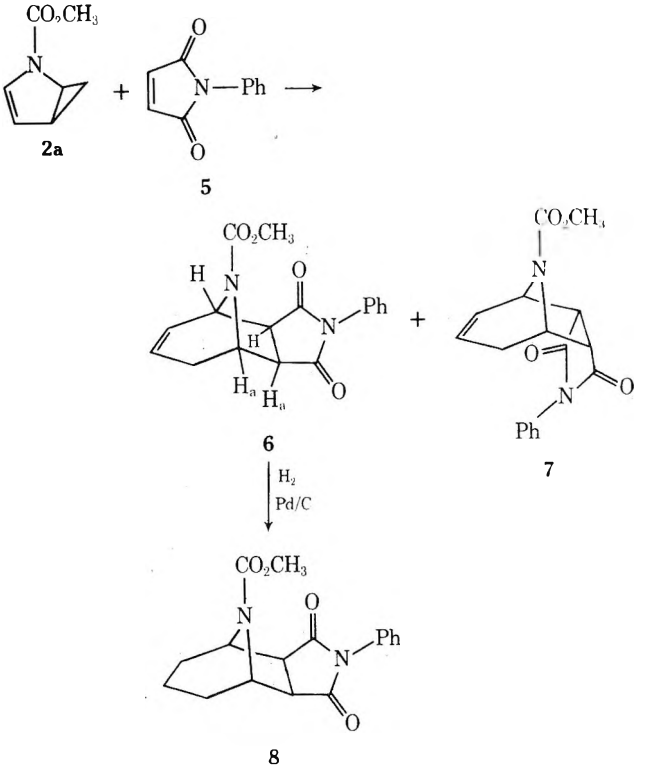


2a **4**

this adduct is based on spectroscopic data, particularly proton magnetic resonance spectroscopy and elemental analyses. The pmr spectrum ($CDCl_3$) showed τ 3.50–3.83 (m, H_3), 4.25–4.61 (m, H_2), 4.90 (d, J = 5.5 Hz, H_6), 5.11 (d, J = 5.0 Hz, H_1), 6.18 (s, 6 H, OCH_3), 6.25 (s, 3 H, OCH_3), and 7.55 (center of a broad AB, H_4 and H_5).

The above assignments were deduced from double-resonance experiments. It is interesting to observe that H_6 occurs as a doublet, suggesting zero coupling between H_6 and either H_4 or H_5. Dreiding molecular models and a comparison with the carbocyclic system[7] indicate that the bond to H_6 forms an angle of approximately 90° with the adjacent bond to the endo hydrogen. This would suggest zero coupling between H_6 and the endo hydrogen H_5.

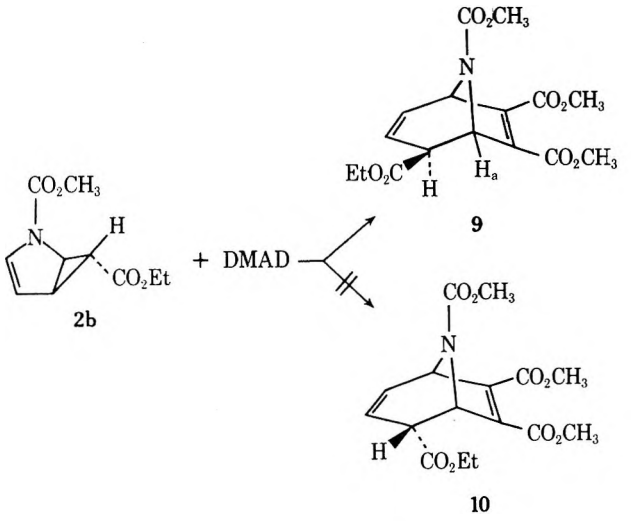
The reaction of **2a** with *N*-phenylmaleimide (**5**) gave adducts **6** and **7** in a ratio of 2:3, respectively, showing only a

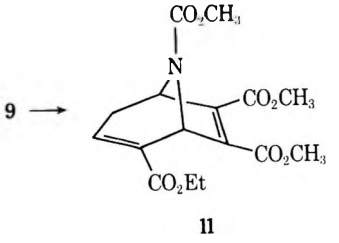


2a **5** **6** **7** **8**

slight preference for the endo isomer. These isomers were readily separated by thin layer chromatography and purified by recrystallization. The product **6** is assigned the exo configuration, since the bridgehead hydrogens H and H′ appear as an AB pattern showing zero coupling to the bridgehead hydrogens H_a and H_a'. Hydrogenation of **6** gives a symmetrical structure where the hydrogens that were responsible for the AB pattern are now equivalent and appear as a singlet. This result is consistent with the above assignment.

The reaction of *N*-carbomethoxy-6-carbethoxy-2-azabicyclo[3.1.0]hex-3-ene (**2b**) with dimethyl acetylenedicarboxylate can in principle give two isomeric adducts, **9** and **10**. In practice, only the exo isomer **9** was detected. This assignment is based on the nmr spectrum. The bridgehead hydrogen H_a shows zero or nearly zero coupling to the hydrogen α to the carbethoxy function. From the previous





discussion on the nmr spectrum of adduct **4**, H_a in **9** must occupy the endo position. Attempts to purify the product **9** by thin layer chromatography resulted in double bond isomerization, giving **11**. This indicates that **9** is the primary product and is not formed by epimerization of **10**.

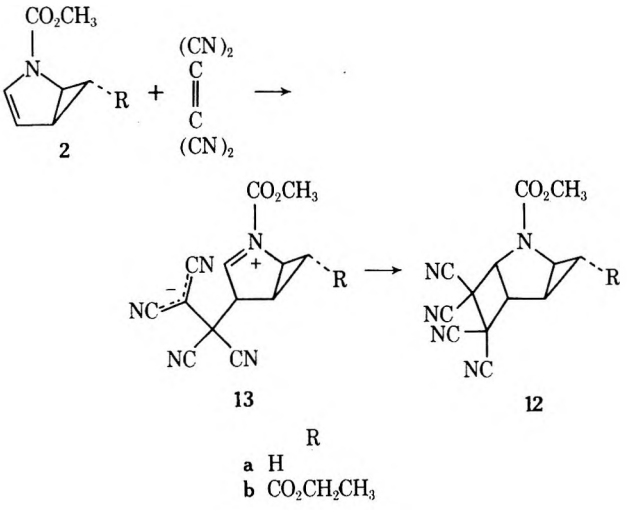
Interestingly, the reaction of tetracyanoethylene (TCNE) with the 2-azabicyclo[3.1.0]hex-3-ene ring system follows a different course. When TCNE in tetrahydrofuran is added to the *N*-carbomethoxy-2-azabicyclo[3.1.0]hex-3-enes (**2a** or **2b**) at room temperature, a colorless solid is produced. The products of these reactions are assigned structures **12a** and **12b**.

This assignment is based partially on the nmr spectrum, which shows high-field absorption indicating the presence of a cyclopropyl substituent and a low-field AB spin system. This low-field AB spin system is assigned to hydrogens that were vinyl in the reactant **2**. The cyclobutyl hydrogen β to the nitrogen atom shows zero or nearly zero coupling with the adjacent cyclopropyl hydrogen. Molecular models indicate that this would be true only in the anti isomer.

Examination of the reactions of vinylcyclopropanes with various dienophiles supports the position that the mechanisms of these reactions appear to be complex. Sarel[4d] and Pasto[4c] have cited dipolar species as reaction intermediates, while Baldwin preferred the concept of a concerted, thermally allowed, $[2_\pi + 2_\sigma + 2_\pi]$ cycloaddition. No specific evidence was obtained for these preferences other than product formation and none of the mechanistic possibilities presented explained the variation of products obtained upon changes in dienophile.

We have made preliminary investigations into the mechanism of the cycloaddition of dienophiles to the 2-azabicyclo[3.1.0]hex-3-ene ring system.

The difference in reactivity of TCNE toward **2a** and **2b** as compared to DMAD is not unprecedented. TCNE is often found to give reaction products arising from a [2 + 2] cycloaddition.[8] Most probably this reaction proceeds through dipole **13**, which can then close to the observed products.



Kinetic results demonstrate that the cycloaddition reaction of **2a** and **2b** with DMAD is second order overall (Table I), while the cycloaddition of **2a** with *N*-phenyl-

Table I
Cycloadditions of the 2-Azabicyclo[3.1.0]hex-3-enes with Dimethyl Acetylenedicarboxylate

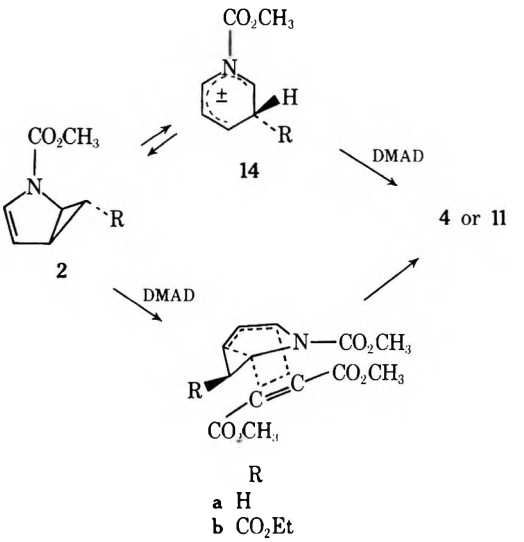
Substrate	Solvent	Mole ratio of DMAD/substrate	Temp, °C	$k \times 10^5$, l. mol^{-1} sec^{-1}
2a	C_6D_6	0.96	91.4	2.98 ± 0.18
2a	C_6D_6	1.92	91.4	2.74 ± 0.07
2b	C_6D_6	0.76	106.3	0.794 ± 0.021

maleimide shows essentially no solvent dependence (Table II). However, two discrete mechanisms are consistent with

Table II
Solvent Dependence of the Cycloaddition of 2a with *N*-Phenylmaleimide

Solvent	Temp, °C	$k \times 10^4$, l. mol^{-1} sec^{-1}
CCl_4	75.8	2.3 ± 0.5
$CH_3C{\equiv}N$	75.8	2.0 ± 0.2

the above results. Compound **2** could be in rapid equilibrium with dipole **14**, which then reacts with DMAD to give the adduct **4** or **9**. Alternatively, DMAD could react with



the 2-azabicyclo[3.1.0]hex-3-ene ring system in a concerted or nearly concerted fashion.

The stereochemical orientation of the carbethoxy-substituted derivative **9** requires, in the dipole mechanism, that DMAD attack the dipole **14b** from the sterically less hindered side. If a concerted or nearly concerted mechanism is operative in these cycloadditions, then DMAD must attack from the endo direction. Although this would appear to be a sterically unfavorable mode of attack, it is most favorable electronically. Endo attack has been established for electrophilic[9] and radical reactions[10] of fused cyclopropanes. Theoretical calculations[11] and physical measurement[12] are consistent with this phenomenon.

If the dipoles **14a** and **14b** were involved in the cycloaddition reactions, then the second-order kinetics suggest that the dipoles **14a** and **14b** must be involved in a rapid preequilibrium with **2a** and **2b.** Also, the effect of the carbethoxy substituent on the rate of reaction would be expected to be electronic in nature, as the approach of DMAD would have to occur exclusively on the sterically less hindered face of the dipole to account for the product stereochemistry.

Using the steady-state approximation the complete kinetic expression for the 1,3-dipole mechanism is

$$\text{rate} = \frac{k_2[\text{DMAD}]k_1[\mathbf{2}]}{k_2[\text{DMAD}] + k_{-1}}$$

Furthermore, it can be shown that

$$k_{\text{obsd}} = K_{\text{eq}}k_2$$

where

$$K_{\text{eq}} = k_1/k_{-1}$$

and k_{obsd} is the observed rate constant.

The substitution of a carbethoxy group at position 6 in **2** might thus be expected to retard the rate of cycloaddition of **2b** as compared to **2a** in two possible ways. First, the substitution of a carbethoxy group will cause a decrease in k_2 qualitatively, assuming that the reaction of dipole **14** with DMAD is controlled by the properties of the highest occupied molecular orbital.[13] Second, the strengthening effect of the 6-carbethoxy group upon the C_1–C_5 bond[5,14] would shift the preequilibrium between dipole **14** and **2** toward **2b** as compared to **2a** and thus $K_{eq}^{(2b)} < K_{eq}^{(2a)}$.

If the breaking of the C_1–C_5 bond in **2** occurs during the rate-determining step, as it does in the concerted mechanism, the strengthened C_1–C_5 bond in **2b** as compared to **2a** could account for the relative slowness of cycloaddition to **2b.** Table III shows that the difference between ΔH^*

Table III
Thermodynamic Functions for the Reaction of 2 with Dimethyl Acetylenedicarboxylate

Substrate	E_a, kcal/mol	A, l. mol^{-1} sec^{-1}	$\Delta H,^*$ kcal/mol	$\Delta S,^*$ eu
2a	17.6	1.00×10^6	16.8	−33.3
2b	20.7	6.5×10^6	19.9	−29.9

values for the cycloaddition of **2a** and **2b** to DMAD is 3.1 kcal/mol.

It has been shown[15] that the retarding effect of a cyano group on the electrocyclic rearrangement of "folded" 9-cyanobicyclo[6.1.0]nonatriene is 3.5 kcal/mol. In light of this, a bond-strengthening effect of 3.1 kcal/mol attributed to a carbethoxy group is not unreasonable.

Experimental Section[16]

Reaction of *N*-Carbomethoxy-2-azabicyclo[3.1.0]hex-3-ene (2a) with Dimethyl Acetylenedicarboxylate. **2a** (130 mg) and 152 mg of DMAD were heated on a steam bath for 15.5 hr. The product **4** proved to be a high-boiling liquid and was purified by preparative thin layer chromatography, giving a 51% yield of **4**: nmr ($CDCl_3$) τ 3.50–3.83 (m, 1 H, C=CH), 4.25–4.61 (m, 1 H, C=CH), 4.90 (d, J = 5.5 Hz, 1 H, NCH), 5.11 (d, J = 5.0 Hz, 1 H, NCH), 6.18 (s, 6 H, OCH_3), 6.27 (s, 3 H, OCH_3), and 7.55 (center of broad AB, J = 19 Hz, $W_{1/2}$ low-field half = 10 Hz, $W_{1/2}$ high-field half = 6.5 Hz, CH_2). Irradiation of the olefinic multiplet at τ 3.50–3.83 caused the doublet at τ 5.11 to collapse into a broad singlet, indicating that these are the H_2 and H_1 protons, respectively. Irradiation of the lower half of the AB centered at 7.55 caused the doublet at τ 4.90 to collapse into a broad singlet. This indicates that the lower half of the AB is H_4 and the doublet at τ 4.90 is the bridgehead proton at H_6. The ir spectrum (neat) showed a broad, strong absorption at 1715 (C=O) and 1640 cm^{-1} (C=C).

Anal. Calcd for $C_{13}H_{15}NO_6$: C, 55.51; H, 5.37. Found: C, 55.76; H, 5.51.

Reaction of *N*-Carbomethoxy-2-azabicyclo[3.1.0]hex-3-ene (2a) with *N*-Phenylmaleimide (5). To 139 mg of **2a** was added 173 mg of *N*-phenylmaleimide. The reaction mixture was heated to 100° under argon for 12 hr. Preparative thin layer chromatography of the product on silica gel (3:1 benzene–ether) separated two products. The major band (116 mg, 38%) proved to be the endo isomer **7**: R_f 0.24; mp 143–145°; nmr ($CDCl_3$) τ 2.42–2.97 (m, 5 H), 3.90–4.25 (m, 2 H), 5.02–5.42 (m, 2 H), 6.13–6.37 (m, 2 H), 6.28 (s, 3 H) and 6.83–h8.00 (m, 2 H); ir (KBr) 1775 and 1710 (C=O) and 1595 cm^{-1} (C=C).

Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.37; H, 5.16; N, 8.97. Found: C, 65.20; H, 5.31; N, 8.90.

The minor band (80 mg) proved to be the exo isomer **6**: R_f 0.34; mp 173–175°; nmr ($CDCl_3$) τ 2.38–2.92 (m, 5 H), 3.67–4.50 (m, 2 H), 5.05–5.35 (m, 2 H), 6.33 (s, 3 H), 6.22 (center of AB, J = 7.5 Hz), and 6.87–8.17 (m, 2 H); ir (KBr) 1778 and 1705 (C=O) and 1593 cm^{-1} (C=C).

Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.37; H, 5.16. Found: C, 65.37; H, 5.02.

Hydrogenation of 6. To 53 mg of **6** was added 20 ml of ethyl acetate and 10% palladium on carbon. Subjecting the solution to 1 atm of hydrogen led to the absorption of 1 equiv of hydrogen within 0.5 hr. Removal of the solvent gave a colorless oil **8**, which could be recrystallized from ethyl acetate–pentane: mp 157–158°; nmr ($CDCl_3$) τ 2.38–2.92 (m, 5 H), 5.28 (s, broad, $W_{1/2}$ = 5 Hz, 2 H), 6.33 (s, 3 H), 6.78 (s, 2 H), and 8.25 (s, broad, $W_{1/2}$ = 4 Hz, 6 H); ir (KBr) 1781 (w) and 1705 cm^{-1} (s, C=O).

Anal. Calcd for $C_{17}H_{18}N_2O_4$: C, 64.95; H, 5.77; N, 8.91. Found: C, 64.88; H, 5.83; N, 9.13.

Reaction of *N*-Carbomethoxy-6-carbethoxy-2-azabicyclo-[3.1.0]hex-3-ene (2b) with Tetracyanoethylene. To a solution of 255 mg of **2b** in 5 ml of anhydrous THF with stirring was added a solution of 155 mg of freshly sublimed TCNE in 5 ml of THF. Immediately upon addition, a yellow-gold color appeared. After a period of 15 min, the solvent was removed *in vacuo*, leaving a red-brown solid which was recrystallized by dissolving in acetone and adding ether until cloudiness developed. **12b** (229 mg, 56% yield) was obtained as small, colorless crystals: mp 135–136°; nmr (acetone-d_6) τ 4.79 (d, 1 H, J = 7.5 Hz), 5.48 (d, 1 H, J = 7.5 Hz), 5.59–5.99 (m, 3 H), 6.14 (s, 3 H, NCO_2CH_3), 7.11 (dd, 1 H, J = 6.0, J' = 4.25 Hz), 7.71 (dd, 1 H, J = 4.25, J' = 1.5 Hz), 8.74 (t, 3 H, J = 7.0 Hz, OCH_2CH_3); ir (KBr) 3010 (CH), 2230 (C≡N), 1720 cm^{-1} (C=O).

Anal. Calcd for $C_{16}H_{13}N_5O_4$: C, 56.63; H, 3.86; N, 20.64; O, 18.86. Found: C, 56.58; H, 3.93.

Reaction of *N*-Carbomethoxy-2-azabicyclo[3.1.0]hex-3-ene (2a) with Tetracyanoethylene. To 129 mg of **2a** in 2 ml of THF was added 128 mg of TCNE in 0.5 ml of THF. The reaction mixture was allowed to stand at room temperature for 1 hr and the solvent was removed at room temperature *in vacuo*. The nmr spectrum of the crude product show only the presence of **12a.** The crude product was dissolved in acetone and ether was slowly added until precipitation of **12a** no longer occurred. This produced 111 mg of yellow crystals, mp 134° dec. The analytical sample was produced by recrystallization from acetone–ether at room temperature: mp 135° dec; nmr (acetone-d_6) τ 4.73 (center AB, 2 H, J = 7.5 Hz), 3.97–3.37 (m, 1 H), 3.84 (s, 3 H, OCH_3), 2.75–2.00 (m, 1 H), and 1.58–0.82 (m, 2 H); ir (KBr) 2259 (C≡N), 1736 (C=O), and strong absorptions at 1451, 1392, and 1339 cm^{-1}.

Anal. Calcd for $C_{13}H_9O_2N_5$: C, 58.42; H, 3.39; N, 26.21. Found: C, 58.40; H, 3.39; N, 26.15.

Reaction of *N*-Carbomethoxy-6-carbethoxy-2-azabicyclo-[3.1.0]hex-3-ene (2b) with Dimethyl Acetylenedicarboxylate. To a Pyrex tube was added 316 mg of **2b** and 228 mg of DMAD. The tube was flushed with argon and sealed. The reaction mixture was heated in an oil bath at 170° for 24 hr. Nmr analysis, by comparing the bridgehead to total methoxyl hydrogens of the crude product, reveals an 87% yield of **9**. The product was purified first by molecular distillation and then by vapor phase chromatography (1 ft × 0.25 in., 212°, 3% SE-30 on Chromosorb Cr 60/70, He 50 cc/min): nmr ($CDCl_3$) τ 3.38–3.73 (m, 1 H), 4.12–4.47 (m, 1 H), 4.42 (s, broad, $W_{1/2}$ = 3 Hz), 5.75 (q, J = 7 Hz, 2 H), 6.18 (s, 6 H), 6.32 (s, 3 H), 6.68–6.83 (m, 1 H), and 8.53 (t, J = 7 Hz, 3 H); ir (neat) 1721 (C=O) and 1645 cm^{-1} (C=C).

Anal. Calcd for $C_{16}H_{19}NO_8$: C, 54.39; H, 5.42. Found: C, 54.12; H, 5.42.

Attempts to purify the above product by preparative thin layer chromatography (20 × 20 × 0.2 cm silica gel, 3:1 ether–benzene) resulted in the production of isomeric compound **11**: nmr ($CDCl_3$) τ 3.17–3.38 (m, 1 H), 4.55 (s, broad, $W_{1/2}$ = 2.5 Hz, 1 H), 4.90 (d, broad, $W_{1/2}$ = 3 Hz, 1 H), 5.77 (q, J = 7 Hz, 2 H), 6.20 (s, 3 H), 6.22 (s, 3 H), 6.30 (s, 3 H), 6.87–7.95 (m, 2 H), and 8.80 (t, J = 7 Hz, 3 H); ir (neat) 1726 cm^{-1} (C=O).

Anal. Calcd for $C_{16}H_{19}NO_8$: C, 54.39; H, 5.42. Found: C, 54.11; H, 5.25.

Kinetics of the Cycloaddition of 2 with Dimethyl Acetylenedicarboxylate. To an nmr tube were added controlled amounts of **2a** or **2b**, DMAD, and C_6D_6. C_6H_6 was used as an internal standard with the total volume being recorded. (The initial concentration of reactants was approximately 1 *M*.) The tube was flushed with nitrogen, sealed under vacuum, and maintained at the appropriate temperature (±0.1°) in an oil bath. Determinations for **2a** were made at 70.5, 80.7, and 91.4° while for **2b** determinations were made at 106.3, 113.6, and 120.9°. The disappearance of **2a** was monitored by periodic integration of the upfield endo cyclopropyl peak in the nmr spectrum of the reaction mixture. The disappearance of **2b** was followed by periodic integration of the cyclopropyl proton at position 5 in **2b**. Second-order rate constants and activation energies were obtained by least-squares fitting.

Acknowledgments. We wish to express our gratitude to the National Science Foundation (Research Grant GP-20099) for support of this work. We would also like to thank Professor R. Huisgen for his helpful comments.

Registry No.—**2a**, 31709-40-7; **2b**, 25088-90-8; **4**, 31709-41-8; **5**, 941-69-5; **6**, 51869-43-3; **7**, 51898-46-5; **8**, 51869-44-4; **9**, 31887-68-0; **11**, 51911-67-2; **12a**, 51869-45-5; **12b**, 51869-46-6; DMAD, 762-42-5; TCNE, 670-54-2.

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Reactions of *N*-Aryl Nitrogen Oxides. 1. Selective Ortho Chlorination in the Reactions of Aryl Nitrones and Amine Oxides with Thionyl Chloride or Phosgene

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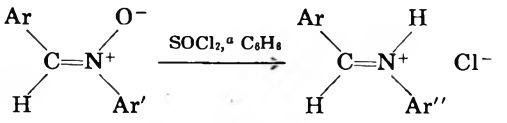
Received February 22, 1974

N-Aryl nitrones react rapidly with phosgene or thionyl chloride to produce ring-chlorinated imine hydrochlorides in high yield. Ring chlorination is shown to proceed exclusively on the aryl system adjacent to the nitrogen atom. The generality of this reaction with other *N*-aryl nitrogen oxides is discussed and a mechanism based upon the experimental observations is proposed.

The classes of *N*-aryl nitrogen oxides which are of current interest in this laboratory include, *inter alia*, *N*-aryl nitrones, *N*-aryl tertiary amine *N*-oxides, *N,N'*-diarylazoxy compounds, nitroaromatic compounds, and *N*-aryl-*N*-nitroso dimers. A few of the above have been reported to react with acid chlorides and anhydrides to yield ring-substituted products. For example, in an investigation of the Polonovski reaction, Huisgen, *et al.*,[1] have observed the production of small to moderate amounts of ortho-acetylated *N,N*-dimethylanilines when ring-substituted *N,N*-di-

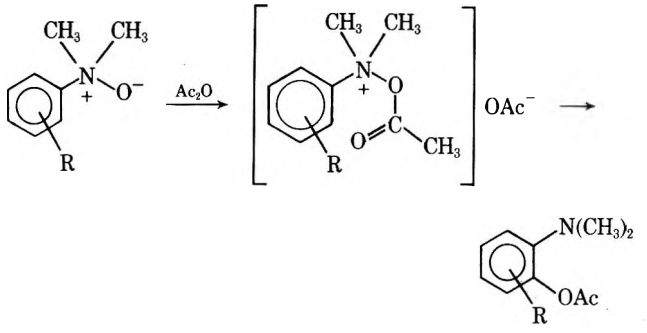
Table I



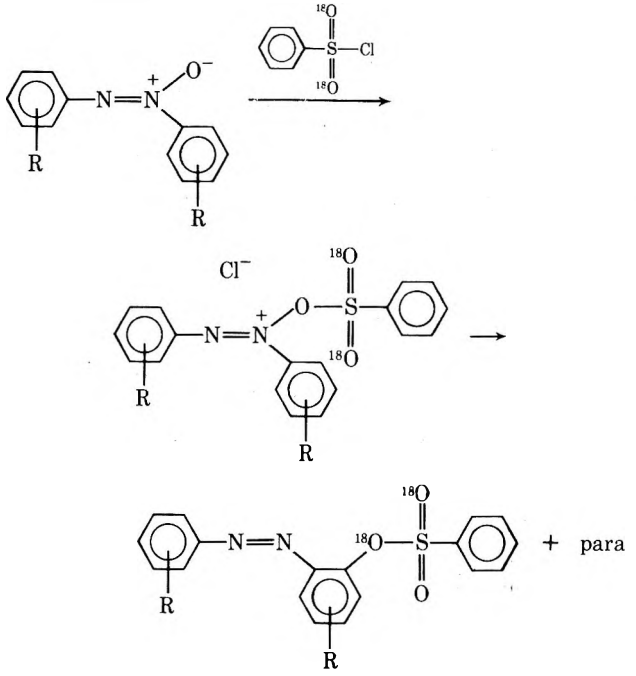
Reactants				Products[b]			
Compd	Ar	Ar'	Registry no.	Compd	Ar''	Isolated yield, %	Registry no.
1	C_6H_5	C_6H_5	1137-76-8	2	2-ClC_6H_4	81	884-29-7
				3	4-ClC_6H_4	6	780-21-2
4	C_6H_5CHCH	C_6H_5	37056-75-0	5	2-ClC_6H_4	72	42549-55-3
				6	4-ClC_6H_4	3	42549-56-4
7	4-$NO_2C_6H_4$	C_6H_5	3585-90-8	8	2-ClC_6H_4	83[c]	42597-13-7
10	C_6H_5	4-$CH_3C_6H_4$	19064-77-8	11	2-Cl-4-$CH_3C_6H_3$	91	42549-58-6
12	C_6H_5	4-ClC_6H_4	19865-58-8	13	2,4-$Cl_2C_6H_3$	92	42549-59-7
14	4-$CH_3OC_6H_4$	4-ClC_6H_4	51911-70-7	15	2,4-$Cl_2C_6H_3$	90	51911-72-9
16	C_6H_5	4-$H_5C_2O_2CC_6H_4$	51911-71-8	17	2-Cl-4-$H_5C_2O_2CC_6H_3$[d]	94	51911-73-0

[a] No significant differences in product ratios were observed when phosgene was used in place of thionyl chloride. [b] The structures of the products (except **17**) were determined by comparison of their physical and spectral properties with those of authentic samples which were prepared independently. [c] Slight heating was necessary to initiate this reaction. [d] The structure of **17** was determined by mass spectrometry, elemental analysis, and chemical degradation to known substances.

methylaniline *N*-oxides were allowed to react with acetic anhydride. The reaction was thought to proceed through an *N*-acetoxy-*N*,*N*-dimethylanilinium acetate as shown below.



Similarly, although *N*,*N*′-diarylazoxy compounds undergo deoxygenation when treated with most acid chlorides,[2] they yield ortho and para ring-substituted products when allowed to react with benzenesulfonyl chloride.[3] The ortho-substituted product has been shown by ^{18}O isotope labeling to be formed from an intermediate similar to the one proposed by Huisgen for the amine oxide reaction.



N-Aryl nitrones are reported to isomerize to the corresponding amides when allowed to react with most acid chlorides and anhydrides.[4] However, in a preliminary communication, we recently reported that *N*-aryl nitrones react rapidly with thionyl chloride or phosgene at room temperature to yield the corresponding ortho-chlorinated imine hydrochlorides in high yield.[5] The remarkable positional selectivity of this reaction prompted us to investigate the mechanism by which it occurs and to test its generality with other *N*-aryl nitrogen oxides and analogous systems. We now report the results of our investigation.

Results and Discussion

A. Nitrones. In general, the reactions are performed as follows. The aryl nitrone is dissolved at room temperature in dry benzene and thionyl chloride (or phosgene dissolved in benzene) is added dropwise. The evolution of a gas and simultaneous production of a precipitate occur almost immediately. After the addition is completed the precipitate is collected and washed with pentane. Although this procedure is usually sufficient to obtain a reasonably pure product, further purification can be accomplished by vacuum sublimation. The results are summarized in Table I.

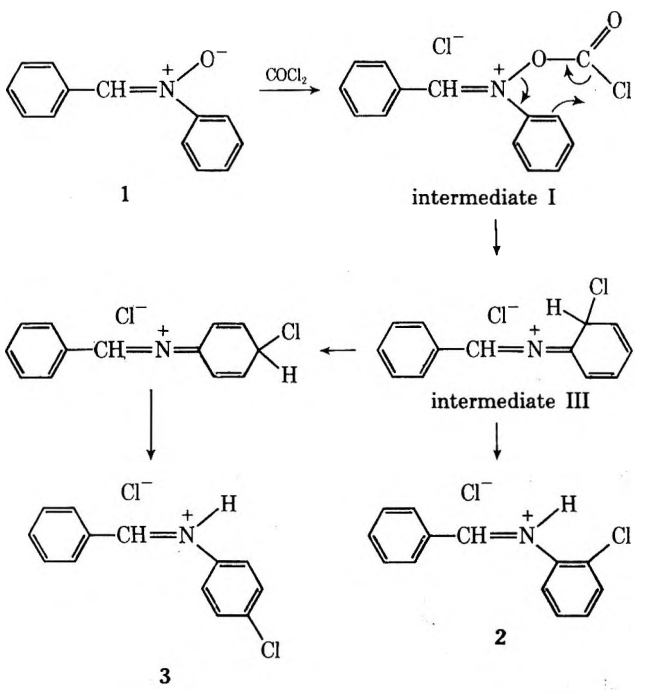
Since aryl nitrones are readily available by several methods,[6,7] the above reaction appears generally useful for the selective, rapid synthesis of ortho-chlorinated imines, and, by hydrolysis, the corresponding amines in high yield.

While several pathways might be proposed for this reaction, only one is reasonable in light of the evidence at hand. This is illustrated in Scheme I for the reaction of α,*N*-diphenylnitrone (1) with phosgene.

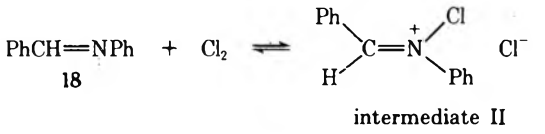
The first step of the reaction undoubtedly involves nucleophilic attack on the phosgene by the negatively charged oxygen atom of the nitrone, yielding intermediate I. An appropriately positioned nitro group would therefore be expected to decrease the rate of reaction by delocalization of the negative charge, and, in fact, α-(4-nitrophenyl)-*N*-phenylnitrone (7) is the only nitrone among those investigated which requires heating for the reaction to occur. The intermediate I may be viewed as decomposing to products *via* a concerted decarboxylation with ring chlorination followed by hydrogen transfer with rearomatization.

The positional selectivity of the reaction rules out two other possible mechanisms which might have been worthy of consideration. For the first of these, intermediate I would be considered to rearrange to an *N*-chloroimmonium

Scheme I



species (intermediate II) followed by ring substitution. As intermediate II is an expected constituent of an equilibrium mixture of **18** and chlorine,[8] generation of this species by addition of a dilute solution of chlorine in benzene to the anil **18** is possible. In fact, when this experiment was performed, a precipitate formed immediately, analysis of which indicated it to be an equal mixture of benzylideneaniline hydrochloride and benzylidene-*p*-chloroaniline hydrochloride;[9] *no ortho isomer was detected.* This result precludes the possibility of the reaction proceeding through intermediate II.[10] Another alternative mechanism, that of chloride attack on the *N*-aryl ring of intermediate I, is excluded as well, as that route would be expected to yield a significant proportion of para product.



The extremely high ortho:para ratio observed in all reactions is indeed significant evidence for the reaction to be considered as proceeding through a six-centered transition state. Comparison with other ring-halogenation processes involving *N*-chloro intermediates is illustrative of this point. Whereas, for example, *N*-chloro-*N*-methylaniline is reported to rearrange to ring-chlorinated products with an ortho:para ratio of approximately 2:1,[11] the products of these nitrone reactions had ortho:para ratios ranging from a minimum value of about 13.5:1 to those cases where no para isomer could be detected.[12] Thus, we consider the reaction to proceed *via* the six-centered transition state and therefore to be analogous to the reactions reported by Huisgen, *et al.*,[1] and by Oae, *et al.*[3] (*vide supra*). In view of this it is not surprising that in all the nitrone reactions studied chlorination was observed only on the *N*-aryl ring even when the *C*-aryl ring contained substituents highly activating for electrophilic substitution, *e.g.*, **14**.

B. Amine Oxides. Since thionyl chloride and phosgene react with *N*-aryl nitrones so selectively, it was of interest to determine if other *N*-aryl nitrogen oxides would react in a similar fashion. To this end, *N*,*N*-dimethylaniline *N*-oxide (**19**), prepared from *N*,*N*-dimethylaniline (**20**) and hydrogen peroxide in aqueous methanol,[13] was allowed to react with thionyl chloride. Because of the hygroscopic nature of **19**, the reaction was performed in a glove bag in a nitrogen atmosphere. Various solvents were used (benzene, chloroform, tetrahydrofuran, petroleum ether). The major competing process with ring chlorination proved to be deoxygenation of the amine oxide to **20**. This latter reaction could be minimized by working with dilute solutions of the amine oxide in petroleum ether or tetrahydrofuran, in which case approximately 90% *N*,*N*-dimethyl-2-chloroanili ne (**21**) was obtained. This compares with 30% **21** and 70% **20** being obtained when the reaction was performed in more concentrated solutions.

Although reaction conditions can be optimized to give good yields of ring-chlorinated product, the reaction is restricted to tertiary amine systems, and hence is less versatile than the ortho chlorination of nitrones. Nevertheless, as this reaction appears to be basically similar to that of nitrones, it is obvious that a π-bonded nitrogen is not required.

C. Other Systems. Other *N*-aryl oxides which might be expected to react with thionyl chloride or phosgene in a similar fashion to nitrones or amine oxides apparently do not.

Nitroaromatic compounds appear to react very slowly with thionyl chloride. A small amount of reaction appears to occur upon setting to reflux for 1 week a mixture of nitrobenzene (**22**) with thionyl chloride, as the solution becomes distinctly purple in color. Nevertheless, it has not proven possible to identify any organic compounds other than **22** in the reaction mixture.

The reaction of *N*,*N*′-diaryl azoxy compounds with a number of acid chlorides including thionyl chloride has been previously investigated.[2] We confirmed that deoxygenation appears to be the major process, with ring chlorination as a minor competing side reaction.

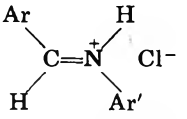
Nitroso compounds exist in the dimeric *N*-oxide form only in the solid state. We have shown in this laboratory that reaction does occur between nitrosobenzene (**23**) and thionyl chloride, but along different lines from the amine oxide and nitrone reactions. The major product is 2,4-dichloroaniline (**24**), presumably arising from rearrangement of *N*,*N*-dichloroaniline.[14] Iodosobenzene (**25**) when treated with thionyl chloride yields iodobenzene dichloride (**26**) quantitatively.[15]

Experimental Section

General. All melting points were measured using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Unless otherwise stated, infrared spectra were measured as Nujol or Fluorolube mulls on a Perkin-Elmer 237-B grating spectrometer; mass spectra were measured using a Varian CH-7 mass spectrometer; nmr spectra were measured using either a Varian A-60A or a Varian EM-60 spectrometer. Benzene and tetrahydrofuran were dried over sodium ribbon and distilled prior to use. Phosgene (12.5% solution in benzene) and thionyl chloride were purchased from Matheson Coleman and Bell and used without further purification.

Nitrones. All nitrones were prepared according to the standard procedure as follows.[16] Equal molar quantities of the aryl hydroxylamine and the aldehyde were mixed in benzene solution and refluxed, water being removed in a Dean-Stark apparatus. In general, these reactions went to completion in a very short time. The solvent was evaporated and the crude nitrone was recrystallized from a 1:1 mixture of low-boiling petroleum ether and benzene. All of the nitrones utilized in this investigation have been reported in the literature[16,17] with the exception of **16**. This was isolated in 80% yield (mp 141–142°) by the above procedure. Compound **16** exhibited a mass spectrum in accord with the nitrone structure[18] (M^+, *m/e* 269; base peak, $[M - 28]^+$, *m/e* 241). Other analytical data are as follows: ir ($CHCl_3$) 3.32, 5.78, 6.14, 6.84, 6.95, 7.09, 7.22, 7.75, 8.13, 8.33, 8.48, 8.93, 9.09, 9.18, 9.71, 11.11, 11.37, 14.39, 14.82

Table II



Compd	Ar	Ar′	Mp, °C	Mass spectral data[a] M+ [b,c]	Mass spectral data[a] Base peak	Ir frequencies, μ
2	C_6H_5	2-ClC_6H_4	215 dec	215, 217	215	3.85, 4.28, 5.05, 6.10
3	C_6H_5	4-ClC_6H_4	189–191	215, 217	215	3.90, 4.30, 6.15
5	C_6H_5CHCH	2-ClC_6H_4	148 dec	241, 243	240	4.30, 5.08, 6.12, 6.23
6	C_6H_5CHCH	4-ClC_6H_4	167–169	241, 243	240	4.25, 5.00, 6.15, 6.28
8	4-$NO_2C_6H_4$	2-ClC_6H_4	188–190 dec	260, 262	51	3.88, 5.02, 6.32
11	C_6H_5	2-Cl-4-$CH_3C_6H_3$	194–197	229, 231	77	3.85, 5.00, 6.32
13	C_6H_5	2,4-$Cl_2C_6H_3$	20–205	249, 251, 253	161	3.90, 4.30, 6.25
15	4-$CH_3OC_6H_4$	2,4-$Cl_2C_6H_3$	182–185	279, 281 283	245	3.90, 6.24
17	C_6H_5	2-Cl-4-$H_5C_2O_2CC_6H_3$	163–166	287, 289	154	3.88, 5.78, 6.25

[a] All mass spectra were observed at 70 eV with a trap current of 100 μA. [b] As is common with hydrochlorides, the highest *m/e* peak observed involves loss of HCl from the parent molecule. [c] Appropriate Cl isotope patterns were observed in all cases.

μ; nmr ($CDCl_3$) δ 1.40 (t, 3 H), 4.38 (q, 2 H), 7.2–8.5 (m, 10 H). *Anal.* Calcd for $C_{16}H_{15}NO_3$: C, 71.37; H, 5.58. Found: C, 71.62; H, 5.86.[19]

General Procedure for the Reaction of Nitrones with Thionyl Chloride (or Phosgene). The aryl nitrone was dissolved in benzene and to it was added thionyl chloride (phosgene in benzene, 12.5%) dropwise in 10% molar excess. The precipitate which immediately formed was collected and washed with pentane. Rigorous purification was effected by vacuum sublimation. The product substituted imine hydrochlorides were compared with authentic materials synthesized by a standard independent means from the appropriate amines and aldehydes *via* azeotropic distillation using a Dean-Stark apparatus.[20] The isolated imines were dissolved in benzene and treated with anhydrous HCl to yield the imine hydrochlorides necessary for product comparison. Such comparisons were made in the usual manner by mixture melting points and by matching infrared and mass spectra. In all cases no depression of melting points was observed and excellent spectral matches were obtained.

Imine hydrochlorides are reasonably stable when stored in a dry atmosphere, but hydrolyze rapidly when exposed to moisture, precluding in some cases satisfactory combustion analysis. Compounds **2**[21] and **3**[22] have been previously reported. Satisfactory combustion analyses were obtained for **9**, **10**, and **17** (**9** and **10** as dihydrates). Compounds **11**, **15**, **13**, and **8** gave unsatisfactory analytical data, presumably owing to rapid hydrolysis. However, this phenomenon of rapid hydrolysis can be exploited to obtain the absolute proof of structure required in the absence of satisfactory analytical data. To this end, the products of the nitrone–phosgene reactions were degraded by hydrolysis to the parent aldehydes and amines, which were then analyzed. The following procedure was followed in all cases. The imine hydrochlorides resulting from the nitrone reactions were dissolved in tetrahydrofuran, and dilute hydrochloric acid was added. The liberated aldehyde component of the imine was extracted into ether and identified by infrared spectroscopy and prepation of its 2,4-dinitrophenylhydrazonederivatives (anisaldehyde 2,4-dinitrophenylhydrazone, mp 252–254°; benzaldehyde 2,4-dinitrophenylhydrazone, mp 236–237°; *p*-nitrobenzaldehyde 2,4-dinitrophenylhydrazone, mp 320°; no depression of melting point was observed on admixture with authentic samples). After extraction of the aldehyde, the remaining reaction mixture was made basic, and the liberated amine was extracted into ether and isolated by evaporation. Structure verification was obtained through comparison of the spectroscopic properties and/or melting points of authentic materials, and also by combustion analysis of the derived amine hydrochlorides, prepared by passing hydrogen chloride into an ethereal solution of the amine. 2,4-Diloroaniline hydrochloride (**29**) had mp 216°. *Anal.* Calcd for $C_6H_6NCl_3$: C, 36.27; H, 3.02. Found: C, 36.50; H, 3.15. 2-Chloro-4-methylaniline hydrochloride (**30**) sublimed at 240–245°. *Anal.* Calcd for $C_7H_9NCl_2$: C, 47.19; H, 5.06. Found: C, 47.42; H, 5.07. 2-Chloroaniline hydrochloride (**31**) sublimed at 200–205°. *Anal.* Calcd for $C_6H_7NCl_2$: C, 43.90; H, 4.27. Found: C, 44.02; H, 4.44.

All the amines derived from the imine hydrochlorides have been reported previously, except that derived from compound **17**, *via* 4-amino-3-chlorobenzoic acid ethyl ester (**27**). Thus, compound **27** was further hydrolyzed with 40% aqueous sodium hydroxide solution at reflux temperature for 15 min. The solution was allowed to cool and the pH was adjusted to 4.5. The 4-amino-3-chlorobenzoic acid (**28**) which precipitated was recrystallized from 85% aqueous tetrahydrofuran, mp 222–224°.[23] Mass spectral and ir data for **17** are given in Table II. *Anal.* Calcd for $C_{16}H_{15}NO_2Cl_2$ (**17**): C, 59.26; H, 4.63. Found: C, 59.39; H, 4.88.

General Procedure for the Reaction of *N,N*-Dimethylaniline *N*-Oxide (19) with Thionyl Chloride. Compound **19** was prepared according to a method described previously.[13] It was dried through azeotropic distillation with benzene, then filtered in a nitrogen atmosphere in a glove bag. A 10% molar excess of thionyl chloride was then added dropwise to a solution of **19** in various solvents (chloroform, tetrahydrofuran, benzene, and petroleum ether were tried in different runs). After the addition was complete, the solution was made basic with aqueous sodium hydroxide and the organic fraction was collected, dried ($MgSO_4$), and evaporated. The crude products obtained in each run were examined by gas–liquid chromatography (30% Carbowax on Chromosorb P, 180°) and by mass spectrometry. Unless dilute solutions (*e.g.*, 1%) of **19** were used, significant quantities of *N,N*-dimethylaniline (**20**) were formed along with 2-chloro-*N,N*-dimethylaniline (**21**), *sym*-trinitrobenzene adduct, mp 108.5–109° (lit. mp 110–111°),[24] *m/e* 154, 156. With dilute solutions of **19** in tetrahydrofuran or petroleum ether, **21** was obtined as the only significant product.

General Procedure for the Reaction of Nitrosobenzene (23) with Thionyl Chloride. Nitrosobenzene (**23**) was dissolved in benzene, and thionyl chloride was added dropwise in 10% molar excess. An immediate reaction occurred. The product was isolated by bringing the reaction mixture to pH 11, extracting with ether, drying the organic material ($MgSO_4$), and evaporating the solvent. The product was proven to be 2,4-dichloroaniline (**24**) by mass spectrometry, *m/e* 161 (100%), 163, 91, preparation of its benzylidene derivative, mp 84° (lit. mp 84°),[25] and by comparison of its ir spectrum with one reported in the literature.[26]

Reaction of Nitrobenzene with Thionyl Chloride. Nitrobenzene (**22**) was refluxed with a 10% molar excess of thionyl chloride for 1 week. After this time the solution had a distinctly purple color. However, it proved impossible to isolate any organic material other than nitrobenzene in quantities sufficient for analysis.

Reaction of Iodosobenzene with Thionyl Chloride. The procedure is exactly the same as that used for nitrosobenzene. The product was identified by comparison with iodobenzene dichloride (**26**), mp 110–111°, which was independently synthesized.

Registry No.—**28**, 2486-71-7; **29**, 29084-76-2; **30**, 51085-51-9; **31**, 137-04-2; thionyl chloride, 7719-09-7; phosgene, 75-44-5.

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(8) The addition of chlorine to benzylideneaniline was reported in the early literature, but the products were not characterized; see T. C. James and C. W. Rudd, *J. Chem. Soc.*, 105 (1914).
(9) Subsequent treatment of the filtrate with hydrogen chloride caused precipitation of the remainder of imines in solution as their hydrochlorides. These were shown to be, again, an approximately equal mixture of benzylideneaniline hydrochloride and benzylidene-*p*-chloroaniline hydrochloride.
(10) Whether intermediate II exists in the form shown or as PhCH(Cl)N(Cl)Ph is irrelevant. The same chlorinated imine hydrochloride should be formed as α-chloroamines readily isomerize to imine hydrochlorides.
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1,3-Oxathiole 3,3-Dioxides and Benzoyl-Substituted Thiirane 1,1-Dioxides

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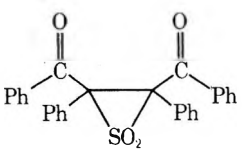
Received January 7, 1974

Bis(phenacyl) sulfone on bromination to bis(α-bromophenacyl) sulfone (**2**) and then treatment with base yielded 2-benzoyl-4-bromo-5-phenyl-1,3-oxathiole 3,3-dioxide (**5**). Reduction of **5** with triphenylphosphine in methanol gave 2-benzoyl-5-phenyl-1,3-oxathiole 3,3-dioxide (**10**), which can be degraded with base to the known 5-phenyl-1,3-oxathiole 3,3-dioxide (**7**). The structural assignments for the compounds previously ascribed to be 2,3-dibenzoyl-2,3-diphenylthiirane (**15**) and the corresponding thiirane 1-oxides and 1,1-dioxide are revised. It is suggested that the compounds are 2-benzoyl-2,4,5-triphenyl-1,3-oxathiole (**14**), and the corresponding 3-oxides **18a** and **18b** and 3,3-dioxide **12**, respectively. The reactions and properties of these compounds will be discussed in terms of the new structural assignments. 2-Benzoyl-5-phenyl-1,3-oxathiole 3,3-dioxide (**10**) can be specifically deuterated in the 2 and 4 positions. There is no deuterium exchange between the two positions at room temperature, or at the melting point (150°). Rearrangement between 1,3-oxathiole 3,3-dioxides and 2,3-dibenzoylthiirane 1,1-dioxides is therefore negligible under these conditions.

Thiirane 1,1-dioxides easily undergo thermal decomposition to yield alkenes and sulfur dioxide. 2,3-Dibenzoyl-2,3-diphenylthiirane 1,1-dioxide (**1**) is, however, reported to be unusually thermostable.[1]

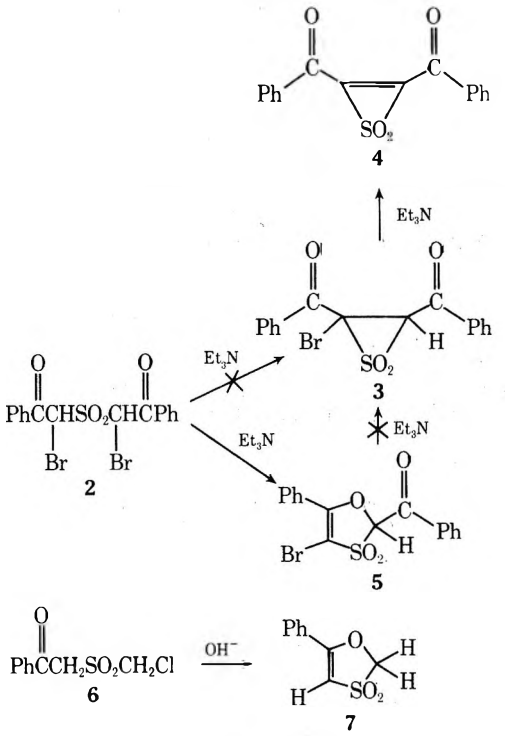


1

It was therefore of interest to investigate the possible synthesis of this and related compounds from the corresponding α-halo sulfones, thus for the first time being able to trap an intermediate thiirane 1,1-dioxide in a Ramberg–Bäcklund rearrangement.[2] However, efforts to prepare 2-bromo-2,3-dibenzoylthiirane 1,1-dioxide (**3**) or the corresponding thiirene 1,1-dioxide **4** from bis(α-bromophenacyl) sulfone (**2**) failed. Instead 2-benzoyl-4-bromo-5-phenyl-1,3-oxathiole 3,3-dioxide (**5**) was formed in a high yield, which is in agreement with a previous synthesis of 5-phenyl-1,3-oxathiole 3,3-dioxide (**7**) from the α-halo keto sulfone **6**.[3]

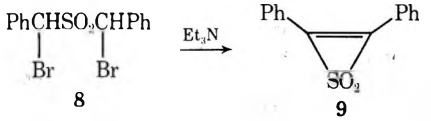
The present paper describes the synthesis and properties of some 1,3-oxathiole 3,3-dioxides. Furthermore, the structure of the compound previously assigned to be 2,3-dibenzoyl-2,3-diphenylthiirane 1,1-dioxide (**1**) will be questioned, and evidence for the 1,3-oxathiole 3,3-dioxide structure **12** will be presented. In view of this new structural assignment the previously reported reactions of this[1] and related compounds[4,5] will be discussed.

Bis(phenacyl) sulfone was prepared from bis(phenacyl) sulfide[6] by oxidation with 3-chloroperbenzoic acid in chloroform. The sulfone was brominated with 2 equiv of bromine in chloroform to yield bis(α-bromophenacyl) sulfone[7] (**2**), which precipitated from the reaction mixture. The compound was almost insoluble in most solvents and was therefore difficult to obtain chromatographically pure (tlc). Treatment of the crude compound with triethylamine in methylene chloride at room temperature gave 2-benzoyl-4-



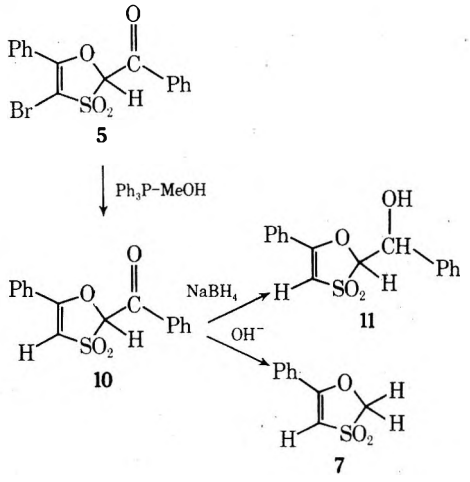
bromo-5-phenyl-1,3-oxathiole 3,3-dioxide (**5**). 2-Benzoyl-5-phenyl-1,3-oxathiole 3,3-dioxide (**10**) was also detected (tlc) in the reaction mixture. It appears to be formed from traces of a monobrominated product in the starting material.

Thiirene 1,1-dioxides are known to be formed from α,α'-dibromo sulfones on treatment with base.[8] Thus bis(α-bromobenzyl) sulfone (**8**) yields the 2,3-diphenylthiirene 1,1-



dioxide (**9**). However, there were no indications of the presence of the thiirene 1,1-dioxide **4** in the reaction mixture from the triethylamine treatment of bis(α-bromophenacyl) sulfone (**2**). The 1,3-oxathiole 3,3-dioxide **5** was stable when treated with excess triethylamine in refluxing benzene for 1 hr and thus does not rearrange to an intermediate bromothiirane 1,1-dioxide **3** which would be expected to give the thiirene 1,1-dioxide **4**.

Treatment of 2-benzoyl-4-bromo-5-phenyl-1,3-oxathiole 3,3-dioxide (**5**) with triphenylphosphine[9] in refluxing methanol for 1 hr gave a product which after recrystallization from ethanol was characterized as 2-benzoyl-5-phenyl-1,3-oxathiole 3,3-dioxide (**10**). Reduction of 2-benzoyl-5-phe-

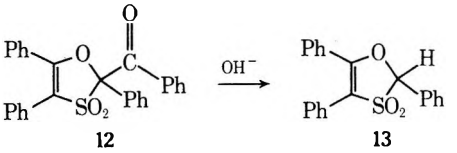


nyl-1,3-oxathiole 3,3-dioxide (**10**) with sodium borohydride in ethanol gave a diastereomeric mixture of 2-(α-hydroxybenzyl)-5-phenyl-1,3-oxathiole 3,3-dioxides (**11**) which were not separated.

It has recently been reported[10] that γ-benzoyl-γ-chloro-γ-methylsulfonylbutyronitrile under alkaline conditions splits off the benzoyl group to give γ-chloro-γ-methylsulfonylbutyronitrile. When 2-benzoyl-5-phenyl-1,3-oxathiole 3,3-dioxide (**10**) is treated with base under similar conditions the known 5-phenyl-1,3-oxathiole 3,3-dioxide (**7**)[3,11] is formed. The structural assignments of compounds **5, 10,** and **7** follow from their mode of preparation and from spectral properties (see Experimental Section), which are all consistent with 1,3-oxathiole 3,3-dioxide structures.

Hoffmann, *et al.*,[12] have presented some theoretical aspects of the bonding in some three-membered rings containing sulfur. They discussed the long C–C bond of thiirane 1,1-dioxides and conclude that π-acceptor substituents will weaken still more this long C–C bond. It is, therefore, not surprising to find that the 1,3-oxathiole 3,3-dioxide **5** is formed instead of the benzoyl-substituted thiirane 1,1-dioxide **3** when the bromo sulfone **2** is treated with base. Furthermore, the structure of the stable compound previously assigned[1] to be 2,3-dibenzoyl-2,3-diphenylthiirane 1,1-dioxide (**1**) must be questioned. According to the predictions, this thiirane 1,1-dioxide **1** should be less stable than the corresponding tetraphenylthiirane 1,1-dioxide. However, the tetraphenylthiirane 1,1-dioxide is reported[13] to undergo a facile thermal rearrangement *via* C–C bond fission.

The compound ascribed the structure **1** was prepared by the method described in the original paper and was found to have spectral properties similar to those of the 1,3-oxathiole 3,3-dioxides **5, 10,** and **7.** Moreover, the compound could be degraded under alkaline conditions in a reaction similar to the formation of **7** from **10.** Consequently, there seems to be no doubt that the compound is 2-benzoyl-2,4,5-triphenyl-1,3-oxathiole 3,3-dioxide (**12**), and that the product formed in the alkaline degradation is 2,4,5-triphenyl-1,3-oxathiole 3,3-dioxide (**13**). A borohydride reduction of **12** also yielded this product, presumably by a re-



duction to the secondary alcohol followed by a cleavage analogous to a retro-aldol condensation.

Main ms fragmentations of the 1,3-oxathiole 3,3-dioxides are shown in Scheme I. The mass spectra of all compounds exhibit peaks corresponding to acetylenic fragments, *e.g.*, bromophenylacetylene (*m/e* 180), phenylacetylene (*m/e* 102), and diphenylacetylene (*m/e* 178). A metastable ion peak at *m/e* 130 occurs in the mass spectra of compounds **12** and **13** due to the breakdown of the ion *m/e* 242 giving the ion *m/e* 178 as indicated in Scheme I. The base peaks in the mass spectra of compounds possessing benzoyl or hydroxybenzyl groups in the 2 position arise from splitting off of these substituents.

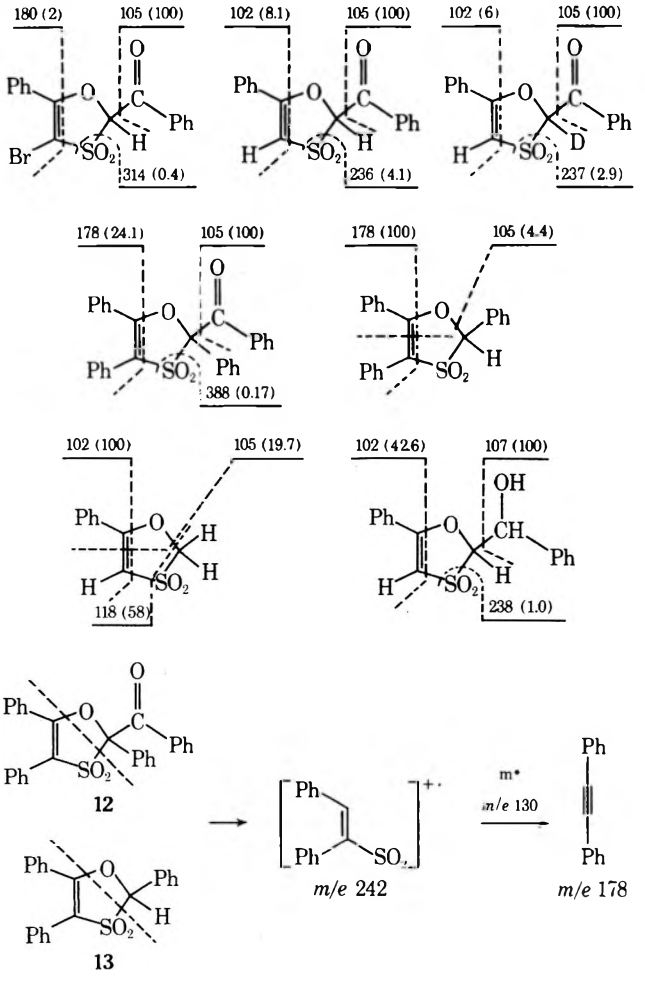
Since it has originally been suggested that the 2-benzoyl-2,4,5-triphenyl-1,3-oxathiole 3,3-dioxide (**12**) was the thiirane 1,1-dioxide **1**, it was of interest to investigate whether the starting material for the synthesis of compound **12** was the 2-benzoyl-2,4,5-triphenyl-1,3-oxathiole (**14**), and not the thiirane **15.** Compound **14** was prepared according to the original method.[1] The ir of this compound exhibits characteristic bands at 1680 and 1625 cm^{-1} due to the car-

Table I
^{13}C Nmr Data of Some 1,3-Oxathiole Derivatives[a]

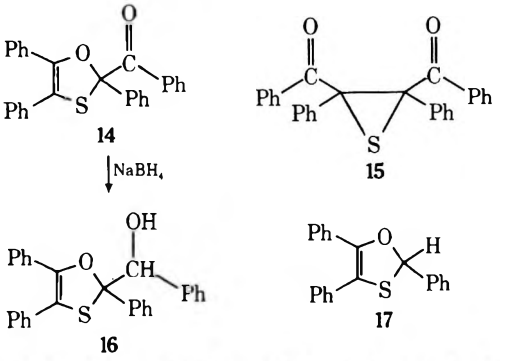
Compd (registry no.)	Ring carbons[b] C—2	C—4	C—5	Substituent carbons: C aromatic				>C=O
5-Phenyl-1,3-oxathiole 3,3-dioxide (**7**) (21120-03-6)	82.3	99.1	164.7	126.6	127.8	128.9	132.4	
2-Benzoyl-5-phenyl-1,3-oxathiole 3,3-dioxide (**10**) (51911-51-4)	90.4	97.6	164.9	126.9 129.2	127.4 132.7	128.6 134.4	129.0 135.0	184.6
2-Benzoyl-2,4,5-triphenyl-1,3-oxathiole 3,3-dioxide (**12**) (51911-52-5)	98.6	114.7	154.9	124.5 128.5 129.6 131.1	125.1 129.0 129.7 131.9	128.2 129.1 130.3 133.3	128.3 129.4 130.4 135.7	191.0
2-Benzoyl-2,4,5-triphenyl-1,3-oxathiole (**14**) (51911-53-6)	100.9	111.1	142.1	126.0 128.4 129.3 131.8	126.9 128.6 129.4 133.0	127.9 128.8 129.8 133.8	128.2 129.1 130.4 138.9	194.1

[a] ^{13}C nmr spectra (22.63 MHz, chemical shifts in parts per million from TMS, internal standard) were recorded on a Brucker pulsed nmr spectrometer B-KR 322S equipped with an external field stabilizer. [b] Numbering of carbon atoms according to the *Chemical Abstracts* nomenclature rules.

Scheme I



bonyl and the carbon–carbon double bond. Compound **14** was reduced with sodium borohydride to yield a mixture of diastereomeric alcohols **16**. The ir of this crude mixture did not exhibit any carbonyl band. The nmr spectrum ($CDCl_3$) of the diastereomeric mixture shows two singlets at δ 5.1 and δ 5.2, together equivalent to one proton, which are due to the methine protons of the two isomeric alcohols. The alcohols were formed in the proportions 1:4. A thiirane structure would have given rise to a more complex mixture possessing two protons of this type.

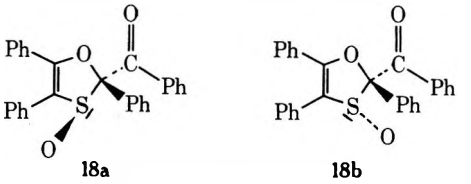


The 2,4,5-triphenyl-1,3-oxathiole (**17**) previously described by Kuhlmann and Dittmer[14] exhibits some very characteristic spectroscopic properties [ir (KBr) 1620 and 1245 cm^{-1}; uv max (EtOH) 342 nm (ϵ 6760)] which are also shown by compound **14** [ir (KBr) 1625 and 1230 cm^{-1}; uv max (EtOH) 330 nm (ϵ 7000)] and the diastereomeric alcohols **16** [ir (KBr) 1625 and 1230 cm^{-1}; uv max (EtOH) 339 nm (ϵ 6330)].

The collected evidence presented above leaves little doubt that the compound previously reported to be the thiirane **15** must be the 2-benzoyl-2,4,5-triphenyl-1,3-oxathiole (**14**).[15]

The structural assignment of compound **14** is also confirmed by its ^{13}C nmr spectrum (Table I). Most significant is the presence of only one signal due to a carbonyl carbon which together with the 20 signals of aromatic carbons (four nonequivalent phenyl groups) rules out the thiirane structure **15**.

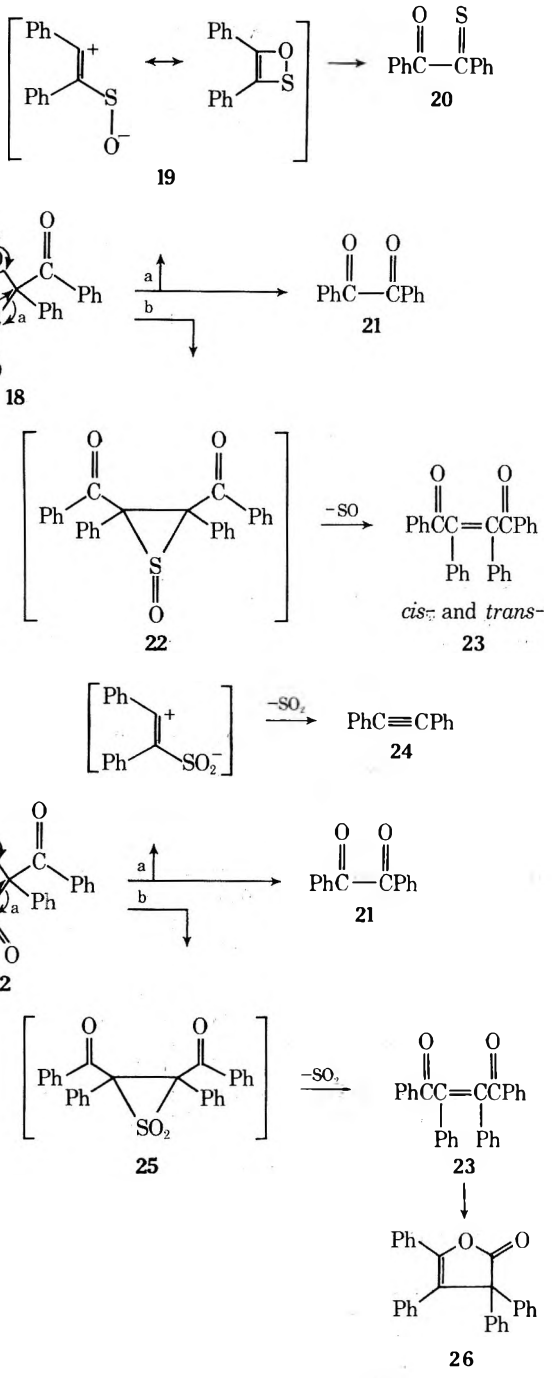
Accordingly, the sulfoxides previously prepared[1a,4] from this oxathiole must be the epimeric mixture of the 2-benzoyl-2,4,5-triphenyl-1,3-oxathiole 3-oxides (**18a** and **18b**). The spectroscopic data reported for this compound are consistent with a 1,3-oxathiole 3-oxide structure.



The 1,3-oxathiole structures of compounds **12** and **18** make it of interest to examine the previously reported[1b,4a] results on the thermal decomposition of these two compounds. Pyrolysis of the 1,3-oxathiole 3-oxides **18a** and **18b**

at 200–210° yields monothiobenzil (**20**), benzil (**21**), and *cis*- and *trans*-dibenzoylstilbene (**23**). Pyrolysis (300°) of the 1,3-oxathiole 3,3-dioxide **12** gives benzil (**21**), diphenylacetylene (**24**), and the lactone **26** of 4-hydroxy-2,2,3,4-tetraphenyl-3-butenoic acid. The lactone **26** could have been formed from an intermediate dibenzoylstilbene (**23**) according to a known[16] reaction. The product patterns of the two pyrolysis reactions can be explained by assuming two reaction paths (Scheme II, a and b). Path a in the pyrolysis of the 1,3-oxathiole 3-oxide **18** gives benzil (**21**) and monothiobenzil (**20**), the latter *via* a rearrangement of a 1,2-oxathiete intermediate **19** (*cf.* the α-dithione–1,2-dithiete equilibrium).[17]

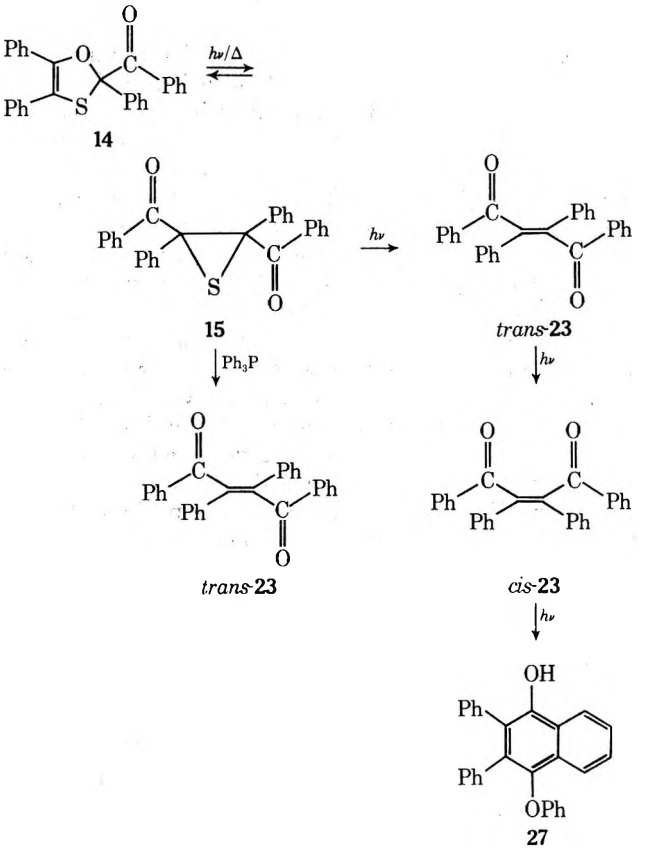
Scheme II



The formation of dibenzoylstilbene (**23**) can be rationalized assuming an intermediate thiirane 1-oxide **22** with elimination of sulfur oxide according to path b.

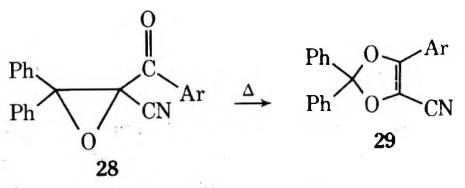
The pyrolysis of the 1,3-oxathiole 3,3-dioxide **12** *via* path a gives benzil (**21**) and diphenylacetylene (**24**) after elimination of sulfur dioxide. Path b gives the lactone **26** and it can be rationalized from an intermediate thiirane 1,1-dioxide **25** which decomposes to dibenzoylstilbene (**23**) and cyclizes at the pyrolysis temperature (300°).

Padwa, *et al.*,[5] have investigated the photochemical transformation of the compound previously ascribed to be the 2,3-dibenzoyl-2,3-diphenylthiirane (**15**). The photolysis afforded the *cis*- and *trans*-dibenzoylstilbenes (**23**) together with minor amounts of 1-hydroxy-2,3-diphenyl-4-phenoxynaphthalene (**27**) and a 2,3-dibenzoyl-2,3-diphenylthiirane (**15**), the configuration of which was assigned to be



cis. Padwa also reported that this thiirane upon heating in refluxing xylene for 30 min was transformed to the thermodynamically more stable starting material of the photolysis reaction. The naphthol **27** was found to be a secondary product derived from the dibenzoylstilbenes.

Padwa's results may well be rationalized using the new structural assignment **14** of the starting material. The photolytic transformation of the 1,3-oxathiole **14** to the dibenzoylstilbene **23** is proposed to proceed *via* the thiirane **15**, which is in equilibrium with the thermodynamically more stable 1,3-oxathiole **14**. The transformation of the thiirane **15** to the 1,3-oxathiole **14** upon heating in xylene is analogous to the known[18] conversion of α-aroyloxiranes **28** to 1,3-dioxoles **29**.



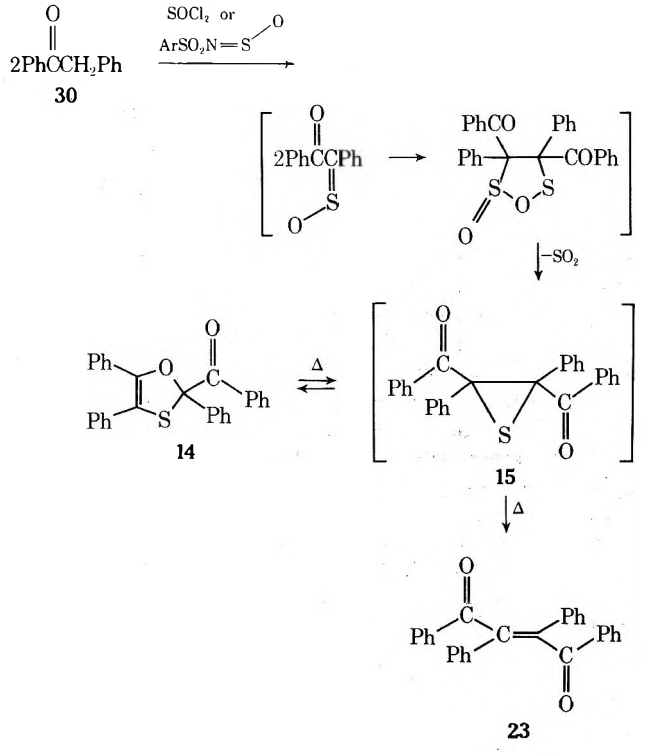
An equilibrium between the 1,3-oxathiole **14** and the thiirane **15** also explains the reactions of the two compounds with triphenylphosphine in refluxing xylene to yield *trans*-dibenzoylstilbene (*trans*-**23**). The desulfurization step is

known to be stereospecific,[19] which suggests that the thiirane **15** possesses a trans configuration.

A comparison of the spectral data reported for the trans thiirane **15** (Padwa's *cis*-dibenzoyldiphenylthiirane)[5] with those of the 1,3-oxathiole **14** gives some further support for the proposed structures of the two compounds. The ir of the 1,3-oxathiole **14** exhibits a strong band at 1625 cm^{-1}, which is assigned to the carbon–carbon double bond of the oxathiole ring. This band is not reported to be present in the thiirane **15**. The 1,3-oxathiole **14** shows strong uv absorption at 330 nm (ϵ 7000) which is assigned to the enethiole ether chromophore of the oxathiole ring. The thiirane **15** exhibits only weak absorption in this region (345 nm, ϵ 900).

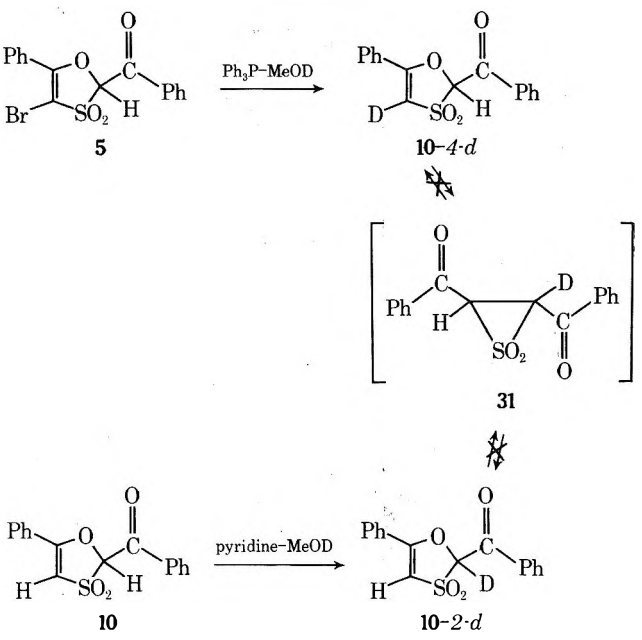
Recently, Ireland and Pizey[20] studied the reaction of deoxybenzoin (**30**) with thionyl chloride (Scheme III). They reported the isolation of a product which upon heating yielded dibenzoylstilbene (**23**). The same product was also prepared by Kresze and Wucherpfennig[21] by treatment of deoxybenzoin (**30**) with *N*-sulfinyl-*p*-toluenesulfonamide. The product was supposed to be 2,3-dibenzoyl-2,3-diphenylthiirane (**15**).[20,21] Its melting point and spectral data were similar to those reported by Dittmer, *et al.*[1] However, the intermediate ought to be2-benzoyl-2,4,5-triphenyl-1,3-oxathiole (**14**). In order to confirm this prediction, we have repeated the experiments by Ireland[20] and Kresze.[21] From the reaction mixtures a compound was isolated which was shown to be identical in all respects with the 1,3-oxathiole **14**. The formation of this product may initially proceed, according to the reaction scheme III proposed by Kresze and Wucherpfennig,[21] to an intermediate thiirane **15** which rearranges to the 1,3-oxathiole **14**.

Scheme III



The possible rearrangement of 1,3-oxathiole 3,3-dioxides to thiirane 1,1-dioxides has been investigated (Scheme IV). When 2-benzoyl-5-phenyl-1,3-oxathiole 3,3-dioxide (**10**) was treated with acetone-d_6 and methanol-*O*-*d* in the presence of triethylamine, deuterium exchange occurred in both 2 and 4 positions. Exchange in the 2 position (followed by nmr) was almost instantaneous at room temperature. The exchange at the 4 position was much slower but was nearly complete after 1 hr at 40° ($t_{1/2}$ 10.5 min). If the deuterium exchange was carried out in a mixture of chloroform-d_1 and methanol-*O*-*d* in the presence of pyridine there was an exchange in the 2 position (**10**-*2*-*d*) but no exchange was observed in the 4 position after 6 hr at 25°. A specific deuteration of the 4 position (**10**-*4*-*d*) was obtained by reduction of the bromo compound **5** with triphenylphosphine in methanol-*O*-*d*. There was no deuterium scrambling in the specifically deuterated compounds **10**-*4*-*d* and **10**-*2*-*d* under the conditions of preparation. Nor was there any scrambling when compound **10**-*2*-*d* was heated above its melting points (150°) for 25 min. Thus, there was no observable equilibrium between the 1,3-oxathiole 3,3-dioxide (**10**-*2*-*d*) and the thiirane 1,1-dioxide **31**

Scheme IV



Experimental Section

All melting points are uncorrected. Uv spectra were recorded in ethanol (95%) on a Beckman DK-2 spectrophotometer and ir spectra on a Perkin-Elmer Model 421 infrared spectrophotometer. Nmr spectra (60 MHz, TMS internal standard) were run on a Varian Model A-60A instrument. Mass spectra were obtained (direct inlet) using an LKB Model 9000 mass spectrometer.

Thin layer chromatograms were run on fluorescent silica gel (Merck HF-254) with light petroleum, bp 40–60°, unless otherwise stated.

Bis(phenacyl) Sulfone.—A solution of bis(phenacyl) sulfide[6] (18.9 g, 0.07 mol) in chloroform (250 ml) was cooled to 5° and solid 3-chloroperbenzoic acid (80%, 30 g, 0.14 mol) was added in small portions. The temperature was not allowed to rise above 20°. After the addition, the solution was stirred at room temperature for 24 hr. The white precipitate of 3-chlorobenzoic acid was filtered off. The filtrate was washed with saturated sodium bicarbonate solution and dried and the solvent was evaporated *in vacuo*. The residue was recrystallized from ethanol to yield bis(phenacyl) sulfone as white crystals: mp 124–126° (lit.[22] mp 124°); yield 17 g (80%); ir (KBr) 1680 (C=O), 1330, 1140 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 4.95 (s, 4, CH_2), 7.5–7.9 (m, 10, aromatic).

Anal. Calcd for $C_{16}H_{14}O_4S$: C, 63.56; H, 4.67; S, 10.61. Found: C, 63.49; H, 4.56; S 10.60.

Bis(α-bromophenacyl) Sulfone (2). A solution of bis(phenacyl) sulfone (6 g, 0.02 mol) in chloroform (100 ml) was treated with bromine (6.4 g, 0.04 mol) in chloroform (50 ml) at room temperature. After stirring for about 2 hr all the bromine had been consumed and the product had precipitated. The solvent was evaporated *in vacuo* and the residue was washed with cold methanol. To obtain an analytically pure sample of bis(α-bromophenacyl) sulfone (**2**), the product was recrystallized from ethanol: mp 185–186°

(lit.[7] mp 186°); yield 9 g (89%); ir (KBr) 1670 (C=O), 1300, 1150 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 7.6–8.1 (m, aromatic and CH).

Anal. Calcd for $C_{16}H_{12}Br_2O_4S$: C, 41.76; H, 2.63; Br, 34.73; S, 6.97. Found: C, 42.22; H, 2.59; Br, 34.39; S, 6.94.

2-Benzoyl-4-bromo-5-phenyl-1,3-oxathiole 3,3-Dioxide (5). To a mixture of crude bis(α-bromophenacyl) sulfone (**2**, 4.6 g, 0.01 mol) in methylene chloride (75 ml) was added triethylamine (1.5 g, 0.015 mol). The clear solution was stirred at room temperature for 1 hr. The solution was then extracted with dilute hydrochloric acid to remove excess triethylamine, washed with water, and dried.

The crude mixture (3.8 g) which remained after evaporation *in vacuo* was chromatographed on silica gel. Benzene eluted a product which after recrystallization from ethanol yielded the 1,3-oxathiole 3,3-dioxide **5**: mp 160–161°; yield 2.4 g (63%); R_f (benzene) 0.25; uv max 254 nm (ε 21,900), 260 (21,900); ir (KBr) 1690 (C=O), 1610 (C=C), 1320, 1150 (SO_2), 1250 cm^{-1} (C=C–O); nmr ($CDCl_3$) δ 6.50 (s, 1, CH), 7.50–7.95 (m, 10, aromatic); nmr (acetone-d_6) δ 7.20 (s, 1, CH), 7.6–8.05 (m, 10, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 380 (1.54), 378 (1.50), 316 (0.42), 314 (0.42), 182 (2.04), 180 (2.08), 106 (7.92), 105 (100), 102 (4.13), 101 (4.04), 89 (2.13), 78 (1.96), 77 (26.3).

Anal. Calcd for $C_{16}H_{11}BrO_4S$: C, 50.67; H, 2.92; Br, 21.07; S, 8.46. Found: C, 50.45; H, 2.85; Br, 21.51; S, 8.22.

2-Benzoyl-5-phenyl-1,3-oxathiole 3,3-Dioxide (10). To the crude 2-benzoyl-4-bromo-5-phenyl-1,3-oxathiole 3,3-dioxide (**5**, 3.8 g) in methanol (50 ml) was added triphenylphosphine (3.2 g, 0.012 mol). The mixture was refluxed during 1 hr. Evaporation of the solvent *in vacuo* gave a solid residue. Recrystallization from ethanol yielded 2-benzoyl-5-phenyl-1,3-oxathiole 3,3-dioxide (**10**): mp 139–140°; yield 1.5 g (50%); R_f (benzene) 0.14; uv max 255 nm (ε 24,000), 259 (24,000); ir (KBr) 1700 (C=O), 1610 (C=C), 1310, 1140 (SO_2), 1250 cm^{-1} (C=C–O); nmr ($CDCl_3$) δ 6.45 (s, 2, CH and =CH), 7.5–8.0 (m, 10, aromatic); nmr (acetone-d_6) δ 7.00 (s, 1, CH), 7.17 (s, 1, =CH), 7.5–8.0 (m, 10, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 301 (0.09), 300 (0.43), 237 (0.74), 236 (4.14), 208 (0.07), 207 (0.09), 179 (0.07), 178 (0.16), 135 (0.07), 134 (0.17), 133 (0.10), 131 (0.09), 118 (0.22), 107 (0.48), 106 (7.93), 105 (100), 103 (1.55), 102 (8.10), 101 (0.22), 91 (0.40), 90 (0.76), 89 (1.34), 78 (2.14), 77 (29.3).

Anal. Calcd for $C_{16}H_{12}O_4S$: C, 63.99; H, 4.03; S, 10.68. Found: C, 64.03; H, 3.96; S, 10.67.

5-Phenyl-1,3-oxathiole 3,3-Dioxide (7). A solution of 2-benzoyl-5-phenyl-1,3-oxathiole 3,3-dioxide (**10**, 1.5 g, 0.005 mol) in methanol (40 ml) was mixed with anhydrous potassium carbonate (0.3 g) in water (10 ml). The solution was refluxed during 4.5 hr and then diluted with water (200 ml) and extracted with chloroform. The chloroform phase was washed with water, dried, and evaporated *in vacuo*. Recrystallization of the residue (1.45 g) from methanol yielded 5-phenyl-1,3-oxathiole 3,3-dioxide (**7**): mp 168–170° (lit.[3] mp 165–168°); yield 0.4 g (27%); R_f (benzene), 0.08; uv max 264 nm (ε 14,300); ir (KBr) 1610 (C=C), 1300, 1285, 1130 (SO_2), 1270 cm^{-1} (C=C–O); nmr ($CDCl_3$) δ 5.05 (s, 2, CH_2), 6.52 (s, 1, =CH), 7.5 (m, 5, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 198 (3.06), 197 (6.39), 196 (58.3), 167 (0.83), 149 (0.56), 148 (1.94), 138 (5.00), 137 (3.33), 121 (3.33), 119 (5.56), 118 (58.3), 110 (3.33), 105 (19.7), 103 (10.0), 102 (100), 94 (8.61), 91 (2.22), 90 (8.06), 89 (4.17), 78 (1.39), 77 (16.4). Spectral data were identical with those reported by Nozaki, *et al.*[11]

Anal. Calcd for $C_9H_8O_3S$: C, 55.09; H, 4.11; S, 16.34. Found: C, 55.20; H, 4.17; S, 16.20.

Diastereomeric 2-(α-Hydroxybenzyl)-5-phenyl-1,3-oxathiole 3,3-Dioxides (11). To a solution of 2-benzoyl-5-phenyl-1,3-oxathiole 3,3-dioxide (**10**, 702 mg, 2.3 mmol) in absolute ethanol (75 ml) was added a solution of sodium borohydride (87.4 mg, 2.3 mmol) in absolute ethanol (25 ml). The reaction mixture was stirred for 1 hr, poured into water (300 ml), acidified with aqueous hydrochloric acid (1 *M*), and extracted with chloroform. The chloroform solution was washed with water, dried, and evaporated *in vacuo*. The oily residue was dissolved in a limited amount of ethyl ether. On addition of light petroleum (bp 40–60°) the diastereomeric alcohols **11** precipitated as white crystals: mp 134–136°; yield 240 mg (35%); uv max 267 nm (ε 10,600); ir (KBr) 3440 (OH), 1615 (C=C), 1290 (broad), 1140 cm^{-1} (SO_2); nmr (acetone-d_6) overlapping signals at δ 5.12 and 5.17 (integrated area 1.3 H) assigned to the two vicinal CH in one of the epimers and at δ 5.32 and 5.37 (0.7 H) assigned to the corresponding CH groups of the other epimer, 7.05 (s, 1, =CH), 7.4 (m, 10, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 304 (0.80), 303 (2.13), 302 (11.9), 278 (0.53), 238 (0.96), 220 (0.96), 198 (2.66), 197 (5.21), 196 (47.9), 150 (1.06), 136 (0.74), 135 (0.64), 134 (0.53), 120 (1.81), 119 (0.74), 118 (1.06), 115 (0.74), 108 (7.77), 107 (100), 106 (2.13), 105 (17.0), 104 (3.72), 103 (40.4), 102 (42.6), 101 (0.96), 92 (0.85), 91 (8.62), 90 (2.23), 89 (3.30), 86 (2.87), 80 (2.45), 79 (37.2), 78 (4.79), 77 (34.0).

Anal. Calcd for $C_{16}H_{14}O_4S$: C, 63.56; H, 4.67; S, 10.61. Found: C, 63.48; H, 4.67; S, 10.49.

2-Benzoyl-2,4,5-triphenyl-1,3-oxathiole (14). This compound, originally suggested[1] to be 2,3-dibenzoyl-2,3-diphenylthiirane (**15**), was prepared according to the previous method by Dittmer, *et al.*[1] The compound was chromatographed on silica. Benzene eluted the product, which after recrystallization from methanol exhibited similar properties to those reported by Dittmer, *et al.*:[1] mp 104–106° (lit.[1] mp 106–122°); R_f (benzene) 0.63; uv max 229 nm (ε 25,000), 250 shoulder (21,500), 330 (7000); ir (KBr) 1680 (C=O), 1625 (C=C), 1230 cm^{-1} (C=C–O); mass spectrum (70 eV) *m/e* (rel intensity) 421 (0.15), 420 (0.45), 389 (0.13), 388 (0.38), 373 (0.05), 372 (0.18), 318 (1.28), 317 (7.00), 316 (21.5), 315 (100), 299 (0.15), 255 (0.33), 210 (0.33), 179 (0.15), 178 (0.80), 106 (1.03), 105 (12.5), 78 (0.10), 77 (0.08).

2-(α-Hydroxybenzyl)-2,4,5-triphenyl-1,3-oxathiole (16). A solution of 2-benzoyl-2,4,5-triphenyl-1,3-oxathiole (**14**, 420 mg, 0.001 mol) in absolute ethanol (40 ml) was mixed with sodium borohydride (76 mg, 0.002 mol) in absolute ethanol (15 ml) and the solution was stirred for 15 min. The reaction mixture was then poured into water (200 ml) and extracted with ethyl ether. The organic phase was washed with water, dried, and evaporated *in vacuo* to a semicrystalline residue: yield 400 mg (95%); R_f (benzene) 0.26; uv max 339 nm (ε 6330); ir (KBr) 3440 (broad, OH), 1625 (C=C), 1230 cm^{-1} (C=C–O); nmr ($CDCl_3$) δ 5.1 and 5.2 (two signals with integrated areas corresponding to 0.2 and 0.8 H, respectively, assigned to the methine proton, CH), 7.1 (m, 15, aromatic); mass spectrum (20 eV) *m/e* (rel intensity) 404 (0.23), 373 (0.39), 372 (1.02), 318 (1.56), 317 (8.36), 316 (26.2), 315 (100), 300 (0.86), 255 (0.55), 228 (0.39), 227 (0.70), 226 (1.02), 212 (0.39), 211 (0.94), 210 (1.02), 196 (1.88), 179 (0.78), 178 (3.40), 167 (0.78), 122 (0.86), 121 (3.83), 107 (0.78), 106 (6.33), 105 (53.1), 91 (0.31), 78 (0.78), 77 (1.56).

2-Benzoyl-2,4,5-triphenyl-1,3-oxathiole 3,3-Dioxide (12). The crude compound (**14**, 11.6 g) was dissolved in hot acetic acid (100 ml) and hydrogen peroxide (30%, 15 ml) was added. The reaction mixture was heated at 90–95° for 3 hr and then allowed to stand at room temperature overnight. White crystals (5 g) precipitated. The crystalline material was dissolved in chloroform and the solution was washed with water and dried. Evaporation of the solvent *in vacuo* gave a product which after recrystallization from benzene–light petroleum yielded crystals of **12**: mp 92–96° (lit.[1] mp 90–93°); R_f (ethyl ether–light petroleum, 40:60) 0.23; uv max 233 nm shoulder (ε 25,300), 253 (21,200), 285 shoulder (11,000); [lit.[1] uv 233 nm shoulder (ε 21,500), 254 max (19,500)]; ir (CS_2) *cf.* lit.[1] 1690 (C=O), 1650 (C=C), 1330, 1155 (SO_2), 1265 cm^{-1} (C=C–O); mass spectrum (70 eV) *m/e* (rel intensity) *cf.* also lit.[1] 454 (0.11), 453 (0.31), 452 (1.01), 389 (0.05), 388 (0.17), 372 (0.07), 347 (0.23), 283 (0.10), 255 (0.06), 254 (0.04), 253 (0.08), 252 (0.12), 242 (0.14), 226 (0.23), 210 (0.10), 180 (0.28), 179 (2.77), 178 (24.1), 177 (1.34), 176 (2.17), 175 (0.31), 166 (0.23), 165 (1.13), 164 (0.20), 163 (0.29), 153 (0.25), 152 (1.69), 151 (1.19), 150 (0.42), 140 (0.07), 139 (0.60), 138 (0.13), 128 (0.20), 127 (0.18), 126 (0.69), 121 (0.41), 115 (0.29), 107 (0.48), 106 (7.23), 105 (100), 102 (0.30), 89 (0.40), 77 (18.1).

2,4,5-Triphenyl-1,3-oxathiole 3,3-Dioxide (13). A solution of 2-benzoyl-2,4,5-triphenyl-1,3-oxathiole 3,3-dioxide (**12**, 0.55 g, 1.2 mmol) in methanol (40 ml) and dimethoxyethane (10 ml) was mixed with anhydrous potassium carbonate (0.2 g) in water (3 ml). The solution was refluxed during 40 min. The mixture was cooled and concentrated *in vacuo*. Ethyl ether was added and the organic phase was washed with water and dried. The residue (0.4 g) after evaporation of the solvents was recrystallized from ethanol to yield 2,4,5-triphenyl-1,3-oxathiole 3,3-dioxide (**13**): mp 167–168°; yield 0.35 g (84%); R_f (ethyl ether–light petroleum, 40:60) 0.29; uv max 279 nm (ε 11,900); ir (KBr) 1640 (C=C), 1310, 1140 (SO_2), 1240 cm^{-} (C=C–O); nmr ($CDCl_3$) δ 6.05 (s, 1, CH), 7.40 (m, 15, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 350 (0.15), 349 (0.37), 348 (1.56), 300 (0.41), 244 (0.37), 243 (0.96), 242 (5.56), 180 (1.07), 179 (13.7), 178 (100), 177 (3.26), 176 (5.56), 165 (1.00), 163 (0.52), 153 (0.52), 152 (3.96), 151 (2.81), 150 (1.07), 139 (1.19), 126 (1.52), 121 (1.04), 105 (4.44), 102 (0.70), 77 (4.44).

Anal. Calcd for $C_{21}H_{16}O_3S$: C, 72.39; H, 4.63; S, 9.20. Found: C, 72.28; H, 4.56; S, 9.22.

Treatment of 2-benzoyl-2,4,5-triphenyl-1,3-oxathiole 3,3-dioxide (**12**) in ethanol with sodium borohydride at room temperature for 2 hr also yielded 2,4,5-triphenyl-1,3-oxathiole 3,3-dioxide (**13**).

2-Benzoyl-2-deuterio-5-phenyl-1,3-oxathiole 3,3-Dioxide (10-2-*d*). A mixture of 2-benzoyl-5-phenyl-1,3-oxathiole 3,3-dioxide (**10**, 0.5 g) in chloroform-d_1 (3 ml), methanol-*O*-*d* (1 ml) and pyridine (0.1 g) was stirred at room temperature for 20 min. On addition of light petroleum the deuterated product **10**-2-*d* crystallized: mp 139–140°; yield 0.4 g; R_f (benzene) 0.14; nmr (acetone-d_6) δ 7.17 (s, 1, =CH), 7.5–8.0 (m, 10, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 301 (0.40), 300 (0.10), 238 (0.50), 237 (2.90), 236 (0.90), 107 (0.45), 106 (7.00), 105 (100), 104 (0.65), 103 (1.25), 102 (6.00), 92 (0.25), 91 (0.30), 90 (0.70), 89 (0.75), 78 (2.20), 77 (23.5).

2-Benzoyl-4-deuterio-5-phenyl-1,3-oxathiole 3,3-Dioxide (10-4-*d*). 2-Benzoyl-4-bromo-5-phenyl-1,3-oxathiole 3,3-dioxide (**5**, 70.9 mg) was added to a solution of acetone-d_6 (0.4 ml) and methanol-*O*-*d* (0.1 ml). The nmr of the mixture showed peaks at δ 7.20 (s, 1, CH), and 7.6–8.05 (m, 10, aromatic). Triphenylphosphine (70 mg) was added and the reduction reaction was followed by nmr at about 40°. The peak at δ 7.2 (CH in **5**) disappeared almost instantly and a peak developed at δ 7.0 (CH in **11**-4-*d*) reaching a maximum in about 20 min. No deuterium scrambling, *e.g.*, the formation of compound **11**-2-*d* (δ 7.17, =CH), was detected under the conditions used.

Acknowledgment. Financial support from The Swedish Natural Science Research Council is gratefully acknowledged. We thank Professor Roald Hoffmann for communicating results concerning the bonding in three-membered rings containing sulfur prior to their publication.

Registry No.—**2**, 51911-54-7; **5**, 51911-55-8; **10**-2-*d*, 51911-56-9; **11**, 51911-57-0; **13**, 51911-58-1; **16**, 51911-59-2; bis(phenacyl) sulfone, 3708-08-5; bis(phenacyl) sulfide, 2461-80-5.

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Sulfonylation of Alkylidene- and Arylidenephosphoranes. An Unexpected Rearrangement

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Received January 15, 1974

Sulfonyl-stabilized alkylidene- and arylidenetriphenylphosphoranes have been synthesized from alkyl- and aralkylsulfonyl fluorides and phosphoranes. A number of these reactions have been interpreted by [2 + 2] cycloadditions of sulfenes and phosphoranes to form four-membered ring intermediates, which will ring open in one or two possible directions, depending on the size of the substituents. This frequently leads to phosphonium ylides of rearranged structure. Relatively large substituents at the ylide carbon are sterically unfavorable.

In a previous paper[1] we have reported a useful method for the synthesis of sulfonyl-stabilized methylenetriphenylphosphoranes. These ylides (**3**, R^2 = H) were obtained in yields of 60–80% according to eq 1 for R^1 = aryl or alkyl.

$$\underset{\mathbf{1}}{R^1SO_2F} + 2\underset{\mathbf{2}}{R^2CH{=}PPh_3} \xrightarrow[20^\circ]{THF} \underset{\mathbf{3}}{R^1SO_2CR^2{=}PPh_3} + R^2CH_2\overset{+}{P}Ph_3\overset{-}{F} \quad (1)$$

For other studies we needed derivatives of the sulfonylmethylenephosphoranes **3** with R^2 = alkyl or aryl, insted of H. However, the results of reaction 1 were unsatisfactory when the less reactive benzylidenetriphenylphosphorane (**2**, R^2 = phenyl) was used. Even under more severe reaction conditions compounds **3** (R^1 = aryl; R^2 = phenyl) were obtained only in 12–15% yields.[1]

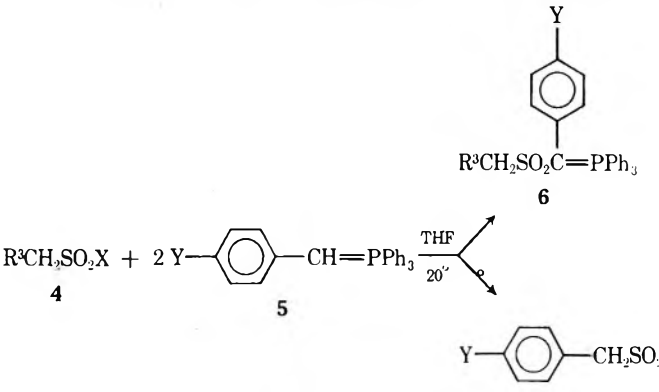
In an attempt to improve these results, we investigated the utility of more reactive sulfonylating agents (*i.e.*, sulfonic anhydrides and alkanesulfonyl fluorides) in the reaction with arylidenetriphenylphosphoranes. During these investigations an unexpected and intriguing rearrangement was discovered, the scope of which is evaluated in the present paper.

Two separate examples of compounds of type **3** with R^2 = phenyl[2a] and benzyl[2b] have been reported previously by other groups.

α-Sulfonylarylidenetriphenylphosphoranes.

The sulfonylation of benzylidenetriphenylphosphorane (**2**, R^2 = phenyl, prepared in the usual way from benzyltriphenylphosphonium bromide and butyllithium) was not improved by using, in reaction 1, *p*-toluenesulfonic anhy-

Table I
Reactions of Arylidenephosphorane and Alkanesulfonyl Fluoride (Anhydride)

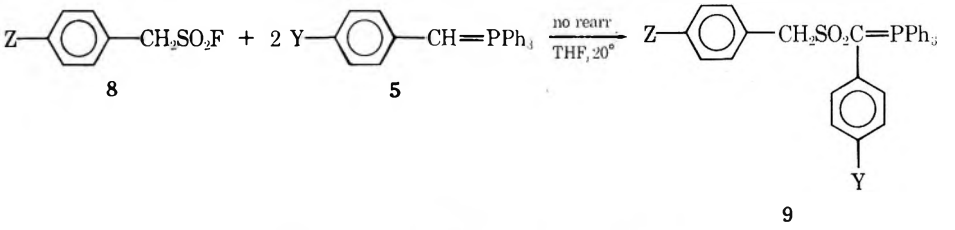


(2)[a]

Expt	R^3	X	Y	Product	Registry no.	Yield, %	Reaction time, hr
1	H	F	H	**7a**[b]	36196-00-6	95	0.5
2	H	OSO_2Me	H	**7a**[b]		54	0.5
3	H	OSO_2Me	MeO	**7b**	51848-88-5	61	0.5
4	Me	F	H	**7c**	51848-89-6	94	0.5
5	*t*-Bu	F	H	**6d**	51848-90-9	77	2

[a] Reference 3. [b] Compound reported previously; see ref 1.

Table II
Reactions of Arylidenephosphorane and Aralkanesulfonyl Fluoride



(3)

Expt	Y	Z	Product	Registry no.	Yield, %	Reaction time, hr	Mass spectra[a,b] $M\cdot^+$	F_1	F_2	F_3	Metastables
6	H	H	**9a**	51848-91-0	91	0.5	506	415	367	351	340.4 (506 → 415), 324.6 (415 → 367), 296.9 (415 → 351)
7	MeO	H	**9b**	51848-93-2	88	1	536	445	397	381	369.4 (536 → 445), 294.0 (536 → 397), 326.2 (445 → 381)
8	H	NO_2	**9c**	51848-92-1	48	1.5	551	415	367	351	312.6 (551 → 415), 324.6 (415 → 367), 296.9 (415 → 351)
9	NO_2	H	**9d**	51848-94-3	82	3	551	460	412	396	384.0 (551 → 460), 308.1 (551 → 412), 369.0 (460 → 412), 340.9 (460 → 396)

[a] Further details of these spectra are given in the Experimental Section. [b] $F_1 = M\cdot^+ - p\text{-}ZC_6H_4CH_2$, $F_2 = M\cdot^+ - p\text{-}ZC_6H_4CH_2SO$, $F_3 = M\cdot^+ - p\text{-}ZC_6H_4CH_2SO_2$.

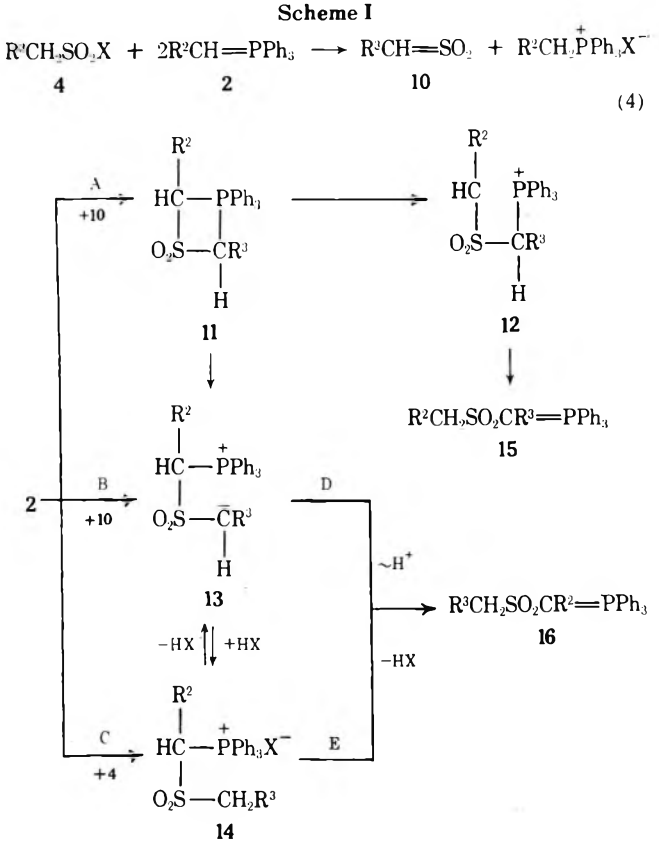
dride instead of tosyl fluoride. The yield of **3a** (R^1 = *p*-tolyl; R^2 = phenyl) was the same in both cases (12%). Much better results, however, were obtained when benzylidenetriphenylphosphorane (**5a**, Y = H, eq 2) was sulfonylated with *methane*sulfonyl fluoride (**4**, R^3 = H; X = F). Surprisingly, the product of this smoothly occurring reaction was not the expected compound **6** (R^3 = Y = H). Instead, the isomeric ylide **7a**, in which an apparent migration of the phenyl group has occurred, was formed in 95% yield. The same product (**7a**) was obtained with methanesulfonic anhydride (**4**, R^3 = H; X = OSO_2Me).

The structure of compound **7a** is supported by its pmr spectrum (see Table V), which shows an one-proton doublet at δ 2.60 with a J_{P-H} of 13 Hz. Further, the same compound was prepared[1] previously according to eq 1, with $R^1 = C_6H_5CH_2$; R^2 = H.

An analogous rearrangement was observed in the reaction of benzylidenephosphorane and ethanesulfonyl fluoride, providing ylide **7c** (eq 21), which means that phenyl can be interchanged with a methyl group also. Rearrangement fails to occur, however, when R^3 becomes the bulky *tert*-butyl group. Here, the only observed product is the unrearranged ylide **6d** (77% yield). These results, summarized in Table I (expt 1–5), demonstrate that steric effects strongly influence the course of the reaction.

The rearranged structure of **7c** (which is identical with ylide **16j**, Table III) follows from the presence of a three-proton doublet for R^3 = Me at δ 1.60 with J_{P-H} = 13 Hz. Compound **7c** shares this feature with a number of similar ylides (**15d, 16e, 16g,** and **17**, Table V), and in particular with α-tosylethylidenetriphenylphosphorane (**3b**), which has been prepared by a reaction occurring without rearrangement (*vide infra*). Futhermore, **7c** shows a benzylic methylene singlet at δ 4.00 (comparable to that of **7a** at δ 3.89), which differs clearly from the neopentyl methylene singlet at δ 2.70 of (unrearranged) **6d**. Also, the singlets of

Scheme I



[a] [2 + 2] cycloaddition.

6d at δ 0.91 (9 H) and 2.70 (2 H) are compatible with the neopentylsulfonyl group by comparison with compounds **15c**, **15d**, and **16h** (Table V).

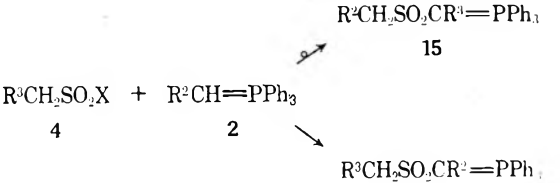
In a subsequent series of reactions the influence of steric effects was elaborated. With substituents of approximately the same size in both reaction partners (*i.e.*, differently para-substituted aryl groups) rearrangement was not observed at all (eq 3, expt 6–9 in Table II).

Although the benzylic protons of **9c** (δ 4.06, Z = NO_2) are found at somewhat lower field than those of **9a,b,d** (δ 3.88–3.98, Z = H; see Table V), the small difference hardly provides a basis for structural assignment. More convincing evidence, however, comes from the mass spectral data given in Table II. All compounds **9** evidently lose the uncharged fragments *p*-$ZC_6H_4CH_2$, *p*-$ZC_6H_4CH_2SO$, and *p*-$ZC_6H_4CH_2SO_2$ from the parent ion ($M\cdot^+$) to give the peaks F_1, F_2, and F_3, respectively. Several of these fragmentations are supported by metastables.

Discussion. The formation of rearranged product (expt 1–4, products **7a–c**, Table I) can be explained by invoking a four-membered ring intermediate **11** (Scheme I). At least three different routes (A, B, and C) to **11** are conceivable, and these will be commented on below. Ring opening of intermediate **11** could lead to **12** and/or **13**. When R^2 = aryl and R^3 = H or CH, relief of steric strain will lead to preferential formation of **12**. Moreover, a phenyl group at R^2 will stabilize the negative charge in **12**, as compared to **13**. Even with a donating methoxy substituent attached to phenyl (*i.e.*, **11**, R^2 = *p*-$CH_3OC_6H_4$; R^3 = H) only rearranged product **15** (*i.e.*, **7b** in eq 2) was obtained.

However, a bulky *tert*-butyl group at R^3 will outweigh any electronic factors. Assuming that a four-membered ring intermediate is reached at all, maximum relief of steric strain is obtained now by going from **11** to **13**. Thus, ylide **16** (*i.e.*, **6d** in eq 2) is formed without rearrangement (expt 5), a product which alternatively can be explained through reactions B–D or C–E (Scheme I).

Table III
Reactions of Alkylidenephosphorane and (Ar)alkanesulfonyl Fluoride (Anhydride)

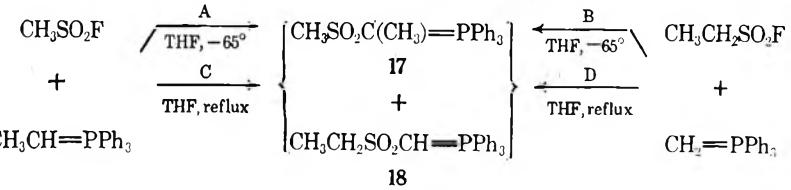


(5)

Expt	R^3	X	R^2	Product	Registry no.	Yield, %	Reaction conditions: Time, hr	Reaction conditions: Temp, °C
10	H	F	H	**16a**[a,b]	5554-83-6	70	1	Room
11	H	OSO_2Me	H	**16a**[a,b]		73	1	Room
12	H	OSO_2Me	1-Adamantyl	**15b**	51848-95-4	51	0.5	Room
13	H	OSO_2Me	*t*-Bu	**15c**	51848-96-5	58	0.5	Room
14	H	F	*t*-Bu	**15c**		69	0.5	Room
15	H	F	*t*-Bu	**15c**[c]		65	1	−90
16	Me	F	*t*-Bu	**15d**	51848-97-6	65	1	Room
17	Me	F	*t*-Bu	**15d**[d]		76	4	−90
18	*t*-Bu	F	Me	**16e**[e]		50	1	Room
19	*i*-Pr	F	H	**16f**	51848-98-7	63	1	−95
20	Me	F	Me	**16g**[a]	51848-99-8	75	0.5	Room
21	*t*-Bu	F	*t*-Bu	**16h**[a]	51849-00-4	3	0.5	Room
22	Ph	F	H	**16i**[b,f]		63	1	Room
23	Ph	F	Me	**16j**[g,h]		30	1	Room
24	Ph	F	*t*-Bu	*i*			1	Room

[a] In those cases where R^2 = R^3, no distinction can be made between rearranged and unrearranged products. [b] Compound reported previously, ref 1. [c] In addition to the rearranged product **15c**, the unrearranged ylide $CH_3SO_2C(t\text{-Bu})=PPh_3$ (**16c**) was obtained in low yield (1.3%). [d] In addition to the rearranged product **15d**, the unrearranged ylide $C_2H_5SO_2C(t\text{-Bu})=PPh_3$ (**16d**) was obtained in 7% yield. [e] Compound **16e** is identical with **15d**. [f] Identical with compound **7a** (Table I). [g] In addition to the compound listed (**16j**), a bis-sulfonylated ylide, still containing an unrearranged ethylidenephosphorane moiety, $PhCH_2SO_2CH(Ph)SO_2C(CH_3)=PPh_3$ (**23**), was obtained in 33% yield (see Experimental Section). [h] Identical with compound **7c** (Table I). [i] In contrast to expt 23, here we isolated only bis-sulfonylated ylide, with a rearranged neopentylidenephosphorane moiety, $t\text{-}BuCH_2SO_2CH(Ph)SO_2C(Ph)=PPh_3$ (**24**) in 31% yield (see Experimental Section).

Table IV
Reaction of Methanesulfonyl Fluoride with Ethylidenephosphorane and Ethanesulfonyl Fluoride with Methylenephosphorane



(6)

Expt	Path	Product	Yield, %	Product	Yield, %	Reaction conditions: Time, min	Reaction conditions: Temp, °C
25	C	**17**	30[a]	**18**	50[a]	15	Reflux
26	A	**17**	62			15	−65
27	D	**17**	32[a]	**18**	64[a]	15	Reflux
28	B	**17**	83			15	−65

[a] Yields of **17** (registry no., 51849-01-5) and **18** (51849-02-6) were determined by pmr analysis of the mixture of isomers.

When R^2 and R^3 are both aryl groups, rearrangement was not observed (expt 6–9, Table II). Since steric factors must be of minor importance here, electronic factors could in principle determine the sense of ring opening in intermediate **11**. Thus, especially when R^2 = *p*-nitrophenyl and R^3 = phenyl (expt 9) at least partial rearrangement *via* **12** to **15** could have occurred; however, such a reaction was not observed. We therefore tend to conclude that for R^2 and R^3 = aryl intermediate **11** is not formed, but that reaction rather occurs through the reaction sequences B–D or C–E (Scheme I). This view is supported by the failure to isomerize ylide **9d** to **9c** by refluxing **9d** with, or without, butyllithium for 15 hr in tetrahydrofuran. Compound **9d** was recovered unchanged.

α-Sulfonylalkylidenetriphenylphosphoranes

Extension of the previously reported[1] reaction of tosyl fluoride and methylenetriphenylphosphorane (**2**, R^2 = H, eq 1) was possible to the homologous ethylidenetriphenylphosphorane, providing **3b** (R^1 = *p*-tolyl; R^2 = CH_3) in 50% yield. When, however, the size of the substituent R^2 in ylide **2** was increased to *tert*-butyl or 1-adamantyl, sulfonylation with either tosyl fluoride or *p*-toluenesulfonic anhydride was no longer possible.

The same bulky substituents in **2** did not prevent, on the other hand, sulfonylation by *aliphatic* sulfonyl fluorides or *aliphatic* sulfonic anhydrides. In general, alkylidenephosphoranes react smoothly according to eq 5.

The majority of the compounds listed in Table III belong either to the category of ylides with an α-methine proton, showing a one-proton doublet at δ 2.6–2.9, J_{P-H} = 13–14 Hz (compounds **15b, 15c, 16a, 16f, 16i**), or to the group of ylides with an α-methyl group characterized by a three-proton doublet at δ 1.6–1.8, J_{P-H} = 13 Hz (compounds **15d, 16e, 16g, 16j, 23**, see Table V). A third group of ylides (**16c, 16d, 16h**, with an α-*tert*-butyl substituent, was obtained in low yield in addition to the more abundant isomers **15c** and **15d** (in expt 15 and 17, respectively), or as the sole product in expt 21. The structures of **16c, 16d**, and **16h** follow from comparison of the pmr spectra of the isomers (Table V), and by the great similarity of the mass spectra after loss of the $R^2CH_2SO_2$ fragments, *i. e.*, by the fragmentation pattern of the *t*-BuC=PPH_3 (315) segment (see Experimental Section).

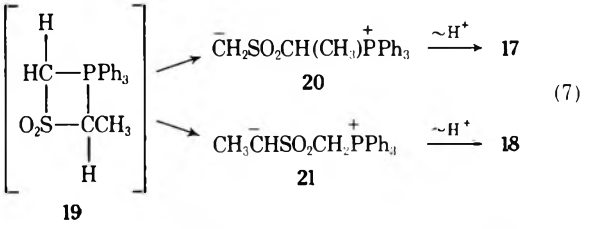
Discussion. Whether rearranged product (**15**) is formed or not depends primarily on the difference in size between R^2 and R^3, and also to some extent on the reaction temperature. For example, the reaction of neopentylidenetriphenylphosphorane (**2**, R^2 = *t*-Bu) with methane- or ethanesulfonyl fluoride led to rearranged product **15** (R^2 = *t*-Bu; R^3 = H or Me, respectively; expt 14 and 16, Table III). At low temperature (−90°) minor quantities of unrearranged product **16** were obtained as well (1.3 and 7%, respectively; expt 15 and 17). Rearrangement also was observed with 1-adamantylmethylenephosphorane (**2**, R^2 = 1-Ad) and methanesulfonic anhydride (expt 12). Conversely, only unrearranged ylides **16** were obtained when a buky substituent was present in the sulfonyl fluoride **4** (R^3 = *t*-Bu or *i*-Pr) against a small substituent in the phosphorane **2** (R^2 = Me or H, respectively; expt 18 and 19). These results can be explained by assuming a cyclic four-membered ring intermediate **11** (see Scheme I). The direction of ring opening (to give **12** or **13**) will be determined by maximum relief of steric strain, in agreement with the main products in expt 12–19.

The unrearranged products in expt 18 and 19 need not necessarily be formed through **11**, but can be explained alternatively by the routes B–D or C–E (Scheme I). The same holds, of course, for the reactions where R^2 equals R^3 (expt 10, 11, 20, and 21). In expt 21, with R^2 = R^3 = *t*-Bu, only a very low yield (3%) of ylide **16** is obtained, which obviously reflects steric problems.

Intermediates 11 and 19. The results of expt 25–28 (Table IV and eq 6) deserve special consideration. The following observations were made. (1) At −65° methanesulfonyl fluoride and ethylidenetriphenylphosphorane gave exclusively ylide **17** (62% yield), which constitutes a reaction *without* rearrangement (reaction 6A; expt 26). (2) On the other hand, ethanesulfonyl fluoride and methylenetriphenylphosphorane gave at the same temperature only the same product **17** (83% yield), which means a reaction occurring exclusively *with* rearrangement (reaction 6B; expt 28). (3) In refluxing tetrahydrofuran after 15 min these two reactions (expt 25 and 27) gave a mixture of the ylides **17** and **18** in nearly the same ratio **17**/**18** = 0.6 and 0.5, respectively. This means a preference for rearranged product in reaction 6C (expt 25), against a comparable preference for unrearranged product in reaction 6D (expt 27). (4) When the reaction mixture, prepared at −65° according to 2 and containing **17** only, was refluxed afterwards for 3.5 hr no 18 was formed at all. Ylide **17** was isolated in a yield of 89%. (5) Pure **17** was recovered unchanged after 19 hr of reflux in tetrahydrofuran in the presence of 0.1 equiv of methylenetriphenylphosphorane.

We feel that these results are explained satisfactorily, in accordance with Scheme I, by eq 7. The four-membered ring structure **19** (analogous to **11** in Scheme I) is the common intermediate in all reactions indicated in eq 6. Without the bulky substituents discussed above, **19** will now, at

reflux temperature, ring open in either of two directions to give **20** and **21**, which will lead to the kinetically controlled products **17** and **18**, respectively. The (small) preponderance of **18** in the ylide mixture, irrespective of the starting materials, indicates that ring opening to **21** is still sterically favored to some extent. Since pure **17** could not be isomerized to **18**, the ring opening and/or the proton shift must be an irreversible process under the conditions studied.



(7)

At −65°, the ring opening of **19** apparently goes in a single direction (to **20**). We tentatively assume that at this low temperature the selectivity is controlled by the greater stability of the carbanion segment in betaine **20** than in **21**.

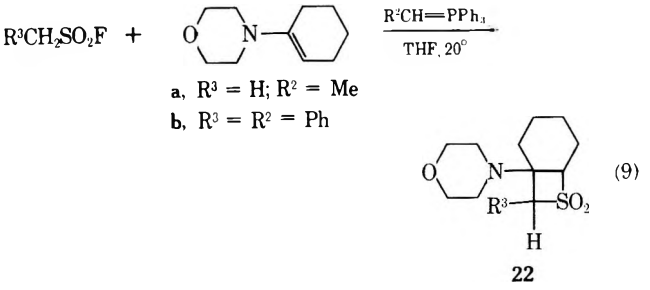
Reaction of ^{13}C-enriched methanesulfonyl fluoride with benzylidenetriphenylphosphorane, as an initial probe into a more detailed mechanistic study, gives rearranged ylide **7a** with the label exclusively at the methine carbon, in agreement with the proposed mechanisms *via* **11**. Furthermore, in a similar reaction with methylenetriphenylphosphorane the label is completely scrambled over the methine carbon and the methyl carbon of the resulting methylsulfonylmethylenetriphenylphosphorane (**16a**). This is consistent with, but not conclusive for, a [2 + 2] cycloaddition leading to a trigonal bipyramidal structure[11] of the intermediate **11** ($R^2 = R^3 = H$). Pseudo-rotation[11] then could distribute the label over the apical and equatorial methylene positions before ring opening occurs.

A four-membered ring transition state, comparable to the intermediate **11** (and **19**), was assumed previously by Ito, *et al.*,[2b] to explain the rearrangement observed in the reaction of α-carboalkoxyethylidenetriphenylphosphorane and sulfene to give α'-carboalkoxyethylsulfonylmethylenetriphenylphosphorane. Furthermore, Bestmann[4] has described a four-membered ring transition state to explain a similar rearrangement in the reaction of isopropylidenetriphenylphosphorane and ketene. In these two instances, substitution at C_α of the already *di*substituted methylenephosphorane derivatives was no longer possible. We now have shown the possibility of rearrangement in phosphorus ylide reactions, even though substitution without rearrangement could have occurred as an alternative.

Intermediacy of Sulfenes. The different reactions observed with arylsulfonyl fluorides on the one hand, and alkyl- or aralkylsulfonyl fluorides on the other, are suggestive of a sulfene intermediate **10**, generated by elimination of hydrogen fluoride from the latter type of sulfonyl fluorides[5] (reaction 4 in Scheme I). Similarly, sulfene may be generated from methanesulfonic anhydride[6] in expt 2, 3, 12, and 13.

$$EtSO_2Cl + CH_2{=}PPh_3 \xrightarrow[20^\circ]{THF} ClCH_2\overset{+}{P}Ph_3EtSO_2^- \quad (8)$$

Support for such a sulfene intermediate was obtained by the following observations. (1) Ethanesulfonyl *chloride* and methylenetriphenylphosphorane reacted by nucleophilic attack on the chlorine atom,[1] without the formation of sulfonylated ylide (reaction 8). (2) When the same reaction was carried out in the presence of an excess of triethylamine, which is known to generate sulfenes,[7] a 1:1 mixture of the ylides **17** and **18** was obtained in a total yield of 33% (compare reaction 6D, with Cl instead of F). (3) When reaction 6C was repeated (at room temperature) in the presence of an excess of the sulfene-trapping reagent *N*-(1-cyclohexenyl)morpholine,[8] thietane *S,S*-dioxide **22a** indeed was formed in 60% yield (reaction 9). (4) The same reaction without the addition of ethylidenetriphenylphosphorane did not give **22a**.[8b,9] (5) Analogous to the formation of **22a**, phenylmethanesulfonyl fluoride gave thietane dioxide **22b**.[10]



(9)

This evidence supports the existence of sulfene intermediates in the reactions of alkyl- and aralkylsulfonyl fluorides with phosphoranes. Therefore path C in Scheme I seems unlikely. It now follows that for the reactions of arylidenephosphoranes with aralkylsulfonyl fluorides (expt 6–9, occurring without rearrangement, see Table II) path B–D is most likely, since path A was already rejected in a previous section of this paper. On the other hand, the failure to isomerize **17** to **18** and the nearly constant ratio **17**/**18** in reactions 6C and 6D (see previous section) are in favor of a [2 + 2] cycloaddition to **19**, followed by an irreversible ring opening to **20** and **21** (eq 7). By extrapolation we propose this mechanism for all other reactions of Tables I, III, and IV that occur with rearrangement, following path A in Scheme I.

Concluding Remarks

The present work offers the opportunity to design a practical synthesis for almost any sulfonylmethylenephosphorane substituted with alkyl or aryl at the ylide carbon. An exception must be made, however, for very large substituents such as *tert*-butyl and adamantyl. The mechanistic interpretation is at this stage unavoidably speculative.

Experimental Section

The ir spectra were run on a Perkin-Elmer 257 grating spectrometer from samples in Nujol, unless stated otherwise. Pmr spectra were taken on Varian A-60 or A-60D apparatus; they were recorded in δ values (parts per million) downfield from TMS used as an internal standard. Mass spectra were determined by Mr. A. Kiewiet with an AEI ms 902 apparatus operating at 70 eV and using a direct inlet system.

Melting points were determined on a Mettler FP 2 apparatus equipped with a Mettler FP 52 microscope attachment.

The elemental microanalyses of all new compounds were carried out in the Analytical Department of this laboratory under the supervision of Mr. W. M. Hazenberg by Mr. H. Draaijer, Mr. J. Ebels, and Mr. J. Vos, and found within 0.4% of the calculated values.

Starting Materials. Literature references to the starting materials follow: $R^3CH_2SO_2F$[12] (R^3 = H, Me, *i*-Pr, Ph); $(MeSO_2)_2O$;[13] $R^2CH{=}PPh_3$ (R^2 = H,[14] Me,[15] Ph,[16] *p*-$CH_3OC_6H_4$,[17] *p*-$O_2NC_6H_4$[18]).

***p*-Nitrophenylmethanesulfonyl Fluoride.** According to Davies and Dick [12] *p*-nitrophenylmethanesulfonyl chloride[19] (10.0 g, 42.5 mmol) was converted into the corresponding fluoride by heating with 70% aqueous potassium fluoride (6 ml) for 1.5 hr at 100 °. The yield, after crystallization from dichloromethane–hexane was 1.5 g (6.8 mmol, 16%) of *p*-nitrophenylmethanesulfonyl fluoride: mp 127–128°; pmr ($CDCl_3$) δ 4.71 (2 H, d, J_{F-H} = 3 Hz), AB quartet at 7.65 (2 H) and 8.32 (2 H) (J = 8.5 Hz); ir (Nujol) 1530 and 1355 (NO_2), 1400 and 1210–1220 cm^{-1} (SO_2).

Neopentanesulfonyl Chloride. Neopentanesulfonyl chloride,

prepared previously by two unattractive methods,[20] was obtained in good yield *via* an alternate route by chlorination[19a] of neopentanethiol[21] in aqueous medium.

Pieces of sodium (19.0 g, 0.83 g-atom) were added all at once, without cooling, to diethyleneglycol monomethyl ether (250 ml) under nitrogen. After 2 hr of vigorous stirring the resulting homogeneous solution was chilled to 0° and saturated with hydrogen sulfide. Neopentyl *p*-toluenesulfonate[22] (130 g, 0.54 mol) was added, after which the mixture was refluxed for 2.5 hr and subsequently cooled to room temperature. Dilution with ice–water (500 ml) was followed by treatment with concentrated hydrochloric acid to pH 3–4. The resulting oil was separated and the water was extracted with diethyl ether (2 × 250 ml). The combined organic layers were dried over anhydrous sodium sulfate and concentrated at atmospheric pressure (bath temperature not exceeding 45°).

A vigorously stirred mixture of the crude neopentanethiol and 500 ml of ice–water was saturated with chlorine as fast as possible at a temperature not exceeding 10°. The reaction mixture was extracted with diethyl ether (3 × 200 ml), and the ethereal solution was washed with 5% sodium hydrogen sulfite solution and then with water and dried over anhydrous sodium sulfate. The ether was removed at atmospheric pressure (bath temperature not exceeding 45°). The crude neopentanesulfonyl chloride was distilled at reduced pressure under nitrogen from solid potassium carbonate.[23] Thus, 66.0 g (0.39 mol, 72% based on neopentyl *p*-toluenesulfonate) of neopentanesulfonyl chloride was obtained: bp 35–36° (0.5 mm); n^{19}D 1.4585 (lit.[20] n^{25}D 1.4556); pmr ($CDCl_3$) δ 1.26 (9 H, s), 3.80 (2 H, s); ir (neat) 1370 and 1170 cm^{-1} (SO_2).

Neopentanesulfonyl Fluoride. A 70% aqueous solution of potassium fluoride (42.0 g, 0.72 mol) was heated to 80°. After addition of neopentanesulfonyl chloride (34.0 g, 0.2 mol) the temperature was raised in 5 min to 100° under vigorously stirring. Additional stirring at 100° over a period of 10 min (a longer reaction time lowered the yield) was followed by rapid cooling to room temperature. The reaction mixture was diluted with ice–water (150 ml) and extracted with diethyl ether (3 × 100 ml). The organic layer was washed with water (50 ml), dried over anhydrous sodium sulfate, and concentrated at atmospheric pressure (bath temperature not exceeding 45°). The residual oil was distilled from solid potassium carbonate, providing 14.3 g (0.093 mol, 46%) of neopentanesulfonyl fluoride: bp 23° (0.4 mm); n^{23}D 1.4121; pmr ($CDCl_3$) δ 1.23 (9 H, d, J = 1 Hz), 3.33 (2 H, d, J_{F-H} = 3 Hz); ir (neat) 1410 and 1206 cm^{-1} (SO_2); mass spectrum (70 eV, 60°, cold inlet system) *m/e* (rel abundance) 139 (55), 138 (26), 75 (40), 71 (42), 70 (100), 64 (11), 57 (100), 56 (49), 55 (100), 43 (64), 41 (96), 39 (57), 29 (82), 27 (49) (no molecular ion present). Sufficiently pure material for elemental analysis could not be obtained even after repeated distillation.

Neopentyltriphenylphosphonium Iodide. The procedure of Seyferth and Singh[24] was modified to avoid the use of an excess of neopentyl iodide. A stirred solution of neopentyl iodide[25] (36.0 g, 0.182 mol) and triphenylphosphine (48.0 g, 0.182 mol) in sulfolane (25 ml) was heated at 160° in a nitrogen atmosphere for 24 hr. Sulfolane was removed at reduced pressure. After work-up as described by Seyferth, *et al.*, 77 g (0.167 mol, 91%) of neopentyltriphenylphosphonium iodide was obtained, decomposing at *ca.* 197° (melting point not reported by Seyferth[24]).

1-Iodomethyladamantane. The starting material 1-hydroxymethyladamantane was obtained by reduction of 1-adamantylcarboxylic acid[26] with $LiAlH_4$ in refluxing diethyl ether over a period of 24 hr, according to the procedure for the reduction of *tert*-butylcarboxylic acid.[27] The yield was 98%, mp 115–117° (lit.[28] mp 115°).

According to the procedure of Stone and Shechter[29] 1-iodomethyladamantane was prepared as follows. Orthophosphoric acid (200 g, 85%, Merck) was added, with stirring, to 52 g of phosphoric anhydride. After cooling of the resulting 95% orthophosphoric acid to room temperature, sodium iodide (34.0 g, 0.226 mol) and 1-hydroxymethyladamantane (24.0 g, 0.145 mol) were added. The mixture was stirred and heated at 105° for 3 hr under nitrogen, and then poured into water (4 l.) under vigorously stirring. The crude product was collected, washed with water, and dissolved in diethyl ether (500 ml). The ethereal solution was washed with 0.2 *N* sodium thiosulfate to remove the color, washed with water (2 × 150 ml), and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was crystallized from hexane (30 ml), providing 32.3 g (0.117 mol, 81%) of 1-iodomethyladamantane: mp 53.5–54.0°; pmr ($CDCl_3$) δ 1.4–1.7 (12 H, m), 1.95 (3 H, br), 3.01 (2 H, s).

1-Adamantylmethyltriphenylphosphonium Iodide. A solution of 1-iodomethyladamantane (12.0 g, 43.5 mmol) and triphenylphosphine (11.4 g, 43.5 mmol) in sulfolane (125 ml) was heated, with stirring, at 205° for 22 hr in a nitrogen atmosphere. Sulfolane was removed at 85° (0.2 mm). The resulting solid was washed intensively with ethyl acetate (200 ml) and, next, crystallized from chloroform (150 ml) and diethyl ether (400 ml), providing 21.7 g (40.3 mmol, 93%) of 1-adamantyltriphenylphosphonium iodide: decomposing at 291–293° (melting block); pmr ($CDCl_3$) δ 1.3–2.0 (15 H, m), 3.63 (2 H, d, J_{P-H} = 13 Hz), 7.5–8.3 (15 H, m). Crystallization from dichloromethane–acetone furnished an analytically pure sample, decomposing at the same temperature.

α-Tosylbenzylidenetriphenylphosphorane (3a, Eq 1). The sulfonylation of benzylidenetriphenylphosphorane with *p*-toluenesulfonic anhydride[30] was performed by the same procedure reported[1] for the sulfonylation of benzylidenetriphenylphosphorane with tosyl fluoride. With both sulfonylating agents the same yield of **3a** (12%) was obtained, identical by mixture melting point, pmr, and ir.

α-Tosylethylidenetriphenylphosphorane (3b, Eq 1) and Hydrolysis. According to the general procedure for the preparation of monosulfonyl-substituted methylenetriphenylphosphoranes,[1] ethylidenetriphenylphosphorane (prepared form 7.42 g, 20 mmol, of the corresponding phosphonium bromide[15]) was tosylated with tosyl fluoride (1.74 g, 10 mmol), affording 2.22 g (5.0 mmol, 50%) of **3b**, mp 185–187°. Analytically pure material with the same melting point was obtained by crystallization from dichloromethane–diethyl ether. Spectral data are compiled in Table V.

Hydrolysis of **3b** (0.60 g, 1.35 mmol) with 0.5 g of sodium hydroxide in 30 ml of refluxing water–dioxane (1:1, 1 hr) provided 0.20 g (81%) of ethyl *p*-tolyl sulfone, mp 54–56° (Beilstein **6**, 417, mp 55–56°).

α-Sulfonylarylidenetriphenylphosphoranes and α-Sulfonylalkylidenetriphenylphosphoranes (Tables I–IV, Expt 1–28). α-Benzylsulfonylbenzylidenetriphenylphosphorane (9a, Expt 6). At room temperature, under nitrogen, a solution of butyllithium in hexane (10 ml, 2.0 *M*, 20 mmol), was added dropwise to a stirred suspension of benzyltriphenylphosphonium bromide[16] (8.66 g, 20 mmol) in tetrahydrofuran (250 ml). After stirring for 30 min, a solution of benzylsulfonyl fluoride[12] (1.74 g, 10 mmol) in tetrahydrofuran (30 ml) was added dropwise in *ca.* 15 min. A white precipitate formed immediately. Stirring was continued for 30 min. The precipitate was removed and the filtrate was concentrated *in vacuo*. The residue was dissolved in chlorobenzene (250 ml) and washed with water (3 × 100 ml). After drying over anhydrous sodium sulfate, the chlorobenzene was removed *in vacuo* and the residue was triturated with ether (50 ml). The white solid was collected and washed with a little ether, providing 4.61 g (9.1 mmol, 91%) of **9a**, mp 209–210.5°. After crystallization from dichloromethane–diethyl ether, material sufficiently pure for elemental analysis was obtained: mass spectrum (70 eV, 200°, direct inlet system) *m/e* (rel abundance >35) 506 (36), 415 (71), 367 (35), 351 (100), 183 (54), 165 (92), 105 (95), 91 (35).

The procedure given for **9a** (expt 6) is typical for most of the experiments 1–28. Experiments, 9, 15, 17, 21, 23, and 24, however, are described separately below.

In some of the experiments, carried out on the same molar scale as **9a**, minor but essential differences have to be considered as follows (number of experiments, milliliters of THF, milliliters of chlorobenzene): 8, 400, 250; 18, 250, 500; 25–28, 500, 250. After the crude product was triturated with the appropriate solvent (*i.e.*, ethyl acetate for expt 2, 3, and 7; ether–pentane for expt 1, 5, 14, 16, 18, and 25–28; and ether for all others), the solid was found to be isomerically pure sulfonylphosphorane by pmr (except, of course, in expt 25 and 27). The concentrated mother liquid was discarded, after the absence of isomeric sulfonylphosphorane had been established by pmr. Also, the precipitated phosphonium salts were dissolved in water to demonstrate the absence of any water-insoluble ylide in these fractions.

Melting points and ir and pmr data of the products are compiled in Table V. Mass spectral data of the products of expt 9, 15, 17, 21, and 23 are described below. The mass spectral data of compounds **9b** and **9c** follow: **9b** (70 eV, 135°, direct inlet system) *m/e* (rel abundance >23) 536 (31), 381 (45), 278 (55), 277 (100), 262 (23), 231 (23), 183 (31), 152 (25), 135 (56), 121 (58), 91 (44), 77 (28); **9c** (70 eV, 180°, direct inlet system) *m/e* (rel abundance > 25) 551 (43), 415 (86), 367 (43), 352 (32), 351 (100), 183 (25), 165 (45), 105 (75).

α-Benzylsulfonyl-*p*-nitrobenzylidenetriphenylphosphorane (9d, Expt 9). Contrary to the procedure given above for **9a**, an excess of solid benzylsulfonyl fluoride[12] (3.48 g, 20 mmol) was added all at once to a solution of *p*-nitrobenzylidenetriphenylphosphorane (prepared from 8.67 g, 20 mmol, of *p*-nitrobenzyltri-

Table V
Melting Points and Spectral Data of the Sulfonyl-Stabilized Phosphonium Ylides

Compd	Mp, °C (from)	Ir (Nujol), cm^{-1} ν_{SO_2} (asym)	Ir (Nujol), cm^{-1} ν_{SO_2} (sym)	Pmr ($CDCl_3$), δ ppm nonaromatic protons[a]
3b	185–187[g]	1260	1120 1100	1.70 (d, 3 H, J_{P-H} = 13 Hz), 2.33 (s, 3 H)
7a = 16i[b]	172–174	1280	1114 1104	2.60 (d, 1 H, J_{P-H} = 13 Hz), 3.89 (s, 2 H)
7b	214–215 (CH_2Cl_2–Et_2O)	1270 1252	1105	2.53 (d, 1 H, J_{P-H} = 14 Hz), 3.78 (s, 3 H), 3.81 (s, 2 H)
7c = 16j	171.5–172.5 (CH_2Cl_2–Et_2O)	1275 1252	1111	1.60 (d, 3 H, J_{P-H} = 13 Hz), 4.00 (s, 2 H)
6d	163.5–164.5 (Et_2O)	1271	1115 1110	0.91 (s, 9 H), 2.70 (s, 2 H)
9a	210–211 (CH_2Cl_2–Et_2O)	1270 1250	1110	3.96 (s, 2 H)
9b	194–195 (CH_2Cl_2–Et_2O)	1247	1100 1097	3.70 (s, 3 H), 3.98 (s, 2 H)
9c[c]	214.5–215 (EtOAc)	1253	1110	4.06 (s, 2 H)
9d[d]	275–276[g]	1285 1263	1106	3.88 (s, 2 H)
16a[b]	202–204	1267	1118 1107	2.75 (s, 3 H), 2.83 (d, 1 H, J_{P-H} = 14 Hz)
15b	140–141 ($CHCl_3$–Et_2O)	1272	1111	1.4–2.1 (br, 15 H), 2.57 (s, 2 H), 2.87 (d, 1 H, J_{P-H} = 14 Hz)
15c	146–147 (CH_2Cl_2–hexane)	1266	1114 1110 1102	1.03 (s, 9 H), 2.70 (s, 2 H), 2.88 (d, 1 H, J_{P-H} = 14 Hz)
16c	222–223.5[g]	1253 1245	1103	1.15 (s, 9 H), 2.76 (s, 3 H)
15d = 16e	*g*	1260	1105	0.98 (s, 9 H), 1.72 (d, 3 H, J_{P-H} = 13 Hz), 2.69 (s, 2 H)
16d	183–184[g] (Et_2O)	1258	1110 1098	1.12 (s, 9 H), 1.02 (t, 3 H, J = 7 Hz), 2.87 (q, 2 H, J = 7 Hz)
16f	125–126 (EtOAc)	1275 1250	1112 1100	0.92 (d, 6 H, J = 6.5 Hz), 2.17 (m, 1 H, J = 6.5 Hz), 2.58 (d, 2 H, J = 6.5 Hz), 2.80 (d, 1 H, J_{P-H} = 14 Hz)
16g	162–163 (EtOAc–$CHCl_3$–Et_2O)	1262	1105	1.17 (t, 3 H, J = 7 Hz), 1.76 (d, 3 H J_{P-H} = 13 Hz), 2.80 (q, 2 H, J = 7 Hz)
16h	219–220 dec[g]	1250	1100	0.85 (s, 9 H), 1.14 (s, 9 H), 2.8 (br, 2 H)
17	200–201 ($CHCl_3$–Et_2O)	1256	1104	2.74 (s, 3 H), 1.72 (d, 3 H, J_{P-H} = 13 Hz)
18		1250	1113 1098	1.18 (t, 3 H, J = 7.5 Hz), 2.68 (q, 2 H, J = 7.5 Hz)
23[e]	191–192[g]	1287	1128 1115 1108	1.60 (d, 3 H, J_{P-H} = 13 Hz), AB quartet consisting of two doublets at 4.40 and 4.70 (2 H, J = 15 Hz), 4.61 (s, 1 H)
24[f]	201–202[g]	1292	1120 1110	1.06 (s, 9 H), 3.30 (q, 2 H, J = 14 Hz), 4.80 (s, 1 H)

[a] All spectra showed the expected aromatic protons. [b] Compound reported previously, ref 1. [c] Ir 1520 and 1354 cm^{-1} (NO_2). [d] Ir 1580 and 1336 cm^{-1} (NO_2). [e] Ir 1326 and 1170–1160 cm^{-1} (SO_2). [f] Ir 1323 and 1142 cm^{-1} (SO_2). [g] See Experimental Section.

phenylphosphonium chloride[18]) in tetrahydrofuran (250 ml). The reaction mixture was stirred for 3 hr. The yellow precipitate was collected and washed by intensively stirring with water (1 l.). The crude material was dissolved in dichloromethane (250 ml), washed with water (3 × 100 ml), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The yellow material was washed with ether (50 ml), affording 3.70 g of **9d** (6.7 mmol, 67% calculated on the theoretically convertible amount of benzylsulfonyl fluoride), mp 269–271°. After crystallization from dichloromethane–diethyl ether, dichloromethane–acetone, and dichloromethane–diethyl ether, respectively, analytically pure material was obtained: mp 275–276°; mass spectrum (70 eV, 225°, direct inlet system) *m/e* (rel abundance >23) 551 (14), 461 (34), 460 (100), 412 (45), 396 (47), 183 (23).

The tetrahydrofuran filtrate was concentrated. The residual oil was dissolved in chlorobenzene (250 ml) and washed with water (3 × 100 ml). During the washings a pH of 7 was maintained by addition of 2 *N* hydrochloric acid to prevent contamination of the chlorobenzene layer with *p*-nitrobenzylidenetriphenylphosphorane, which would have been liberated from its salt under basic conditions. After drying over anhydrous sodium sulfate, the chlorobenzene was removed *in vacuo*. The resulting yellow oil was treated with ether (50 ml), affording an additional fraction (0.83 g, 1.5 mmol, 15%) of **9d**, mp 269–271°.

Neopentylsulfonylmethylenetriphenylphosphorane (15c) and α-Methylsulfonylneopentylidenetriphenylphosphorane (16c, Expt 15). A solution of neopentylidenetriphenylphosphorane (prepared from 8.19 g, 17.8 mmol, of neopentyltriphenylphosphonium iodide, see above) in tetrahydrofuran (500 ml) under nitrogen was cooled to −90°. Methanesulfonyl fluoride[12] (0.88 g, 9.0 mmol) in tetrahydrofuran (5 ml) was added all at once. After additional stirring for 1 hr at −90° the temperature was raised to room temperature in 30 min. The precipitate was separated and extracted with tetrahydrofuran. The combined organic layers were concentrated *in vacuo*. The residual oil was dissolved in chlorobenzene (250 ml), washed with water (3 × 100 ml), and dried over anhydrous sodium sulfate. After removal of the solvent, the resulting oil was dissolved in diethyl ether (100 ml). After stirring for 4 hr, 1.75 g 14.27 mmol, 48%) of **15c** was collected. The mother liquid was concentrated to a volume of 10 ml. Addition of pentane (100 ml) furnished an additional amount of **15c** (0.61 g, 1.49 mmol, 17%): mass spectrum (70 eV, 150°, direct inlet system) *m/e* (relative abundance >9) 410 (19), 395 (12), 354 (21), 353 (28), 339 (33), 289 (9), 277 (23), 276 (60), 275 (91), 200 (16), 199 (100), 185 (21), 183 (30), 165 (19), 152 (9), 121(9), 91 (9), 77 (9).

The volume of the mother liquid was then reduced to 50 ml and the liquid was cooled to −30°. A fraction of 0.26 g of **16c** was obtained (contaminated with some **15c**). Recrystallization from chloroform–ether yielded 47 mg (0.12 mmol, 1.3%) of pure **16c**: mp 222–223.5°; mass spectrum (70 eV, 180°, direct inlet system) *m/e* (rel abundance >5) 410 (9), 395 (100), 316 (9), 315 (28), 301 (20), 261 (5), 201 (5), 185 (5), 183 (16), 108 (9), 91 (5), 57 (5), 43 (5), 41 (10).

α-Neopentylsulfonylethylidenetriphenylphosphorane (15d)

and α-Ethylsulfonylneopentylidenetriphenylphosphorane (16d, Expt 17). A solution of neopentylidenetriphenylphosphorane (prepared from 9.20 g, 20 mmol, of the corresponding phosphonium iodide, see above) in tetrahydrofuran (500 ml) under nitrogen was cooled to −90°. Ethanesulfonyl fluoride[12] (1.12 g, 10 mmol) in tetrahydrofuran (30 ml) was added dropwise in 1 hr. After additional stirring for 4 hr at −90° the temperature was raised to room temperature. The work-up was carried out as above for expt 15. Chlorobenzene was removed *in vacuo*. The resulting viscous oil was dissolved in diethyl ether (150 ml) and pentane (100 ml) was added. After stirring for 1.5 hr 2.28 g (5.4 mmol, 54%) of **15d** was collected. The solid softened at different temperatures (>120°), strongly depending on the initial temperature of the melting block. Ylide **15d** was identical by pmr and ir with **16e** (expt 18): mass spectrum (70 eV, 190°, direct inlet system) *m/e* (rel abundance >5) 424 (5), 353 (6), 289 (41), 278 (49), 277 (100), 263 (9), 262 (10), 213 (10), 202 (16), 201 (29), 199 (14), 185 (13), 183 (27), 152 (10), 133 (5), 108 (9), 77 (29), 71 (18), 57 (10), 55 (8), 51 (18), 47 (10), 43 (22), 41 (11), 39 (7).

After addition of pentane (100 ml) to the mother liquid, followed by concentration of the solution to *ca.* 100 ml, an additional crop of **15d** (0.93 g, 2.2 mmol, 22%) was obtained. After the mother liquid was concentrated further, the resulting viscous oil was dissolved in diethyl ether (10 ml). Crystallization at −30° afforded 300 mg (0.7 mmol, 7%) of **16d,** mp 183–184°. After four recrystallizations from diethyl ether, a still unsatisfactory elemental analysis was obtained for carbon. Therefore, the absolute mass of **16d** was determined, relative to the standard ^{12}C = 12.000000: calcd 424.162578; found 424.164 ± 0.003. **16d** had mass spectrum (70 eV, 150°, direct inlet system) *m/e* (rel abundance >5) 424 (14), 409 (100), 395 (7), 331 (5), 315 (25), 301 (16), 289 (11), 262 (7), 261 (9), 201 (6), 185 (7), 183 (20), 108 (9), 91 (5), 57 (7), 43 (5), 41 (8).

α-Neopentylsulfonylneopentylidenetriphenylphosphorane (16h, Expt 21). To a solution of neopentylidenetriphenylphosphorane (prepared from 9.20 g, 20 mmol, of the corresponding phosphonium iodide, see above) in tetrahydrofuran (250 ml) under nitrogen was added dropwise at room temperature a solution of neopentanesulfonyl fluoride (1.54 g, 10 mmol, see above) in tetrahydrofuran (30 ml). After additional stirring for 0.5 hr the white suspension was filtered. Water (*ca.* 6 drops) was added to the filtrate (to decompose unreacted neopentylidenetriphenylphosphorane). After filtration and evaporation *in vacuo,* the resulting viscous oil was dissolved in diethyl ether (250 ml), washed with water (3 × 50 ml), and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residue was crystallized from carbon tetrachloride (3 ml) at −30°, providing 137 mg (0.29 mmol, 3%) of **16h,** decomposing at *ca.* 210°. After recrystallization from diethyl ether–pentane, 47 mg (0.1 mmol, 1%) of **16h** sufficiently pure for elemental analysis was obtained: mp 219–220° dec; mass spectrum (70 eV, 180°, direct inlet system) *m/e* (rel abundance >5) 466 (11), 451 (100), 437 (24), 395 (9), 331 (8), 316 (10), 315 (28), 301 (20), 262 (5), 202 (5), 185 (5), 183 (13), 108 (8), 57 (8), 41 (9).

α-Benzylsulfonylethylidenetriphenylphosphorane (16j) and α′-Benzylsulfonyl-α-benzylsulfonylethylidenetriphenylphosphorane (23, Expt 23). To a solution of ethylidenetriphenylphosphorane (prepared from 7.42 g, 20 mmol, of the corresponding phosphonium bromide[15]) in terahydrofuran (250 ml) under nitrogen was added dropwise at room temperature, until the yellow color disappeared, a solution of benzylsulfonyl fluoride[12] (*ca.* 2.1 g, 12 mmol) in tetrahydrofuran (30 ml). Stirring was continued for 1 hr. The precipitate was removed and the filtrate was concentrated *in vacuo.* The residue was dissolved in chlorobenzene (250 ml) and washed with water (3 × 100 ml). After drying over anhydrous sodium sulfate the chlorobenzene was removed *in vacuo.* To the resulting oil was added, consecutively, dichloromethane (5 ml) and diethyl ether (100 ml). After stirring for 16 hr the suspension was filtered, providing 1.29 g (2.2 mmol, 33%) of crude **23.** Crystallization from dichloromethane–ethyl acetate (two times) and dichloromethane–diethyl ether, respectively, furnished analytically pure material, mp 191–192°.

Addition of pentane (200 ml) to the mother liquid provided 1.21 g (3.0 mmol, 30%) of **16j,** identical by pmr, ir, and mixture melting point with **7c** (expt 4): mass spectrum (70 eV, 150°, direct inlet system) *m/e* (rel abundance >5) 444 (9), 353 (100), 305 (9), 289 (33), 262 (19), 261 (7), 185 (5), 183 (19), 133 (5), 108 (12), 77 (5), 43 (7).

α′-Neopentylsulfonyl-α-benzylsulfonylbenzylidenetriphenylphosphorane (24, Expt 24). To a solution of neopentylidenetriphenylphosphorane (prepared from 9.20 g, 20 mmol, of the corresponding phosphonium iodide, see above) in tetrahydrofuran (250 ml) under nitrogen was added dropwise at room temperature, until the yellow color disappeared, a solution of benzylsulfonyl fluoride[12] (*ca.* 2.3 g, 13.3 mmol) in tetrahydrofuran (25 ml). After additional stirring for 1 hr the white suspension was filtered off. The filtrate was concentrated *in vacuo* to a viscous oil (*ca.* 5 g). Chromatography over silica gel with chloroform–diethyl ether (1:4) provided 1.3 g (2.05 mmol, 31%) of crude **24.** Crystallization from ethyl acetate–diethyl ether (two times) furnished an analytically pure sample, mp 201–202°.

Reaction of Ethanesulfonyl Chloride with Methylenetriphenylphosphorane in the Presence of Triethylamine. To a solution of methylenetriphenylphosphorane (prepared from 7.14 g, 20 mmol, of the corresponding phosphonium bromide[14]) in tetrahydrofuran (250 ml) under nitrogen was added at room temperature triethylamine (50 g, 0.5 mol), immediately followed by dropwise addition of *ca.* 25 ml of a solution of ethanesulfonyl chloride[19a] (2.57 g, 20 mmol) in tetrahydrofuran until the yellow color of methylenetriphenylphosphorane disappeared. Work-up according to the general procedure given above for **9a** afforded 1.21 g (3.3 mmol, 33%) of a mixture of **17** and **18** in a ratio of 1:1.

Reaction of Methanesulfonyl Fluoride with Ethylidenetriphenylphosphorane in the Presence of N-(1-Cyclohexenyl)morpholine. A solution of ethylidenetriphenylphosphorane (prepared from 3.71 g, 10 mmol, of the corresponding phosphonium bromide[15]) in tetrahydrofuran (250 ml) was added dropwise in 70 min to *N*-(1-cyclohexenyl)morpholine[31] (16.7 g, 0.1 mol) and methanesulfonyl fluoride[12] (0.98 g, 10 mmol) in tetrahydrofuran (100 ml) under nitrogen at room temperature. After additional stirring for 15 min the white precipitate was collected and identified as ethyltriphenylphosphonium bromide (3.42 g, 9.2 mmol, 92%) by comparison of the ir and pmr spectra with those of authentic material.[15] (The THF solution of ethylidenetriphenylphosphorane contains lithium bromide generated from ethyltriphenylphosphonium bromide with butyllithium. Dehydrofluorination of methanesulfonyl fluoride to the corresponding sulfene with ethylidenetriphenylphosphorane yields ethyltriphenylphosphonium fluoride, which apparently exchanges a fluoride ion against the bromide ion of lithium bromide.)

The tetrahydrofuran layer was concentrated *in vacuo.* The residual oil was dissolved in dichloromethane (250 ml), washed with water (3 × 100 ml), and dried over anhydrous sodium sulfate. After removal of dichloromethane, the yellow oil was vigorously stirred with pentane (250 ml). The pale yellow precipitate was collected and washed with pentane, affording crude thietane dioxide **22a** (2.41 g). The ylides **17** and **18** could not be detected by pmr. Crystallization from methanol (25 ml) yielded **22a** (1.48 g, 6.0 mmol, 60%) mp 137–138.5°, identical by pmr, ir, and mixture melting point with an authentic sample.[8]

Reaction of Benzylsulfonyl Fluoride with Benzylidenetriphenylphosphorane in the Presence of N-(1-Cyclohexenyl)morpholine. Under the same conditions as described above, we obtained benzyltriphenylphosphonium bromide (3.57 g, 8.2 mmol, 82%) and thietane dioxide **22b** (2.28 g, 7.1 mmol, 71%, crystallized from methanol), mp 135–136° (lit.[10] mp 136°).

Acknowledgment. The authors are indebted to Dr. R. M. Kellogg for stimulating discussions during this work, and to Mr. O. Possel for carrying out the ^{13}C experiments.

Registry No.—**2,** R^2 = H, 3487-44-3; **2,** R^2 = 1-adamantyl, 51849-03-7; **2,** R^2 = *t*-Bu, 3739-96-6; **2,** R^2 = Me, 1754-88-7; **3a,** 36196-01-7; **3b,** 51849-04-8; **4,** R^3 = H; X = F, 558-26-8; **4,** R^3 = H; X = OSO_2Me, 7143-01-3; **4,** R^3 = Me; X = F, 754-03-0; **4,** R^3 = *t*-Bu; X = F, 51849-05-9; **4,** R^3 = *i*-Pr; X = F, 659-90-5; **4,** R^3 = Ph; X = F, 329-98-6; **4,** R^3 = Me; X = Cl, 594-44-5; **5,** Y = H, 16721-45-2; **5,** Y = MeO, 21960-26-9; **5,** Y = NO_2, 6933-17-1; **8,** Z = H, 368-43-4; **8,** Z = NO_2, 349-96-2; **16c,** 51849-06-0; **16d,** 51849-07-1; **23,** 51849-08-2; **24,** 51849-09-3; 1-iodomethyladamantane, 51849-10-6; 1-hydroxymethyladamantane,770-71-8; 1-adamantyltriphenylphosphonium iodide, 51849-11-7.

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Alkyl Metal Asymmetric Reduction. VI. Alkyl Phenyl Ketone Reductions by Dialkylzinc Compounds. Some Dynamic and Stereochemical Aspects

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Received January 8, 1974

The reactivity of organozinc compounds having β-branched alkyl groups toward alkyl phenyl ketones has been investigated; at 86° the dialkylzinc compounds are shown to reduce the carbonyl substrate to the corresponding carbinol, which is the only product formed. On the basis of the results obtained, the reduction process is assumed to involve the formation of a coordinative bond between the ketone and the dialkylzinc compound, followed by a β-hydride transfer from the alkyl group of the organozinc compound to the carbonyl carbon atom in a six-membered cyclic transition state. The eventual occurrence of side reduction processes, like the Meerwein–Ponndorf–Verley reaction, in the experimental conditions was tested too. Finally, the reduction of alkyl phenyl ketones by (+)-bis[(*S*)-2-methylbutyl]zinc affords (*S*)-alkylphenylcarbinols. The stereoselectivity of the process is discussed and compared with that encountered in other alkyl metal reductions.

Although the reactivity of the organozinc compounds should correspond in principle to that of their Grignard counterparts, it is generally accepted that organozinc compounds, isolated by distillation, are scarcely reactive toward carbonyl substrates.[1,2] On the contrary, *in situ* organozinc reagents react rapidly and efficiently with simple carbonyl compounds to give mainly addition products.[2,3] Concerning the reactivity of *isolated* dialkylzinc compounds, diethylzinc was observed to eliminate ethylene quantitatively in the reaction with benzophenone at 110°, giving ethylzinc diphenyl methoxide.[4]

Therefore, in the course of studies on the reactions of organometallic compounds with functional substrates[5] and on the alkyl metal asymmetric reductions,[6,7] we have investigated the actual reactivity of dialkylzinc compounds toward alkyl phenyl ketones and, in this connection, the stereochemistry of their reduction by optically active organozinc compounds.[7]

Results

At relatively high temperatures, dialkylzinc compounds having branched alkyl groups[7] react with alkyl phenyl ketones; the reactions have been carried out mainly in the absence of solvents at 86.5°. In the experimental conditions adopted, after hydrolysis of the reaction mixtures, secondary carbinols corresponding to the reduction of the carbonyl group are recovered together with the unreacted ketone. No addition product was detected in the reaction of alkyl phenyl ketones with Zn(*i*-Bu)$_2$ or with bis(2-methylbutyl)zinc, while γ- or δ-branched alkylzinc compounds were observed to yield also tertiary carbinols, although to a low extent.[7] The main results we have obtained are summarized in Tables I and II, from inspection of which several general observations can be noted.

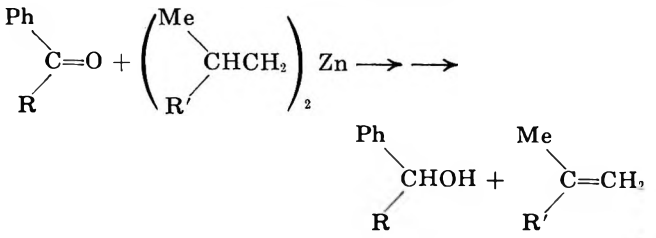
(1) The reaction rate seems to be dependent on the structure and on the nature of the carbonyl substrate; while trifluoromethyl phenyl ketone reacts completely within 20 min at room temperature (runs 11 and 12), the reduction of the alkyl phenyl ketones occurs with conversions higher than 50% only after heating at 86.5° for 5 hr (runs 5–7). Moreover, as the bulk of the alkyl group in the ketone increases, the conversions (after 5 hr) of the reaction decrease from 90–100 to 50–60%.

(2) The reactivity of the organozinc compounds used seems to be nearly comparable; the conversions in the reduction of *tert*-butyl phenyl ketone are, however, slightly lower using Zn(*i*-Bu)$_2$ than using bis(2-methylbutyl)zinc (runs 9 and 10).

(3) The increase of the concentration of the reagents in toluene solution (runs 14 and 15), as well as the use of an excess of the organozinc compound (run 16), determines higher conversions in the reduction of *tert*-butyl phenyl ketone.

Bis[(*S*)-2-methylbutyl]zincis able to accomplish asymmetric reduction of alkyl phenyl ketones (Table III): all the carbinols recovered have the absolute (*S*) configuration. In agreement with the data obtained in the reduction of the same ketones by (+)-tris[(*S*)-2-methylbutyl]aluminum,[6] the stereoselectivity of the reduction is dependent on the structure of the ketone, increasing in the order Me < Et < *t*-Bu < *i*-Pr. Finally, it is to be noted that the reduction of trifluoromethyl phenyl ketone occurs with very low stereo-

Table I
Reduction of Alkyl Phenyl Ketones by Dialkylzinc Compounds



Run	R	Temp, °C	R′	Conversion % in carbinol[a] after 5 hr
1	Me	86.5	Me	94
2			Et	97
3	Et		Me	75
4			Et	75
5	*i*-Pr	46.5	Me	9
6		67.5		27
7		86.5		69
8			Et	66
9	*t*-Bu		Me	62
10			Et	51
11[b]	CF_3	25.0	Me	100
12[b]			Et	100

[a] Based on glpc analyses of the crude reaction mixture after hydrolysis. All the values refer to runs carried out at least in duplicate. [b] The reaction is complete within 20 min.

selectivity at 80° in benzene (run 25); the extent of asymmetric reduction is, however, higher at 0° (run 26).

Discussion

In agreement with previous observations,[4,7] at relatively high temperatures organozinc compounds react effectively with carbonyl substrates (Table I).

Although in principle mixtures of products may be obtained arising from addition, reduction, and enolization processes, the reaction affords essentially the secondary carbinol corresponding to a reduction of the carbonyl group. No addition product has been detected in the reaction mixture in the experimental conditions we have adopted. Moreover, the high conversions of the reduction of alkyl phenyl ketones (Table III) and the recovery of low-boiling material containing 97% of 2-methyl-1-butene in the reduction of isopropyl phenyl ketone by bis(2-methylbutyl)zinc[7] seem to exclude also enolization phenomena of relevant extent.[8]

Table II
Reduction of *tert*-Butyl Phenyl Ketone by Diisobutylzinc at 86.5°

Run	Solvent	Molar ratio $Zn(i\text{-}Bu)_2$/ketone	Conversion[a] % after 2 hr	5 hr	9 hr	15 hr
13		1	37	62	74	79
14	Toluene[b]	1		41	55	67
15	Toluene[c]	1		26	38	49
16		2	50	76	94	99

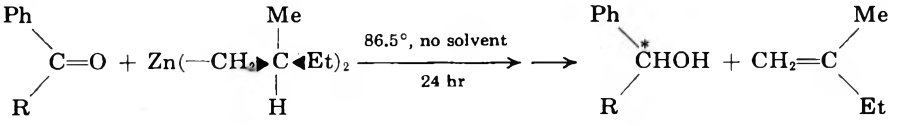
[a] Based on glpc analyses of the crude reaction mixture after hydrolysis. [b] Molar concentration of $Zn(i\text{-}Bu)_2$ 0.93 *M*. [c] Molar concentration of $Zn(i\text{-}Bu)_2$ 0.55 *M*.

It has already been hypothesized[4] that the reaction between organozinc compounds and ketones involves a six-center transition state, analogous to that suggested for the reduction of ketones by aluminum alkyls.[9] The dependence of the reduction rate on the molar ratio $Zn(i\text{-}Bu)_2$/ketone (Table II) seems to indicate that the reduction involves a bimolecular process. This hypothesis agrees moreover with the fact that the reaction, carried out in toluene, was found to exhibit second-order kinetics: the plot of *t* against reciprocal concentration of the ketone is in fact a straight line (runs 14 and 15) and the reaction rate depends on the initial concentration of both the reactants in the solution (Table II).

On this basis, also in view of mechanisms already proposed for the reduction of ketones by other organometallic compounds,[6,9,10] it seems reasonable to assume that the reaction proceeds through the formation of a complex between the ketone and the organozinc compound,[3b,4] followed by the migration of the β hydrogen from the alkyl group of the dialkylzinc to the carbonyl carbon in a six-center transition state (Scheme I).[4,7]

Effectively, when the phenyl alkyl ketone is added to the organozinc compound, the reaction mixture assumes a yellow color which might be attributed to a complex formation;[4] however, the kinetic results indicate that such a formation occurs either quantitatively or to a very small extent. Actually, although we were unable to determine the exact extent of complexation, the assumption that the

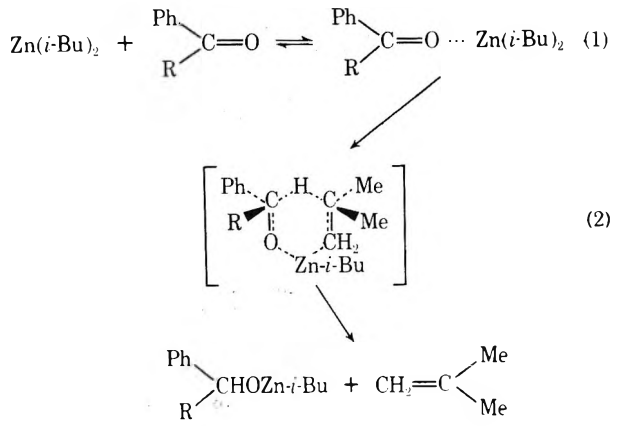
Table III
Asymmetric Reduction of Alkyl Phenyl Ketones by (+)-Bis[(*S*)-2-methylbutyl]zinc[a]



Run	R	Ph(R)C=O registry no.	S Carbinol: Conversion[b] %	Chemical purity,[c] %	$\alpha^{25}D$, deg, l = 1 (*c*, ether)	$[\alpha]^{25}D$	$[\alpha]^{25}D$[d]	Optical purity,[e] %	Registry no.	Asymmetric reduction,[f] %
17	Me	98-86-2	*g*	98.3	−0.16 (4.73)[h]	−1.69	−1.72	2.6	1445-91-6	2.6
18			98.2	98.2	−0.15 (4.94)[h]	−1.52	−1.55	2.4		2.4
19	Et	93-55-0	78.4	78.6	−0.13 (7.26)	−1.79	−2.28	4.4	613-87-6	4.5
20			79.8	80.0	−0.11 (6.39)	−1.72	−2.15	4.2		4.3
21[i]	*i*-Pr	611-70-1	89.2	89.3	−0.43 (6.65)	−6.47	−7.24	15.2	34857-28-8	15.5
22[i]			86.7	86.8	−0.52 (8.29)	−6.27	−7.22	15.2		15.5
23	*t*-Bu	938-16-9	84.4	84.6	−0.33 (10.50)	−3.14	−3.71	10.2	15914-85-9	10.4
24			84.7	85.3	−0.36 (10.94)	−3.29	−3.86	10.6		10.8
25[j]	CF_3	434-45-7	~100	~100	+0.18 (neat)		+0.14	0.4	340-06-7	0.4
26[k]			~100	~100	+0.17 (10.49)		+1.62	5.1		5.2

[a] Optical purity 98.2%. [b] Based on glpc analyses of the crude products. [c] Estimated by glpc analyses on redistilled samples, other impurities being the ketone. [d] Corrected for the chemical purity of the carbinol. [e] See Experimental Section. [f] Corrected on the basis of the optical purity of the dialkylzinc. [g] Not determined. High-boiling materials were formed too. [h] l = 2. [i] See ref 7. [j] Reaction carried out at 80° in benzene for 1 hr. [k] Reaction carried out at 0° for 1 hr.

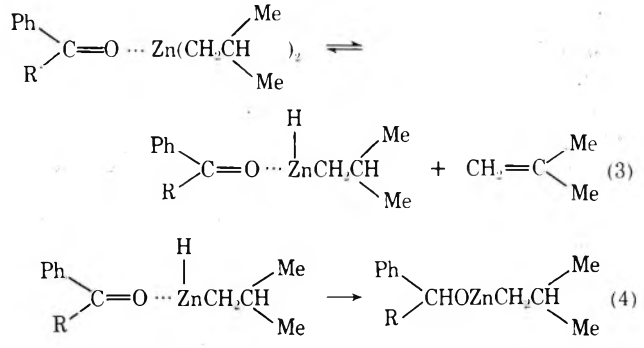
Scheme I



equilibrium constant for complex formation (eq 1) is small seems very reliable.[11] Therefore the rate-determining step of the reaction should be reasonably the transfer of the β hydrogen of the alkyl group to the ketone (eq 2).

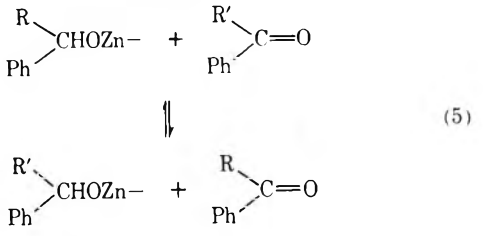
An alternative mechanistic pathway might be based on the olefin elimination as a consequence of the ketone attack, followed by reduction of the ketone by isobutylzinc hydride[9,12] (Scheme II). Though the reduction occurs at

Scheme II



relatively high temperatures, this mechanism does not, however, seem probable since dialkylzinc compounds do not form olefin even at temperatures higher than we have adopted.[13] Moreover, the asymmetric induction observed in the reaction between (+)-bis[(*S*)-2-methylbutyl]zinc and phenyl alkyl ketones (Table III) is effectively consistent with the hypothesis of a β-hydrogen transfer in a six-membered cyclic transition state (eq 2).[6a] This transfer should be aided by electron-withdrawing groups attached to the carbonyl carbon atom. The structure and the nature of the ketone seem to have a determining influence on the reactivity of such a substrate toward the organozinc compounds, in relation to both steric and electronic factors. The conversion of the reductions after 5 hr at 86.5° decreases, in fact, as the structure of the phenyl alkyl ketone is changed, in the order Me > Et > *i*-Pr > *t*-Bu; moreover, the reduction of trifluoromethyl phenyl ketone occurs very fast even at 0° (Table I). The decrease of both the steric hindrance to the carbonyl carbon atom and the electron-donor power of the substituent may act to increase the reaction rate, which is, however, strongly enhanced when powerful electron-withdrawing groups are bonded to the carbonyl carbon atom,[14] as in trifluoroacetophenone. The availability of the second alkyl group of the organozinc compound was tested by treating the diisobutylzinc with *tert*-butyl phenyl ketone in the molar ratio 1:2. At 86.5° after 72 hr, the ketone was reduced with a conversion of 54% and this indicates that the reaction of the second alkyl group occurs at a very reduced rate, analogously to what is observed for the reduction of benzophenone by triisobutylaluminum.[9] However, in the reaction conditions adopted, the zinc hemialkoxide formed might act as a new reducing agent in a Meerwein–Ponndorf–Verley (MPV) type reaction[15] (Scheme III). Such a reaction should be competing in principle with the alkyl metal reduction, taking into account that the oxygen atom could better stabilize the developing charge on the β-carbon atom and thus favor the hydride transfer from the alkoxide group.[16]

Scheme III



As a consequence of this competitive oxidation–reduction mechanism, the optical purity of the carbinols formed in the reduction of the alkyl phenyl ketones by (+)-bis[(*S*)-2-methylbutyl]zinc might change during the reaction time. In fact, when the concentration of the hemialkoxide species in the reaction mixture becomes appreciable the eventual MPV reaction should lead to the racemization of the optically active alkoxide groups formed.[17]

Bis[(*S*)-1-phenyl-2-methylpropoxy]zinc (optical purity 29.4%) was shown to racemize completely if heated at 86.5° for 24 hr in the presence of a stoichiometric amount of the corresponding ketone.[18] In similar conditions bis[(*R,S*)-1-phenylpropoxy]zinc reacts with *tert*-butyl phenyl ketone to yield *tert*-butylphenylcarbinol (48%), as a consequence of a MPV reaction. In order to check if such an oxidation–reduction process occurs even by the zinc hemialkoxide formed by the alkyl metal reduction, isobutyl[(*R,S*)-1-phenyl-2,2-dimethylpropoxy]zinc was heated at 86.5° for 24 hr with the equivalent amount of propiophenone. Upon hydrolysis of the reaction mixture, ethylphenylcarbinol (50% yield) and the corresponding amount of *tert*-butyl phenyl ketone were recovered. Such products are certainly derived from a MPV reaction involving the alkoxide groups (eq 5).

Nevertheless the optical purity of *tert*-butylphenylcarbinol from reduction of the corresponding ketone by (+)-bis[(*S*)-2-methylbutyl]zinc (runs 23 and 24) does not change with the reaction time (2–48 hr) and consequently with the conversion of the reaction (14–95%). Only when the (*S*)-2-methylbutylzinc hemialkoxide was heated for an additional 24 hr in the presence of the ketone did the carbinol recovered have a lower optical purity (7.7%) (run 27, Experimental Section).[19]

These overall findings and the kinetic results seem to indicate that the MPV reaction is not competing with the transfer of the β hydrogen of the alkyl group bound to the zinc atom, in the experimental conditions adopted for the asymmetric reduction investigations; therefore the stereochemical data reported in Table III are to be considered quite reliable.

In this connection, the first consideration we can make is that the trend of the asymmetric reduction of phenyl alkyl ketones by (+)-bis[(*S*)-2-methylbutyl]zinc (Table III) is similar to those encountered in the reduction of the same series of ketones by (+)-tris[(*S*)-2-methylbutyl]aluminum derivatives[6] or by (*S*)-2-methylbutylmagnesium halides.[10] Such a trend and the absolute configuration of the carbinol

recovered can be reasonably rationalized on the stereochemical model previously suggested.[20]

However, the general extent of asymmetric reduction of the phenyl alkyl ketones by (+)-bis[(*S*)-2-methylbutyl]zinc is lower than that by the corresponding optically active beryllium,[6a] magnesium,[10] or aluminum derivatives.[6c] Even if the different reaction conditions adopted in these reactions play an important role, it is our opinion that the different extent of asymmetric reduction encountered with the various alkyl metal compounds[6,10] is to be connected also with stereoelectronic factors related to the nature of the metal atom and in particular to the Lewis acid strength of the organometallic compound. Such factors should operate to make the cyclic transition states more or less loose, affecting therefore the steric interactions among the groups which are compressed.[6c]

Experimental Section

General. The alkyl phenyl ketones employed were purified through their semicarbazone derivatives. The dialkylzinc compounds were prepared as described,[13a] carefully purified by distillation under nitrogen, and stored in sealed capillary-necked glass vials in weighed amounts. All the reactions were carried out in a dry, purified nitrogen atmosphere. Glpc analyses were performed on a C. Erba Fractovap Model GT instrument, with flame ionization detectors, using 200 × 0.30 cm 10% butanediol succinate on 60–80 mesh Chromosorb W columns, operating in the range 130–160°. All rotations were taken on a Schmidt-Haensch polarimeter in 1-dm tubes. The optical purity of the carbinols recovered from the asymmetric reduction experiments were evaluated on the basis of the optical rotations of ether solutions containing both pure carbinol and appropriate amounts of the corresponding ketone.

Reactions of Alkyl Phenyl Ketones with Dialkylzinc Compounds (Runs 1–16). In a typical run *tert*-butyl phenyl ketone (3.0 mmol) was added by a 500-μl hypodermic syringe to Zn(*i*-Bu)$_2$ (3.0 mmol) contained in a 25-ml two-necked flask equipped with a Teflon stopper with a rubber septum and a glass stopcock. The reaction vessel was then placed in a thermostatted oil bath, the temperature of which was kept constant at 86.5 ± 0.3°. At intervals samples of the mixture were withdrawn by the hypodermic syringe and hydrolyzed by dilute sulfuric acid. Glpc analyses were performed directly on the ether extracts and showed ketone:carbinol ratios of 1.703, 0.613, 0.351, and 0.266 after 2, 5, 9, and 15 hr, respectively (run 13, Table II).

When 1.78 mmol of Zn(*i*-Bu)$_2$ was treated at 86.5 ± 0.3° for 72 hr with 3.25 mmol of *tert*-butyl phenyl ketone, glpc analysis on the hydrolyzed reaction mixture showed a ketone:carbinol ratio of 0.852.

Kinetic runs were carried out in a analogous manner using 5 ml of a toluene solution of diisobutylzinc and *tert*-butyl phenyl ketone of known concentrations.

Asymmetric Reductions of Alkyl Phenyl Ketones. A. Runs 17–26. The following procedure (run 24) is representative for all the experiments. To a flame-dried two-neck 100-ml flask, fitted with a magnetic stirrer, a dropping funnel, and a reflux condenser, was added 3.944 g (18.9 mmol) of (+)-bis[(*S*)-2-methylbutyl]zinc, bp 49° (0.6 mm), $[\alpha]^{25}D$ +9.91° (neat),[13] followed by 2.777 g (17.1 mmol) of *tert*-butyl phenyl ketone. The flask was then placed for 24 hr in a thermostatted oil bath at 86.5 ± 0.3°. At last the reaction mixture was cooled at 0°, diluted with anhydrous diethyl ether, and cautiously hydrolyzed with dilute sulfuric acid (pH 5). The solvent was removed and the crude product, containing the carbinol and 15.3% of the unchanged ketone, was distilled to yield 2.550 g of (−)-(*S*)-*tert*-butylphenylcarbinol (85.3% pure), bp 111° (18 mm), $\alpha^{25}D$ (l = 1) −0.36° (*c* 10.94, ether).

B. Run 27. As above, 1.411 g (6.8 mmol) of (+)-bis[(*S*)-2-methylbutyl]zinc, $[\alpha]^{25}D$ +9.91° (neat), was treated with 1.102 g (6.8 mmol) of *tert*-butyl phenyl ketone at 86.5 ± 0.3° for 48 hr. To the reaction mixture 0.739 g (4.5 mmol) of the ketone was then added and the heating was prolonged for an additional 24 hr. The product, recovered after the usual work-up and containing 64.5% of *tert*-butylphenylcarbinol together with unchanged ketone, showed $\alpha^{25}D$ (l = 1) −0.19° (*c* 10.58, ether), $[\alpha]^{25}D$ −1.79°, $[\alpha]^{25}D$ −2.77° (corrected), optical purity 7.7%.

Reaction between Bis[(*S*)-1-phenyl-2-methylpropoxy]zinc and Isopropyl Phenyl Ketone. To a 10-ml pentane solution containing 1.4 mmol of diisobutylzinc, cooled at 0°, was added 2.8 mmol of (−)-(*S*)-isopropylphenylcarbinol, $[\alpha]^{25}D$ −14.01° (c 9.37, ether). After 0.5 hr the solvent was removed at reduced pressure, and the solid mass formed was diluted with 3.0 mmol of isopropyl phenyl ketone and heated at 86.5 ± 0.3° for 24 hr. The reaction mixture was then worked up as above; the carbinol recovered (54% pure) showed $\alpha^{25}D$ (l = 2) 0.00° (*c* 12.70, ether).

When bis[(*S*)-1-phenyl-2-methylpropoxy]zinc, prepared as above, was heated at 86.5 ± 0.3° for 24 hr in the absence of the ketone, the carbinol recovered after hydrolysis showed $\alpha^{25}D$ (l = 1) −1.20°, $[\alpha]^{25}D$ −12.97° (*c* 9.25, ether).

Reaction between Bis[(*R*,*S*)-1-phenylpropoxy]zinc and *tert*-Butyl Phenyl Ketone. Bis[(*R*,*S*)-1-phenylpropoxy]zinc (5.1 mmol), prepared from Zn(*i*-Bu)$_2$ and ethylphenylcarbinol according to the above procedure, was treated with 5.1 mmol of *tert*-butyl phenyl ketone. The mixture was heated at 86.5 ± 0.3° for 24 hr, diluted with diethyl ether, and hydrolyzed to pH 5. Glpc analysis on the ether extracts revealed the presence of ethyl phenyl ketone (16%), ethylphenylcarbinol (51%), *tert*-butyl phenyl ketone (17%), and *tert*-butylphenylcarbinol (17%).

Reaction between Isobutyl[(*R*,*S*)-1-phenyl-2,2-dimethylpropoxy]zinc and Propiophenone. To 0.275 g (1.5 mmol) of diisobutylzinc was added 0.249 g (1.5 mmol) of *tert*-butyl phenyl ketone and the mixture was heated at 86.5 ± 0.3° for 48 hr until completion of the reduction reaction. To the isobutyl[(*R*,*S*)-1-phenyl-2,3-dimethylpropoxy]zinc thus obtained was successively added 0.251 g (1.5 mmol) of ethyl phenyl ketone and the heating was prolonged for 24 hr. The mixture was hydrolyzed and extracted by ether; glpc analysis on the crude reaction product showed the presence of ethylphenylcarbinol (25%) and of *tert*-butyl phenyl ketone (25%).

Acknowledgment. This work was supported by the Consiglio Nazionale delle Ricerche, Roma.

Registry No.—Zn(*i*-Bu)$_2$, 1854-19-9; (+)-bis[(*S*)-2-methylbutyl]zinc, 1731-05-1; bis[(*S*)-1-phenyl-2-methylpropoxy]zinc, 51849-39-9; bis[(*R*,*S*)-1-phenylpropoxy]zinc, 51849-40-2; isobutyl[(*R*,*S*)-1-phenyl-2,2-dimethylpropoxy]zinc, 51849-41-3.

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(17) The racemization of the optically active alkoxide groups might not occur if the MPV reaction is 100% stereoselective; this eventuality seems in effect very unprobable.[15]
(18) After 24 hr at 86.5°, in the absence of the ketone, (−)-(*S*)-isopropyl-

phenylcarbinol, optical purity 27.2%, was recovered upon hydrolysis.

(19) A control of the residual optically active 2-methylbutyl group bound to the zinc atom on the stereochemistry of the MPV reaction seems to be excluded.[17] In fact, a similar result was obtained when isobutyl[(*S*)-1-phenyl-2,2-dimethylpropoxy]zinc (optical purity 10.2%) was heated at 86.5° for 24 hr with an equivalent amount of *tert*-butyl phenyl ketone; the carbinol recovered was 7.2% optically pure.

(20) See ref 6c and 7a and references cited therein.

Silane Reductions in Acidic Media. III. Reductions of Aldehydes and Ketones to Alcohols and Alcohol Derivatives. General Syntheses of Alcohols, Symmetrical Ethers, Carboxylate Esters, and Acetamides[1a]

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Received April 29, 1974

Aldehydes and ketones are reduced by alkylsilanes to alcohols in aqueous acidic media; both concentrated hydrochloric acid and aqueous sulfuric acid are suitable aqueous acids. A nonreactive solvent such as acetonitrile or ethyl ether is required to minimize ether formation. Symmetrical ethers are formed by silane reductions of aldehydes and ketones in anhydrous acidic solutions under conditions where acid-catalyzed alcohol dehydration does not occur. Carboxylate esters and symmetrical ethers are formed by silane reductions of aldehydes and ketones in carboxylic acid media. Low temperatures and a low concentration of carboxylic acid favors the production of symmetrical ether; ester formation is favored in the reductions of ketones and in reductions using carboxylic acids comparable in acid strengths to formic and acetic acids. In acetonitrile using aqueous sulfuric acid silane reductions of ketones and aryl aldehydes yield N-substituted acetamides. The optimum reaction conditions and limitations of these reactions are described. Evidence concerning the mechanism of these interrelated reactions is presented and discussed.

In recent years silanes have received increased interest as reducing agents for organic compounds. Organosilanes are nonpolar liquids or solids, soluble in a wide range of organic solvents, and stable to strong bases and strong acids, except concentrated mineral acids.[2] Like the boron and aluminum hydrides, silicon hydrides are polarized with a greater electron density at hydrogen than at silicon; hydride transfer from silicon to electropositive carbon is thermodynamically favorable.[3] Unlike reductions by the boron and aluminum hydrides which require no external acid catalyst, however, organosilanes require activation of the carbon center by a Lewis acid before hydride transfer can occur.

Few reducing agents are as selective as organosilanes toward the carbonyl group of aldehydes and ketones. We have previously reported that reduction of the carbonyl group of aryl aldehydes and ketones to methylene in trifluoroacetic acid occurs without concurrent reduction of the carboxylic acid, carboxylate ester, cyano, nitro, or bromide functional groups.[1a] Olefins and alcohols are reduced to hydrocarbons in acidic media only if a relatively stable carbenium ion intermediate can be formed.[4] Terminal arylacetylenes are reduced in low yield to the corresponding alkane by triethylsilane in trifluoroacetic acid;[5] however, reaction times are long and acid-catalyzed solvation of the carbon–carbon triple bond may have preceded reduction by the silane.

Excluding photochemical reductions involving silanes,[6] three methods, trichlorosilane–tertiary amine reductions, zinc chloride catalyzed reductions, and reductions in trifluoroacetic acid, have had the widest application for reductions of aldehydes and ketones. Benkeser has used trichlorosilane–tertiary amine combinations to effect reductive silylation of aromatic aldehydes and ketones;[7] this reaction probably involves the trichlorosilyl anion[7b] and is, at present, generally applicable only to nonenolizable carbonyl compounds. With trialkylsilanes, however, reactions catalyzed by zinc chloride and leading to either the corresponding symmetrical ether and alkyl silyl ether with aldehydes or to the alkyl silyl ether with ketones appear to have no such limitation for enolizable carbonyl compounds.[8] Kursanov and coworkers have reported several examples of triethylsilane reductions of aldehydes and ketones in trifluoroacetic acid;[4a,9] aldehydes are reduced to the corresponding symmetrical ethers and trifluoroacetates while ketones are reduced to trifluoroacetate esters. We wish to report that aldehydes and ketones can be selectively reduced by organosilanes to alcohols, carboxylate esters, symmetrical ethers, or acetamides by suitable changes in the reaction media.

Results

Preparation of Alcohols. Although trifluoroacetate esters, formed by silane reduction of aldehydes and ketones in trifluoroacetic acid,[4a,9] and alkyl silyl ethers, formed from aldehydes and ketones by silane reduction with zinc chloride catalysis,[8] are readily hydrolyzed to the corresponding alcohols under relatively mild conditions, these methods offer little advantage over existing reduction methods for the preparation of simple alcohols. In addition, the production of symmetrical ethers from aldehydes in a competitive process further complicates the reduction process. Even though alcohols may be the primary products in these reactions, there has been no report of a direct and general method for the synthesis of alcohols from aldehydes and ketones by silane reduction. We have found, however, that silane reductions can be directed to form alcohols if water is added to the reaction medium (eq 1).

$$R_2C{=}O + R'_3SiH + H_2O \xrightarrow{H^+} R_2CHOH + R'_3SiOH \quad (1)$$

The product composition from the reductions of representative aldehydes and ketones by triethylsilane in aqueous acidic media is given in Table I. (Additional data on benzaldehyde are summarized in supplementary material; see paragraph at end of paper). Triethylsilanol was either

Table I
Triethylsilane Reductions of Aldehydes and Ketones in Aqueous Acidic Media[a]

Carbonyl compd (mmol)	Registry no.	Et_3SiH, mmol	Solvent (ml)	Acid[b] (ml)	H_2O, ml	Reaction time,[c] hr	Yield, %[d] R_2CHOH	Yield, %[d] $(R_2CH)_2O$	Yield, %[d] Other[c]
C_6H_5CHO (9.9)	100-52-7	11.2	CH_3CN (5.0)	HCl (1.0)		3.5	88	6	6[f]
C_6H_5CHO (5.0)		5.5	CH_3CO_2H (2.5)	HCl (1.0)		4.0	9	3	88[g]
C_6H_5CHO (5.0)		6.4	CH_3CN (2.5)	H_2SO_4 (1.0)		1.0	0	50	50[h]
C_6H_5CHO (5.1)		6.2	CH_3CN (2.5)	H_2SO_4 (2.0)	1.0	1.25	32	27	41[h]
C_6H_5CHO (5.0)		6.3	CH_3CN (2.5)	H_2SO_4 (1.0)	1.0	1.25	88	12	0
C_6H_5CHO (5.0)		6.3	CH_3CN (2.5)	H_2SO_4 (0.5)	1.0	24	96	4	0
C_6H_5CHO (5.0)		6.4	Sulfolane (2.5)[i]	H_2SO_4 (0.5)	1.0	32	98	2	0
Cyclohexanone (5.0)	108-94-1	5.5	CH_3CN (2.5)	HCl (2.0)		2.5	100	0	0
Cyclohexanone (20.0)		25.1	CH_3CN (10)	H_2SO_4 (4.0)	4.0	1.5	100	0	0
$(CH_3)_2CO$ (5.1)	67-64-1	5.6	CH_3CN (2.5)	HCl (2.0)		2.5	100	0	0
$CH_3(CH_2)_5CHO$ (5.0)	111-71-7	5.6	CH_3CN (2.5)	HCl (2.0)		3.0	100	0	0
$CH_3(CH_2)_5CHO$ (10.1)		12.6	CH_3CN (5.0)	H_2SO_4 (2.0)	2.0	1.25	97	3	0
2-Ethylhexanal (20.1)	123-05-7	25.0	CH_3CN (10)	H_2SO_4 (4.0)	4.0	2.0	90	10	0
$(CH_3)_3CCOCH_3$ (20.0)	75-97-8	25.0	CH_3CN (10)	H_2SO_4 (4.0)	4.0	1.2	100	0	0
$(C_6H_5)_2CO$ (20.0)	119-61-9	50.2	CH_3CN (10)	H_2SO_4 (4.0)	4.0	72	0	0	100[j]

[a] Reactions were run at room temperature (28 ± 3°). Carbonyl compounds, acids, and triethylsilane were commercially available and used without prior purification. Reaction mixtures were heterogeneous. [b] Concentrated hydrochloric acid (37–38% by weight); trifluoroacetic acid (99+%); concentrated sulfuric acid (96.8% by weight). [c] Time at which reaction solution was analyzed; does not necessarily reflect required reaction time. [d] Relative yields of products based on pmr analyses using an internal standard. Greater than 80% recovery of products was obtained. Analyses prior to work-up showed no difference between absolute and relative yields of products. Unless noted otherwise, complete reduction of the carbonyl compound was observed. [e] Product identified by pmr and/or glpc analyses. [f] Approximately equal amounts of benzyl chloride and benzyl acetate. [g] Benzyl acetate. [h] *N*-Benzylacetamide. [i] Reaction solution was homogeneous. [j] 17% diphenylmethane + 83% unreacted benzophenone. Attempted reduction using concentrated hydrochloric acid gave similar results.

the only or the major silane product in these reactions; hexaethyldisiloxane was present in only minor amounts. Both concentrated hydrochloric and aqueous sulfuric acids were satisfactory for alcohol production with a minimum of side reactions. Greater than 1 molar equiv of hydrochloric acid, compared to the carbonyl compound, was used for the reactions described in Table I. When less than 1 molar equiv of hydrochloric acid (0.5 equiv) was used, reduction did occur but was slow; only 30% reduction occurred over a 20-hr period.

Although all mixtures of sulfuric acid and water between 96 and 20% aqueous sulfuric acid (by volume) were sufficiently acidic to effect reduction by triethylsilane, long reaction times were necessary in 20% aqueous sulfuric acid (>48 hr) and the yield of alcohol was low when the ratio of water to sulfuric acid was less than that in 50% aqueous sulfuric acid. The optimum molar ratio of water to sulfuric acid used for reductions of carbonyl compounds to alcohols was between 6.3 and 3.3 (33–50% aqueous sulfuric acid).

An interfacing nonhydroxylic organic solvent is a necessary requirement for the production of alcohols from aldehydes and, to a lesser extent, from ketones. When either benzaldehyde or heptanal was reduced by triethylsilane using 50% aqueous sulfuric acid at room temperature without added organic solvent, the corresponding symmetrical ether was formed as the sole or major product. Cyclohexanone was reduced to cyclohexanol with cyclohexyl ether formed as a minor product when no organic solvent was used. When benzaldehyde was reduced by triethylsilane using concentrated hydrochloric acid, benzyl alcohol was converted to benzyl chloride; the formation of benzyl chloride was minimized when acetonitrile was employed as a reaction solvent.

Acetonitrile and sulfolane were satisfactory as interfacing solvents. However, no reduction of benzaldehyde occurred over a 3-hr period when either benzene or dimethylformamide was used. Although relative product yields were not changed by varying the amount of nonhydroxylic organic solvent with respect to the aqueous acid, reaction times were lengthened as more organic solvent was used. With acetonitrile reaction times were less than 1 hr when the volumes of acetonitrile and aqueous acid were approximately equal; doubling the volume of acetonitrile over that of the aqueous acid increased reaction times to approximately 3 hr. When the hydroxylic solvent, acetic acid, was used in the reduction of benzaldehyde by triethylsilane with hydrochloric acid, benzyl acetate was formed in greater than 80% yield. Aqueous trifluoroacetic acid or an acetonitrile solution of aqueous trifluoroacetic acid led to the production of the trifluoroacetate product as a major competing process.

Benzophenone was reduced at a much slower rate than either benzaldehyde or the aliphatic aldehydes and ketones, and only diphenylmethane was produced. Benzhydrol is apparently reduced at a faster rate than benzophenone.[1a] 9,10-Anthroquinone was not reduced in 50% aqueous sulfuric acid media.

That the acidic conditions used for these reductions are not sufficiently strong to ionize the alcohols produced from aliphatic aldehydes and ketones is shown by the production of 3,3-dimethyl-2-butanol without rearrangement from 3,3-dimethyl-2-butanone using 50% aqueous sulfuric acid (Table I). Similarly, 2-ethyl-1-hexanol did not rearrange under the reaction conditions employed.

We have previously described suitable methods for the isolation of organic reduction products from silane products.[1a] Ketones may be reduced by an alternate procedure using *n*-butylsilane as the reducing agent and ethyl ether as the interfacing solvent. The silane product is a polymeric siloxane from which the alcohol can be conveniently distilled following simple extraction procedures. Using this latter method cyclohexanol was isolated in 56% yield and cyclooctanol in 78% yield following reduction of the respective ketone; analysis prior to work-up showed that the alcohol was the only organic product. Aldehydes are reduced primarily to symmetrical ethers when *n*-butylsilane is used; for example, octanal was reduced to an alcohol–ether mixture from which 1-octanol was isolated in 31% yield and 1-octyl ether in 61% yield. Tetramethyldisiloxane similarly reduced octanal to a mixture of 1-octanol and 1-octyl ether.

Table II
Triethylsilane Reductions of Aldehydes and Ketones in Carboxylic Acid Media[a]

Carbonyl compd (mmol)	Registry no.	Et_3SiH, mmol	R''COOH (mmol)	Solvent (ml)	Reaction time,[b] hr	Yield,[c] % $(R_2CH)_2O$	Yield,[c] % $R_2CHOOCR$	Other[d]
C_6H_5CHO (20.0)		24	CF_3CO_2H (30)		0.50	87	13	0
C_6H_5CHO (2.5)		2.8	CF_3CO_2H (25)	$CHCl_3$ (2.5)	0.25	93	7	0
C_6H_5CHO (2.5)		2.8	CF_3CO_2H (25)	CCl_4 (2.5)	0.25	89	11	0
C_6H_5CHO (2.5)		2.6	CF_3CO_2H (5.0)	CCl_4 (2.5)	24	49	51	0
C_6H_5CHO (2.5)		2.8	CF_3CO_2H (5.0)	CH_3CN (2.5)	0.25	96	4	0
C_6H_5CHO (2.5)		2.8	Cl_2CHCO_2H (15)		0.5	93	7	0
C_6H_5CHO (2.5)		2.8	HCO_2H (35)		8	12	88	0
C_6H_5CHO (2.5)		2.8	CH_3CO_2H (23)		5	8	27	65[e]
p-$NO_2C_6H_4CHO$ (5.0)	555-16-0	11.0	CF_3CO_2H (55)		5	33	67	0
p-ClC_6H_4CHO (5.0)	104-88-1	11.0	CF_3CO_2H (55)		10	80	20	0
p-$CH_3C_6H_4CHO$ (5.0)	104-87-0	30	CF_3CO_2H (12.5)	CH_2Cl_2 (2.5)	6	81	17	2[f]
					118	70	22	8[f]
p-$NO_2C_6H_5COCH_3$ (5.0)	100-19-6	30	CF_3CO_2H (50)	CCl_4 (2.5)	22	7	93	0
1-Naphthaldehyde (5.0)	66-77-3	30	CF_3CO_2H (12)		1.5[h]	67	33	0
2-Naphthaldehyde (5.0)	66-99-9	30	CF_3CO_2H (12)		18	84	16	0
$C_6H_5COCH_2Br$ (2.5)	70-11-1	6.3	CF_3CO_2H (50)		0.25	5	80	15[g]
					44	0	12	88[g]
$(CH_3)_2CO$ (5.0)		5.5	CF_3CO_2H (100)		1.3	32	68	0
Cyclohexanone (5.0)		5.5	CF_3CO_2H (100)		1.5	25	75	0
Cyclohexanone (1.0)		1.0	CF_3CO_2H (3.0)		1.0	42	58	0
$CH_3(CH_2)_5CHO$ (5.0)		5.5	CF_3CO_2H (100)		0.75	90	10	0
$CH_3(CH_2)_{10}CHO$ (20)	112-54-9	20	CF_3CO_2H (50)		16[h]	93	7	0

[a] Reactions were run at room temperature (28 ± 3°) unless specified otherwise. Reaction solutions were homogeneous. [b] Time at which reaction solution was analyzed; does not necessarily reflect required reaction time. [c] Relative yields of products based on pmr analyses using an internal standard. [d] Product identified by pmr and/or glpc analyses. [e] Unreacted benzaldehyde. [f] p-Xylene and small amount of Friedel–Crafts alkylation product. [g] β-Phenylethyl bromide. [h] Reaction run at 0°.

Reductions by n-butylsilane in aqueous acidic media require 0.33 mol of silane per mole of carbonyl compound. In aqueous acidic media initial hydride transfer from n-butylsilane is slow compared to subsequent hydride transfer reactions from soluble silane compounds. An equivalent excess of n-butylsilane was usually added, however, because insoluble polymeric hydrosiloxane formed during the reaction, noticeably decreasing the rate of further reduction of aldehydes or ketones, and because n-butylsilane slowly hydrolyzed in the aqueous sulfuric acid media.

Formation of Symmetrical Ethers and Carboxylate Esters. When aldehydes or ketones are reduced in acidic media, symmetrical ethers are formed in competition with the desired product.[4a,8,9] In reactions in which a carboxylic acid is used both the unsymmetrical ether and carboxylate ester are produced (eq 2). Table II describes the results

$$R_2C{=}O + R'_3SiH + R''COOH \longrightarrow R_2CHOCHR_2 + R_2CHOOCR'' + R'_3SiOOCR'' + R_3'SiOSiR_3' \quad (2)$$

from the reductions of aldehydes and ketones by triethylsilane in carboxylic acid media. Ethers are not formed from alcohols under the reaction conditions reported in Table II. The relative yield of symmetrical ether is greater in the reductions of aldehydes than in the reductions of ketones under similar reaction conditions. For example, heptanal yields 90% of 1-heptyl ether and 10% of 1-heptyl trifluoroacetate, whereas cyclohexanone gave 75% of cyclohexyl trifluoroacetate and only 25% of cyclohexyl ether when triethylsilane reductions were performed in trifluoroacetic acid.

In the reductions of para-substituted benzaldehydes in trifluoroacetic acid media the relative yield of the symmetrical ether increased with the electron-donating ability of the substituent in the order p-NO_2 (32%) < p-Cl (80%) < H (89%). Under the reaction conditions employed the ether and trifluoroacetate were not interconverted. With aryl aldehydes having para-substituted electron-donating groups such as methyl, however, the symmetrical ether was converted to the trifluoroacetate, and the trifluoroacetate was reduced to the corresponding hydrocarbon.[1a]

Acids whose acidity constants are greater than that of acetic acid can be used as solvents as well as the proton source in the reductions of carbonyl compounds by triethylsilane at room temperature. Acetic acid is effective in causing reduction only at steam bath temperatures; no reduction occurred over a 12-hr period in acetic acid at room temperature. Increasing the basicity of the carboxylic acid also increases the relative proportion of carboxylate ester to symmetrical ether; whereas only 19% benzyl trifluoroacetate is produced in the reduction of benzaldehyde in trifluoroacetic acid, 88% benzyl formate formed in the corresponding reduction in 97% formic acid. With trifluoroacetic and stronger acids the acid need not be used as the solvent; reductions occurred in carbon tetrachloride or acetonitrile using 1–2 equiv of trifluoroacetic or p-toluenesulfonic acids. Reduction of benzaldehyde (2.5 mmol) by triethylsilane (2.8 mmol) using 1 equiv of p-toluenesulfonic acid in acetonitrile (2.5 ml) gave benzyl ether (70%), benzyl alcohol (18%), and benzyl p-toluenesulfonate (12%). Both reaction times and the relative yields of symmetrical ether are, however, dependent on the amount of acid present.

In the reduction of benzaldehyde by triethylsilane in dilute trifluoroacetic acid the symmetrical ether is formed as the sole or major product during the first half-life; benzyl trifluoroacetate is produced later in the reduction (Figure 1). Benzyl alcohol and benzyl triethylsilyl ether are present during the reaction and the sum of their yields remains constant throughout the second half-life. Under the reaction conditions employed benzyl ether is not formed from benzyl alcohol, benzyl trifluoroacetate, or benzyl triethylsilyl ether. Nearly identical results were obtained when tri-n-hexylsilane was used as the reducing agent.

As shown by the data in Table II, symmetrical ethers of aldehydes can be conveniently prepared in good yields by triethylsilane reductions in trifluoroacetic acid media. With the exception of the p-nitrobenzaldehyde, aryl aldehydes form symmetrical ethers in greater than 80% yield.

Table III
Reductions of Cyclohexanone in Trifluoroacetic Acid[a]

Temp, C°	Cyclohexanone, mmol	*n*-BuSiH$_3$, mmol	CF_3CO_2H, mmol	Reaction time,[b] hr	Yield,[c] % Ether	Yield,[c] % Trifluoroacetate
55	2.0	1.0	12.0	3.5	38	62
55	2.0	1.0	5.0	1.5	47	53
25	1.0	0.5	3.0	24	49	51
0	2.0	1.0	12.0	3.5	60	40
0	2.0	1.0	6.0	24	67	33
−15	30	15	90	25	82	18
−15[d]	40	20	100	72	90	10

[a] Reaction solutions were homogeneous. [b] See footnote *b*, Table II. [c] See footnote c, Table II. [d] Acid added slowly over a 1-hr period. Cyclohexyl ether was isolated in 80% yield.

Table IV
Triethylsilane Reductions of Aldehydes and Ketones in Acetonitrile Mixtures with Aqueous Sulfuric Acid[a]

Carbonyl compd	Registry no.	Reaction time, hr	Amide product	Relative yield, %[b]	Isolated yield, %[c]
Benzophenone		48	*N*-(Diphenylmethyl)-acetamide	85[d]	63
Acetophenone	98-86-2	72	*N*-(1-Phenylethyl)-acetamide	100	85[e]
Benzaldehyde		74	*N*-Benzylacetamide	89[f]	80
Cyclohexanone		72	*N*-Cyclohexylacetamide	50[g]	30
Norcamphor	497-38-1	65	*N*-(*exo*-Bicyclo[2.2.1]hept-2-yl)acetamide	90[h]	78
Octanal	124-13-0	72		0[i]	

[a] Reactions were run at room temperature (28 ± 3°) using 60 mmol of the aldehyde or ketone, 66 mmol of triethylsilane, 9.0 ml of concentrated sulfuric acid, 3.0 ml of water, and 15 ml of acetonitrile. [b] Of the amide product. [c] Of the purified amide product after recrystallization. [d] 15% diphenylmethane. [e] Average of two reactions. [f] 11% benzyl ether. [g] 50% of a mixture of cyclohexyl ether and cyclohexanol. [h] 10% of the symmetical ether was detected. [i] Only 1-octanol and 1-octyl ether were observed.

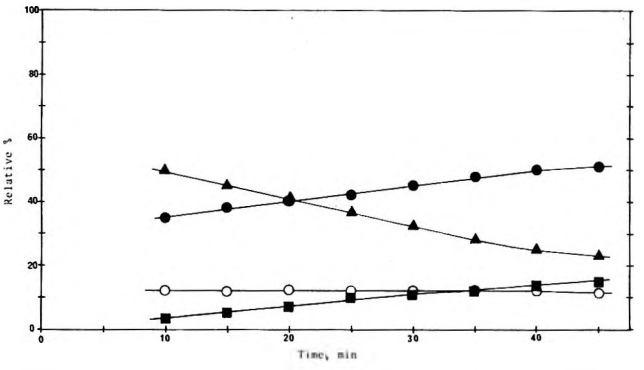


Figure 1. Relative percentages of benzaldehyde (▲), benzyl ether (●), benzyl trifluoroacetate (■), and the sum of benzyl alcohol and benzyl triethylsilyl ether (○) *vs.* time from the reduction of benzaldehyde by triethylsilane in carbon tetrachloride containing trifluoroacetic acid (2 equiv).

p-Toluyl ether was formed in 91% yield when *p*-tolualdehyde (5.0 mmol) was reduced at room temperature by triethylsilane in acetonitrile (2.5 ml) using a small amount of concentrated sulfuric acid (0.25 molar equiv); competitive production of *p*-xylene[1a] was minimized under these conditions. Symmetrical ethers of aldehydes were isolated by conventional methods: 2-naphthyl ether was isolated in 80% yield by crystallization, and benzyl ether (88%), *n*-heptyl ether (70%), and *n*-dodecyl ether (82%) were distilled from silane products.

Silane reductions of ketones do not favor the formation of symmetrical ethers under reaction conditions where aldehydes yield predominantly ether products. Previous reports of silane reductions of ketones indicate an overwhelming preference for trifluoroacetate derivatives when the reductions are performed in trifluoroacetic acid,[4a,9] or for alkyl silyl ethers when Lewis acid catalysts are used.[8] We have found, however, that reduction of cyclohexanone by *n*-butylsilane in trifluoroacetic acid at −15° produces cyclohexyl ether as the predominant product. The effects of changes in temperature, silane, and the amount of trifluoroacetic acid on the relative yields of products from cyclohexanone reductions are given in Table III. Concentrated sulfuric acid, even when only 1 molar equiv was used, hydrolyzed the silane and gave complex mixtures of products. In addition to the preference for ether production when *n*-butylsilane is used, this silane forms a polymeric siloxane from which the ether is conveniently separated. Cyclohexyl ether was isolated in 80% yield from the reduction of cyclohexanone by *n*-butylsilane at −15°.

When carboxylate esters are the desired reaction products, silane reduction of the carbonyl compound in the presence of a carboxylic acid gives the ester directly when a mineral acid catalyst is used (Table I). Modification of these reaction conditions may be useful in preparing other alcohol derivatives and alkyl halides in one step from an aldehyde or ketone.

Poly(methylsiloxane) (PMS) was unsuitable as a reducing agent in attempts to produce symmetrical ethers from aldehydes. Under reaction conditions that gave high yields of symmetrical ethers in rapid reductions of heptanal and dodecanal by triethylsilane, reduction by PMS was slow and gave mixtures of alcohol and ether.

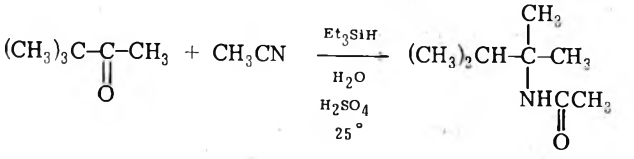
Preparation of Acetamides. Reductions of ketones and aryl aldehydes by triethylsilane in acetonitrile using aqueous sulfuric acid give N-substituted acetamides in good yields (eq 3) and provide a convenient method for the introduction of an amino functionality onto a hydrocarbon skeleton. Yields of products from reductions of representative carbonyl compounds are given in Table IV. Only ali-

$$R_2C{=}O + Et_3SiH + CH_3C{\equiv}N + H_2O \xrightarrow{H^+} R_2CHNHCOCH_3 + Et_3SiOSiEt_3 \quad (3)$$

phatic aldehydes did not form amides under the reaction conditions used. Significantly lower isolated yields of amide products (15–20%) were obtained when the reactions were run in 67% aqueous sulfuric acid rather than in the 75% aqueous sulfuric acid solutions reported in Table IV.

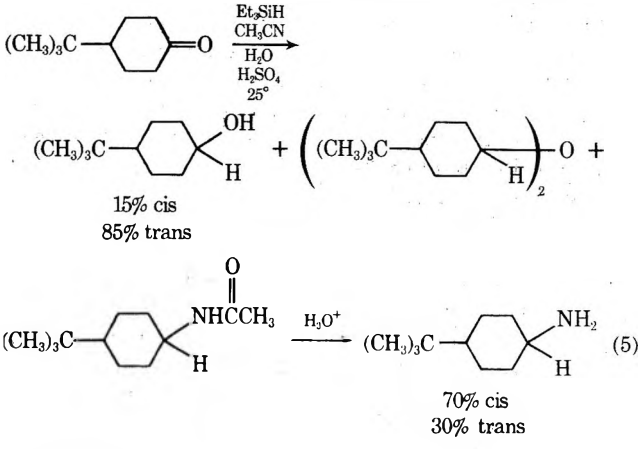
The acetonitrile solution of aqueous sulfuric acid is suitable to convert alcohols to acetamides by the Ritter reaction.[10] Under the same reaction conditions used for the reductive transformation of carbonyl compounds to acetamides, but without added silane, benzyl alcohol and *exo*-bicyclo[2.2.1]heptan-2-ol gave *N*-benzylacetamide and *N*-(*exo*-bicyclo[2.2.1]hept-2-yl)acetamide in 71 and 73% isolated yield, respectively. Cyclohexanol gave a mixture of *N*-cyclohexylacetamide (16%) and cyclohexyl ether (18%) indicating both incomplete reaction and competitive formation of symmetrical ether. The reaction conditions employed are milder than those generally used for the Ritter reaction[11] and, with the exception of cyclohexanol in this study, are preferable for acetamide formation.

Only the rearranged product was observed when 3,3-dimethyl-2-butanone was reduced by triethylsilane in an acetonitrile solution of aqueous sulfuric acid (eq 4), indi-



67% (4)

cating that reduction precedes the Ritter reaction and that the alcohol produced by silane reduction (see Table I) undergoes carbon-skeleton rearrangement in the formation of the acetamide product. Under the same reaction conditions described in Table IV for cyclohexanone, 4-*tert*-butylcyclohexanone gave a mixture of products (eq 5) con-



15% cis
85% trans

70% cis
30% trans (5)

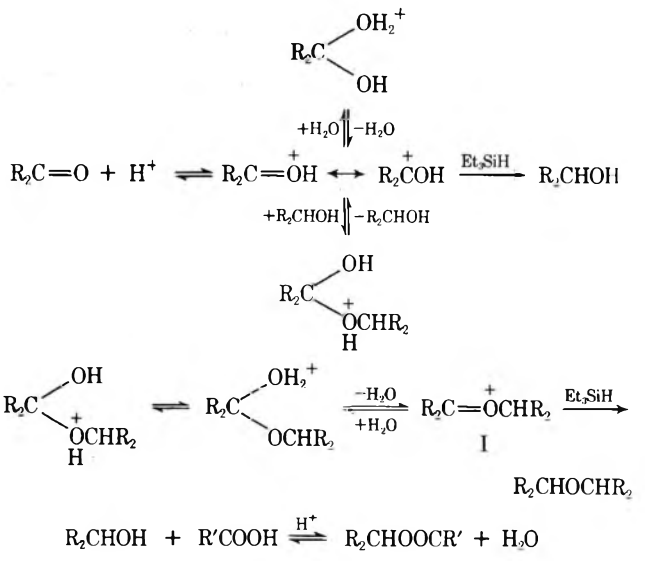
sisting of 4-*tert*-butylcyclohexene (4%), unrearranged alcohols and symmetrical ethers (70%), and acetamides (21%). The ratio of cis to trans alcohol was 15:85; and all stereochemical combinations of ethers, cis,cis, cis,trans, and trans,trans, were observed. Hydrolysis of the isomeric *N*-(4-*tert*-butylcyclohexyl)acetamides gave the corresponding amines.

Discussion

In acidic media aldehydes and ketones are converted by silane reduction to alcohols, symmetrical ethers, unsymmetrical ethers,[12] carboxylate esters, or acetamides in good yields. The nature of the product is highly dependent on the reaction conditions used for the reduction. In aqueous acidic solutions alcohols are formed when a solvent such as acetonitrile, sulfolane, or ethyl ether is used; unsymmetrical ethers predominate in alcoholic acidic media.[12] Symmetrical ethers form in competition with alcohols in aqueous acidic media and in competition with carboxylate esters in carboxylic acid solutions.

The interrelated processes for alcohol, carboxylate ester, and ether formation can be explained by the mechanism described in Scheme I. Reduction occurs in acidic media even when less than an equivalent amount of acid is employed. When a sufficient amount of water is present in the reaction medium, the protonated carbonyl compound is present in equilibrium with its hydrate; under such conditions the alcohol is the predominant reaction product. When the amounts of mineral acid and water are comparable, the yield of alcohol reflects the molar excess of water; thus, when benzaldehyde is reduced by triethylsilane using sulfuric acid (Table I) no alcohol was formed when concentrated sulfuric acid was used, 32% benzyl alcohol was produced when the molar ratio of water to sulfuric acid was 1.5:1.0 (67% aqueous sulfuric acid), and with the molar ratio of water to sulfuric acid at 3.0:1.0, the relative yield of benzyl alcohol was 88%. Comparable results for alcohol formation were obtained with concentrated hydrochloric acid and aqueous sulfuric acid at similar molar ratios of water to acid.

Scheme I



Ether formation is explained by reduction of the oxonium ion (I) formed from the nucleophilic addition of alcohol to the protonated carbonyl compound followed by elimination of a molecule of water. Such as intermediate, formed independently, has been reduced by trialkylsilanes to a symmetrical ether.[13]

In carboxylic acid media the production of carboxylate ester competes with symmetrical ether formation. The relative yields of ether and ester formed in the reduction of substituted benzaldehydes in trifluoroacetic acid reflects the relative basicity of the carbonyl compound. The yield of symmetrical ether increases with decreasing acidity of the conjugate acid of para-substituted benzaldehydes: *p*-$NO_2C_6H_4CHO$ ($pK_a = -8.45$,[14] 32% ether), *p*-ClC_6H_4CHO ($pK_a = -7.26$,[14] 80% ether), and C_6H_5CHO ($pK_a = -7.10$,[14] 89% ether). Additionally, ether formation is favored over the formation of trifluoroacetate esters in polar solvents; the relative yield of benzyl ether from the reduction of benzaldehyde using limited amounts of trifluoroacetic acid was 49% in carbon tetrachloride and 96% in acetonitrile (Table II). These results are consistent with the involvement of I in the production of symmetrical ethers; the

mechanism of esterification does not involve a comparable substituent-sensitive intermediate.[15]

Ether formation is also sensitive to steric effects. Despite the greater basicity of ketones compared to aldehydes,[16] aldehydes gave higher relative yields of symmetrical ethers than did ketones under comparable reaction conditions. Additionally, 1-naphthaldehyde ($pK_a = -6.34$)[17] gave 67% of the corresponding symmetrical ether whereas the less basic 2-naphthaldehyde ($pK_a = -6.68$)[17] yielded 84% of the less sterically hindered symmetrical ether.

The necessity of using a reaction solvent such as acetonitrile to prevent ether formation in the preparation of alcohols can be explained as being due to the insolubility of the carbonyl compound, alcohol, and triethylsilane in the aqueous solution. The reaction solvent provides a medium for protecting the alcohol product from nucleophilic addition to the carbonyl group leading to ether formation. In *N,N*-dimethylformamide protonation of the amide[16] prevents protonation of the carbonyl group.

The results obtained from the reduction of benzaldehyde by triethylsilane using trifluoroacetic acid (Figure 1) show that the rate of symmetrical ether formation from aldehydes is rapid compared to ester formation during the first half-life. Only as the concentration of the aldehyde decreases in the second half-life does ester formation become important. Since the amount of benzyl alcohol and benzyl triethylsilyl ether remains relatively constant with time as the yields of both benzyl ether and benzyl trifluoroacetate increase, the rate of hydride transfer to I must be at least as fast as the corresponding reduction of protonated benzaldehyde.[18]

In ketone reductions steric factors decrease the relative rate of ether formation compared to ester formation. The production of symmetrical ethers is favored by low temperatures and a low concentration of acid (Table III). The effect of acid concentration on the relative yield of ether in silane reductions in trifluoroacetic acid is not nearly so dramatic in aldehyde reductions as in ketone reductions.

One advantage of silane reductions of carbonyl compounds in acidic media is that the alcohol product can be made to undergo subsequent acid-catalyzed reactions in the same reaction medium. This potential for use in organic synthesis is evident in the formation of carboxylate esters from aldehydes and ketones and is indicated by the formation of benzyl chloride in the reduction of benzaldehyde by triethylsilane using concentrated hydrochloric acid. The versatility of this reduction method is shown by the coupling of the Ritter reaction to the silane reduction reaction in the preparation of acetamides from ketones and aryl aldehydes.

Silane reduction precedes the Ritter reaction. Those alcohols formed by reduction that normally undergo the Ritter reaction[10] form N-substituted amides in the coupled sequence. Water is necessarily used in the reaction medium to favor the formation of alcohol rather than ether in the reduction reaction; without water ether formation becomes an important process (Table I). The concentration of sulfuric acid is higher than that normally used for alcohol formation in silane reductions of aldehydes and ketones.

Structural rearrangement is observed in the formation of amides in the silane reduction–Ritter reaction sequence. The reaction conditions employed, however, do not favor the extensive degree of rearrangement observed when concentrated sulfuric acid is used. We find that 4-*tert*-butylcyclohexanone gives *N*-(4-*tert*-butylcyclohexyl)acetamide without rearrangement in 75% aqueous sulfuric acid; 4-methylcyclohexanol, on the other hand, has been shown to yield only rearranged products in the Ritter reaction in concentrated sulfuric acid.[19]

The reduction of 4-*tert*-butylcyclohexanone by triethylsilane using aqueous sulfuric acid under milder conditions than those reported for acetamide formation gave 4-*tert*-butylcyclohexanol in an isomeric distribution of 30% cis and 70% trans alcohol. This isomeric distribution does not noticeably change when the acid strength is varied.[18] The ratio of isomeric amines formed by hydrolysis of the corresponding amides is, however, significantly different from the isomeric ratio of alcohols. Although only one experiment is reported here, the results indicate that the cis alcohol reacts faster in the Ritter reaction than the trans alcohol and that axial attack by acetonitrile is preferred over equitorial attack in the formation of *N*-(4-*tert*-butylcyclohexyl)acetamides. The greater reactivity of *cis*-4-*tert*-butylcyclohexylderivatives has been previously observed in solvolytic studies.[20] The preference for axial bond formation in reactions of 4-*tert*-butylcyclohexyl cations has also been described.[21]

Experimental Section

General. Instrumentation has been previously described.[22] Use was made of 10-ft columns of 10% Carbowax 20M and 5-ft columns of 20% Carbowax 20M on Chromosorb P and 5-ft columns of 3% SE-30 on Varaport 30. Melting points and boiling points were uncorrected. Aldehydes, ketones, tri-*n*-hexylsilane, tetramethyldisiloxane, and triethylsilane, were commercially available and used without further purification. Triethysilanol and hexaethyldisiloxane were prepared by conventional methods.[2,23]

***n*-Butylsilane** was prepared by lithium aluminum hydride reduction of commercially available *n*-butyltrichlorosilane. *n*-Butyltrichlorosilane (192 g, 1.00 mol) was added dropwise over a 1.5-hr period to an ice-water bath cooled mixture of lithium aluminum hydride (36.0 g, 0.95 mol) in 350 ml of *n*-butyl ether. The constantly stirred mixture was contained in a 1-l., three-necked flask equipped with a condenser, drying tube, addition funnel, and mechanical stirrer. After addition was complete the flask was warmed to room temperature, and stirring was continued for an additional 1 hr. Distillation through a 2-ft Vigreux column gave 80.5 g (0.91 mol, 91% yield) of *n*-butylsilane, bp 55–58°. Redistillation gave *n*-butylsilane with bp 54–56° (lit.[24] bp 56°); pmr (neat) δ 3.53 (t, 3 H), 1.65–1.1 (m, 4 H), and 1.1–0.5 (m, 5 H); ir (neat) 2130 cm^{-1} (Si–H stretch).

Triethylsilane Reductions of Aldehydes and Ketones in Aqueous Acidic Media. In a typical reaction the carbonyl compound and triethylsilane were weighed into a round-bottom flask, and the appropriate amount of organic solvent was added. The premixed acid–water solution was then slowly added to the reaction flask at room temperature. Stirring was effected at a uniform and rapid rate using a magnetic stirrer. The reaction was allowed to proceed at room temperature. For all experiments in which aqueous mineral acid-acetonitrile or sulfolane was used the reaction mixture was heterogeneous. With the exception of anthroquinone the carbonyl compounds were soluble in the reaction media. An aliquot of the reaction solution was removed for pmr analysis prior to work-up to determine the extent of reduction. This aliquot generally yielded the same results for relative product yield as analysis of the product mixture after work-up, indicating that the work-up procedure did not selectively retain or remove a particular reduction product.

After reduction was complete the reaction solution was diluted with 25 ml of a saturated sodium chloride solution, and 25 ml of ether was added. The resultant layers were separated after thorough mixing, and the aqueous solution was washed twice with 25-ml portions of ether. The combined ether solution was washed with 25-ml portions of water and saturated sodium bicarbonate and was passed through anhydrous magnesium sulfate. The ether was removed by distillation at atmospheric pressure. Isolated yields of reduced products averaged 80% in small-scale reductions (5–10 mmol). Silane products were not separated from the organic products by this extraction method.

Each product mixture was analyzed from its pmr spectrum; yields were calculated from averaged integrations of proton absorptions by comparison to an internal standard. Reproducibility was shown to be ±2% in duplicate runs. The yields of products for several reactions were also obtained by glpc analysis; these results were nearly identical with those obtained by pmr analysis. Prod-

Table V
Reduction of Benzaldehyde by Tri-*n*-hexylsilane in Carbon Tetrachloride–Trifluoroacetic Acid at 40°

	Relative % yield			
Time, min	C_6H_5CHO	$C_6H_5CH_2O_2CCF_3$	$(C_6H_5CH_2)_2O$	$C_6H_5CH_2OH$ + $C_6H_5CH_2OSi(Hex)_3$
10	51	1	34	15
15	44	5	36	15
20	41	6	38	15
25	37	8	40	15
30	35	9	41	15
35	31	12	42	15
40	26	15	44	15
45	25	16	44	15
55	22	19	44	15

ucts were identified from their pmr spectra by comparison to authentic samples and by observing signal enhancements when a small amount of the known was added to the pmr sample. With the exception of 2-propanol, which was not isolated, alcohol products were additionally confirmed by glpc or ir identification methods.

Silane Reductions in Ether–Aqueous Sulfuric Acid Media. The reduction of cyclooctanone exemplifies the procedure used. To 6.3 g (50 mmol) of cyclooctanone and 2.2 g (25 mmol) of *n*-butylsilane in 6 ml of ethyl ether was added 3.5 ml of 73 g % aqueous sulfuric acid. The reaction mixture was heterogeneous, and the reaction was slightly exothermic. After rapidly stirring overnight the acid was neutralized by adding an excess of 10% aqueous sodium hydroxide, and the mixture was extracted with four 20-ml portions of ethyl ether. The combined ether extracts were dried over potassium hydroxide and filtered, and the ether was removed under reduced pressure. The residue was distilled giving 4.9 g (39 mmol, 78% yield) of cyclooctanol, bp 92–93° (23 Torr) [lit.[25] bp 99° (16 Torr)]. Only a small amount of pot residue remained after the distillation.

Reduction of octanal by *n*-butylsilane followed by extraction and distillation gave 1-octanol in 31% yield and 1-octyl ether in 61% yield. With tetramethyldisiloxane 1-octanol and 1-octyl ether were formed in 50 and 50% yield, respectively; using a lower acid concentration (37 g % aqueous sulfuric acid), the relative yield of alcohol was increased to 65%.

Silane Reductions of Aldehydes and Ketones in Carboxylic Acid Media. In a typical reaction the carbonyl compound and silane were weighed into a round-bottom flask and the reaction solvent, if different from the carboxylic acid, was added. The carboxylic acid was added last, and the resultant homogeneous solution was stirred at room temperature with a magnetic stirrer. Aliquots were removed at appropriate times and subjected to pmr analysis to determine the extent of reduction. Products were identified from the pmr spectra of the reaction solutions by comparison with authentic samples, when available; relative yields of products were determined from averaged integrations of the individual and characteristic absorption signals of each compound through reference to an internal standard. Ethers were generally isolated by direct distillation of the reaction mixture under reduced pressure. 2-Naphthyl ether was insoluble in trifluoroacetic acid and was filtered and recrystallized. Isolated ethers were identified from their pmr spectra and by comparison of boiling or melting points with the literature values.

p-Toluyl ether was obtained in 91% yield from the reduction of *p*-tolualdehyde (5.0 mmol) by triethylsilane (6.0 mmol) using 0.25 equiv of concentrated sulfuric acid in 2.5 ml of acetonitrile. Reaction time was 5 days.

Cyclohexyl ether was prepared by reduction of cyclohexanone (3.92 g, 40 mmol) with *n*-butylsilane (1.78 g, 20 mmol) in trifluoroacetic acid. The acid (75 mmol) was added slowly over a period of 1 hr to the reaction mixture cooled at −35°. After complete addition the reaction flask was placed in a freezer at −15° for 70 hr. Direct distillation gave 2.91 g (16 mmol, 80% yield) of cyclohexyl ether, bp 119–121° (18 Torr) [lit.[26] bp 97–98.5° (8 Torr)].

Reduction of Benzaldehyde in Carbon Tetrachloride–Trifluoroacetic Acid. Product Yields with Time. Benzaldehyde (5.0 mmol) and trifluoroacetic acid (10.0 mmol) were weighed into a round-bottom flask, and carbon tetrachloride (2.5 ml) was added. The solution was heated to 40 ± 1° and the silane (5.0 mmol) was added. An aliquot was removed from the homogeneous reaction solution after thorough mixing, and a pmr spectrum was taken of the sample. Proton absorptions were integrated, and the integrations were repeated every 5 min over a reaction period of 1 hr. The reaction temperature was maintained at 40°. The results with triethylsilane are described graphically in Figure 1. Data for the reduction of benzaldehyde with tri-*n*-hexylsilane are given in Table V. Reduction of benzaldehyde by diphenylsilane was at least 20 times slower than the corresponding reduction by either triethylsilane or tri-*n*-hexylsilane.

Preparation of Acetamides. To the carbonyl compound (60 mmol) and triethylsilane (66 mmol) in 15 ml of acetonitrile was added 3.0 ml of water followed by 9.0 ml of concentrated sulfuric acid. Sulfuric acid was added slowly to the reaction solution cooled in an ice bath; the acid addition was exothermic. The heterogeneous reaction mixture was stirred rapidly at room temperature for between 48 and 72 hr. The reaction was quenched by adding 30 ml of 50% aqueous sodium hydroxide, and the aqueous mixture was extracted three times with 50-ml portions of methylene chloride. The combined methylene chloride extract was passed through anhydrous magnesium sulfate, and the methylene chloride was removed under reduced pressure. With the exception of the norcamphor and benzophenone reduction products the product mixtures were distilled under reduced pressure to give hexaethyldisiloxane and amides in separate fractions. In the cyclohexanone reduction cyclohexyl ether and *N*-cyclohexylacetamide were collected in the same fraction; *N*-cyclohexylacetamide was separated from the ether by recrystallization. The product mixtures from the benzophenone and norcamphor reductions were washed three times with pentane to remove hexaethyldisiloxane and other soluble reaction products. The solid amide products were recrystallized from ether and characterized by pmr analysis and by their melting points through comparison to authentic samples or literature values. Isolated yields of acetamides from reactions with benzaldehyde, cyclohexanone, and norcamphor were 15–20% lower when 6 ml of concentrated sulfuric acid was used instead of 9 ml in the above procedure owing to incomplete reaction of the reduced carbonyl compound.

The same procedure was used for the Ritter reaction with the exception that the alcohol was used instead of the carbonyl compound and no triethylsilane was added.

3,3-Dimethyl-2-butanone (5.0 mmol) was reduced by triethylsilane (10.0 mmol) using 1.5 ml of 67% aqueous sulfuric acid and 2.5 ml of acetonitrile. The product mixture from the reduction was analyzed by pmr spectroscopy and by glpc methods. Only one amide product other than acetamide was observed; this product was collected by glpc and characterized as *N*-2-(2,3-dimethylbutyl)acetamide by pmr and ir spectroscopy and from its melting point by comparison to the literature value.

Reduction of 4-*tert*-Butylcyclohexanone in an Acetonitrile Mixture with Aqueous Sulfuric Acid. Reaction occurred as previously described. After work-up pmr analysis was used to give the relative yields of reaction products. Alcohol and other products were additionally characterized and the relative yields of the isomeric alcohols were determined by glpc analysis through comparison with authentic samples. Refluxing the reaction products overnight with 50% aqueous sulfuric acid, followed by work-up, gave the isomeric 4-*tert*-butylcyclohexylamines, which were analyzed by pmr spectroscopy and by glpc.

Acknowledgment. We gratefully acknowledge the support of the Research Corporation and the National Science Foundation for this work. We wish to thank Martha Patrie and Vern Roelofs for preliminary results.

Registry No.—Triethylsilane, 617-86-7; *n*-butylsilane, 1600-29-9; *n*-butyltrichlorosilane, 7521-8-4; tetramethyldisiloxane, 30110-74-8; tri-*n*-hexylsilane, 2929-52-4; 4-*tert*-butylcyclohexanone, 98-53-3.

Supplementary Material Available. Additional data for Tables I and II will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for pho-

tocopy or $2.00 for microfiche, referring to code number JOC-74-2740.

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Reduction Products in Copper(I)-Promoted Diazonium Ion Reactions. Hydrogen Abstraction from Amines Coordinated to Copper(I), from Water, and from Transient Radicals

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Received November 28, 1973

Reduction products are observed in amine–copper(I) perchlorate promoted decomposition of aryldiazonium salts when the amine ligands are capable of hydrogen atom donation. The effective reducing agents evidently are the complexed rather than the free ligands, *i.e.*, the tris(amine)copper(I) cation in the case of tetra- and tricoordinated salts and the bis(amine)copper(I) cation in the dicoordinated systems. In the presence of excess ligand a new product is obtained, which is probably an ammonium salt formed from the amine and the incipient aryl cation. In the absence of hydrogen-donating ligands it has been shown that the small but consistent amount of benzophenone formed in the copper(I)-promoted decomposition of 2-diazobenzophenone tetrafluoroborate arises from (a) the precursor to 9-fluorenone and (b) the solvent, water. Hydrogen atom abstraction from both these sources is rate determining and subject to a kinetic isotope effect. Since water is a notoriously poor hydrogen atom donor, transfer of a hydrogen atom from the aquated coordination sphere of copper(I) *via* a bridged intermediate is postulated.

In the course of our investigations of copper(I) oxide and copper(I) perchlorate decompositions of aryldiazonium tetrafluoroborates,[2] it was noted that reduction products were consistently produced. A thorough study of the hydrogen source in these decompositions was, therefore, undertaken.

The tetrafluoroborate salt of 2-diazobenzophenone (1) was selected for this purpose because of the large amount of reliable data that were already available. This compound, as are all aromatic diazonium compounds, is capable of cleaving homolytically and/or heterolytically, depending on conditions. The decomposition of 2-diazobenzophenone tetrafluoroborate (1) was first carried out by Graebe and Ullman,[3] who found that 1 could be converted into 9-fluorenone (4). DeTar and Relyea[4] showed the formation of *o*-hydroxybenzophenone (3, Z = OH) along with 9-fluorenone (4) in the system, in the presence and absence of a copper catalyst. Lewin and Cohen[5a] then elucidated conditions under which homolytic and heterolytic cleavage of the carbon–nitrogen bond occurred. They found that thermal decomposition of diazonium salts in acidic solution produced phenyl cations, whereas the room temperature reaction, with a catalyst, led to a phenyl radical. Their proposed mechanism of the copper(I)-catalyzed decomposition of 2-diazobenzophenone tetrafluoroborate seemed to hold for amine–copper(I) perchlorate promoted decompositions with the addition of dimerization of radical A.[2] Thus, it has been shown that good yields of the phenol (3, Z = OH) can be obtained in the presence of a large excess of cupric ion and that benzophenone (2) is produced in the presence of hydrogen donors such as acetone and ethanol.[2] However, benzophenone was formed in both the copper(I) oxide and the amine–copper(I) perchlorate promoted reactions even in the absence of such hydrogen donors. A similar observation had been previously made[5a] and several possible pathways for benzophenone (2) formation were considered in conjunction with the proposed reaction scheme;[5a] the authors concluded, however, that "the nature of the reducing agent remains obscure." See Scheme I.

Results and Discussion

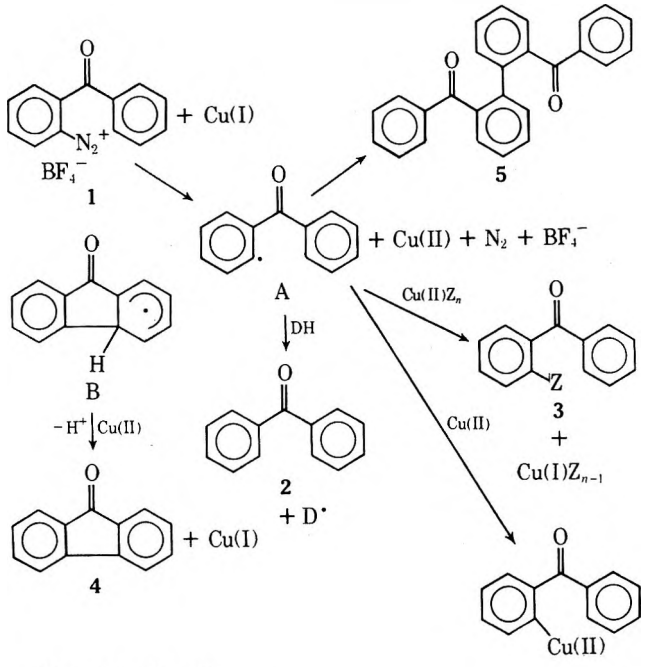
Reduction Products. A. In Amine–Copper(I) Perchlorate Promoted Reactions. Benzophenone (2) was formed in amine–copper(I) perchlorate promoted decom-

Table I
Product Composition in Amine–Copper(I) Perchlorate Promoted Decompositions of 2-Diazobenzophenone Tetrafluoroborate (1)[a]

No.	Catalyst	Product yields, %[b] Benzophenone (2)	2-Hydroxybenzophenone (3)	9-Fluorenone (4)	2,2′-Dibenzoylbiphenyl (5)
1	Tetrakis(pyridine)copper(I) perchlorate	0.8	2.8	28.7	53.0
2	Tetrakis(quinoline)copper(I) perchlorate	*c*	*c*	67.0	10.5
3	Tetrakis(4-picoline)copper(I) perchlorate	7.6	3.7	28.7	31.4
4	Tris(2-picoline)copper(I) perchlorate	1.8	1.1	27.6	76.5
5	Tris(2-ethylpyridine)-copper(I) perchlorate	8.6	1.0	31.5	73.0
6	Bis(2,6-lutidine)copper(I) perchlorate	4.1	0.8	35.0	13.1
7	Bis(γ-collidine)copper(I) perchlorate	10.3	0	87.0	*c*
8	Bis(2-methylquinoline)-copper(I) perchlorate	3.1	0.5	57.1	9.0
9	Bis(8-methylquinoline)-copper(I) perchlorate	7.8	*c*	44.7	8.6

[a] Reaction of 0.6 mmol of 2-diazobenzophenone tetrafluoroborate and 1.0 mmol of catalyst in 30 ml of water. [b] The yields were determined by vpc analysis *vs.* hexadecane as the added internal standard. [c] Present but as less than 1% of the overall reaction.

Scheme I
Homolytic Decomposition Pathway of 2-Diazobenzophenone Tetrafluoroborate[a]



[a] References 2 and 5.

positions of 1, as shown in Table I.[5b] It was noted that a rough correlation existed between the extent of benzophenone (2) formation and the number of methyl groups on the ligating amine of the copper(I) perchlorate. Thus, reactions promoted by tetrakis(pyridine)- and tetrakis(quinoline)copper(I) perchlorate, neither of which have methyl groups (entries 1, 2), gave practically no benzophenone and the reaction promoted by bis (γ-collidine)copper(I) perchlorate, with six methyl groups per mole, gave *ca.* 10% benzophenone (entry 7). In fact, the relative hydrogen atom donating ability of the methyl- and ethylpyridines (entries 4, 5) seems to parallel that of the methyl- and ethylbenzene analogs. Thus, it is known that the hydrogen donating ability of ethylbenzene toward phenyl radicals is 3 times greater than that of toluene.[6] Similarly, the data in Table I suggest that the hydrogen-donating ability of tris(2-ethylpyridine)copper(I) perchlorate is 4.8 times greater than that of tris(2-picoline)copper(I) perchlorate toward the benzophenone radical.[7] On the other hand, the considerably lower yield of benzophenone obtained when the reaction was promoted by tris(2-picoline)copper(I) perchlorate as compared to tetrakis(4-picoline)copper(I) perchlorate is in striking contrast to the somewhat greater hydrogen-donating ability reported for 2-picoline *vs.* 4-picoline.[8]

In addition, it was noted that whenever relatively large yields of benzophenone were formed, high-boiling, basic materials were also produced. These were expected to be heterocyclic-amine disubstituted ethanes arising from the dimerization of the radicals formed by hydrogen abstraction. In fact, the high-boiling base produced in the tris(2-picoline)copper(I) perchlorate promoted reaction of 1 was separated and shown to be 1,2-di(2-pyridyl)ethane by comparison with an authentic sample.[9]

Increased yields of reduction product 2 were also observed with the addition of excess heterocyclic amine ligand to the reaction mixture (Table II) and a rough correlation can be seen between the yield of benzophenone and the number of moles of methyl groups in each system.

Two major differences are seen between reduction by substituted pyridines and the hydrogen donor dioxane. Whereas the addition of the hydrogen donor dioxane leads to increasing yields of benzophenone, tending asymptotically to 100% conversion,[10] none of the substituted pyridines exhibited such behavior. In fact, some of the amines lead to a broad maximum in the yield of benzophenone with higher amine concentrations. In addition, the effectiveness of the heterocyclic amines as reducing agents is not as expected.

The extent of reduction was expected to be relatively independent of the position of the methyl substituent on the pyridine ring, since the hydrogen-donating abilities of 2- and 4-picoline are known to be essentially the same[8] and γ-collidine is 3 times as effective as 4-picoline,[6] by virtue of having three methyl groups. It was observed that this in-

Table II
Product Composition as a Function of Excess Ligand in Amine–Copper(I) Perchlorate Promoted Decompositions of 2-Diazobenzophenone Tetrafluoroborate (1)[a]

Catalyst (registry no.)	Added ligand,[b] mmol	Total methyl[c] groups, mmol	Product yield, %[d] Benzophenone (2)	2-Hydroxybenzophenone (3)	9-Fluorenone (4)	2,2'-Dibenzoylbiphenyl (5)	Total
Tetrakis(pyridine)-copper(I) perchlorate (21465-66-7)	0	0	0.8	2.8	28.7	53.0	85.3
	3	0	*e*	0.6	40.3	56.0	96.9
	30	0	*e*	*e*	25.4	40.5	65.9
Tetrakis(quinoline)-copper(I) perchlorate (52019-93-9)	0	0	*e*	*e*	67.0	10.5	77.5
	3	0	*e*	*e*	47.2	64.0	111.2
Tetrakis(4-picoline)-copper(I) perchlorate (35232-25-8)	0	4	7.6	3.7	28.7	31.4	71.4
	2	6	15.4	2.5	27.1	0	45.0
	3	7	18.0	2.3	22.4	*f*	*f*
	4	8	21.3	2.3	18.5	*f*	*f*
	10	14	24.4	2.8	1.8	*f*	*f*
Tris(2-picoline)-copper(I) perchlorate (37834-33-6)	0	3	1.8	1.1	27.6	76.5	107.0
	1.5	4.5	3.0	21.8	11.1	*f*	*f*
	5	8	4.4	27.4	6.1	*f*	*f*
	7	10	6.0	25.4	6.0	*f*	*f*
	11	14	9.1	22.6	7.3	*f*	*f*
	17	20	10.6	22.2	4.3	*f*	*f*
Tris(2-ethylpyridine)-copper(I) perchlorate (37834-25-6)	0	3	8.6	1.0	31.5	73.0	113.1
	3	6	19.0	*e*	7.3	*f*	*f*
	6	9	15.5	6.0	*e*	*f*	*f*
Bis(2-methylquinoline)-copper(I) perchlorate (51933-28-9)	0	2	3.1	0.5	57.1	9.0	69.7
	3	5	14.3	31.1	3.7	32.2	71.3
Bis(8-methylquinoline)-copper(I) perchlorate (51933-30-3)	0	2	7.8	*e*	44.7	8.6	61.1
	3	5	12.7	6.2	5.5	72.0	96.4
Bis(2,6-lutidine)-copper(I) perchlorate (51933-32-5)	0	4	4.1	0.8	35.0	13.1	52.2
	0.5	5	9.0	*e*	42.5	32.8	84.3
	1	6	11.3	*e*	26.2	*f*	*f*
	2	8	15.0	*e*	31.7	*f*	*f*
	3.5	11	22.5	*e*	20.4	4.0	46.9
	7	18	23.4	*e*	15.6	*f*	*f*
	9	22	28.6	1.8	9.2	*f*	*f*
	11	26	18.2	1.3	7.2	*f*	*f*
Bis(γ-collidine)-copper(I) perchlorate (51933-34-7)	0	6	10.3	0	87.0	*e*	97.3
	0.3	7	12.8	*e*	33.4	24.0	70.2
	2	12	27.7	*e*	12.2	5.7	45.6
	2.6	14	31.5	*e*	10.0	3.5	46.0
	3.5	16.5	30.8	*e*	2.7	*f*	*f*
	5.3	22	25.3	1.6	0.9	16.0	43.8

[a] Reaction of 0.6 mmol of 2-diazobenzophenone tetrafluoroborate and 1.0 mmol of catalyst in 30 ml of water. [b] The ligand corresponds to that in the catalyst. [c] Sum of the millimoles of methyl groups from the added excess ligand and from the catalyst. [d] The yields were determined by vpc analysis *vs.* hexadecane as the added internal standard. [e] Present but less than 1% of the overall product. [f] Not determined.

deed was the case when the amount of benzophenone formed in reactions with similar methyl group concentrations was compared for 4-picoline, 2,6-lutidine, and γ-collidine. The results for 2-picoline are, however, in striking disagreement with expectation and with those obtained for other substituted pyridines. The extremely low yields of benzophenone obtained with excess 2-picoline cannot be accounted for by the change in the position of the methyl substituent on the pyridine ring from para to ortho, since such an explanation would be inconsistent with the observed results for benzophenone formation from the copper(I) complexes of 2,6-lutidine and γ-collidine.

It thus appears that the copper catalyst plays a significant role in the reducing ability of the excess ligand. In order to understand such a role we considered the possible dissociation of the copper(I) complexes in the reaction medium.

The formation constants for tetrakis(4-picoline)copper(I) and tris(2-picoline)copper(I) have been reported[11] and we have calculated the equilibrium concentrations of the various species present, starting with known amounts of total ligand and total metal and solving the equations for equilibrium numerically.[12] The results of these calculations in each case implicate the tricoordinated species, as an important reducing agent, for the yield of benzophenone follows the concentration of that species (Appendix). However, the reducing ability of tris(4-picoline)copper(I) appears to substantially exceed that of tris(2-picoline)copper(I).Thus, a concentration of 5×10^{-3} *M* tricoordinated copper(I) leads to the production of 7.4% benzophenone with 4-picoline as the ligand but to only 1.8% benzophenone when 2-picoline is used (Table II). In view of the known structure of tris(2-picoline)copper(I) perchlorate[13] it is tempting to suggest that possibly only one of the three methyl groups in this cation is available as a hydrogen donor, the other two being sterically inaccessible to the relatively bulky benzophenone radical, A. This situation would not obtain in the tris(4-picoline)copper(I) ion, since the methyl groups would be peripherally accessible, independent of whether copper(I) had trigonal or tetrahedral bonding.

No formation constants are available for bis(γ-collidine)copper(I) or for bis(2,6-lutidine)copper(I). These may be estimated using the relationship $\log K_1 = apK_a + b$

Table III
Product Composition in the Copper(I) Oxide Promoted Decomposition of 2-Diazobenzophenone Tetrafluoroborate (1)[a]

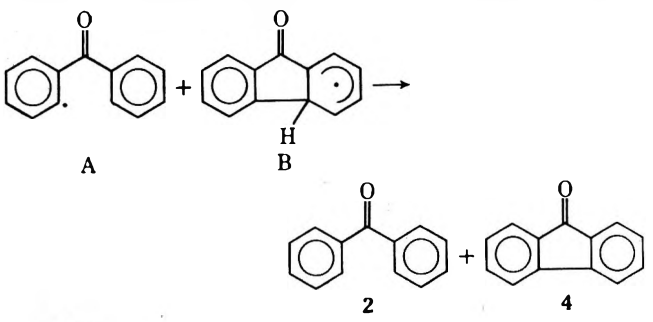
Molarity of H_2SO_4	Product yields, %[b,c] Benzophenone (2)	2-Hydroxybenzophenone (3)	9-Fluorenone (4)
0.25	11.4	*d*	51.4
0.38	14.3	*d*	44.5
0.50	22.7	*d*	38.4
0.63	2.1	*d*	49.1
0.75	3.2	*d*	51.3
1.50	3.1	*d*	60.5

[a] Reaction of 0.6 mmol of 2-diazobenzophenone tetrafluoroborate and 0.42 mmol of copper(I) oxide (99+% pure) in 30 ml of aqueous H_2SO_4. [b] The yields were determined by vpc analysis *vs.* hexadecane as the added internal standard. [c] The balance of the reaction was 2,2′-dibenzoylbiphenyl; overall yields were 95–100%. [d] Present but less than 1% of the overall reaction.

where a and b are constants;[14] the approximate relationship K_1/K_2 = constant can then lead to an estimate of K_2. Using these approximations we calculated values of $K_1 = 1 \times 10^6$ for 2,6-lutidine and 8.7×10^6 for γ-collidine; $K_2 = 7 \times 10^2$ for 2,6-lutidine and 6.2×10^3 for γ-collidine. Concentrations of free metal, free ligand, and monoligated and diligated copper(I) were then calculated using these values and the total metal and total ligand concentrations used in each experimental run. The results, although approximate, implicate the dicoordinated copper cation and account for the leveling off observed for the yield of benzophenone. At total ligand concentrations above 0.13 *M* all the metal is essentially dicoordinated; thus the concentration of the reducing agent is constant and consequently the extent of benzophenone formation remains at its maximum.

B. In Copper(I) Oxide Promoted Reactions. A small, but persistent, amount of benzophenone (2) was consistently formed in the copper(I) oxide promoted decomposition of 1 in acid medium. In this investigation, ultrapure (99+%) copper(I) oxide was used, and although no pH effect on the product composition had been observed when amine–copper(I) perchlorates[2] or partially (20%) oxidized copper(I) oxide had been used,[15] a rather striking relationship between benzophenone formation and acidity was noted (Table III).[16] All further experiments were conducted at accurately determined sulfuric acid concentrations in the range 0.25–0.5 *M*.

A possible reaction pathway for benzophenone formation, which had previously been considered and rejected,[5a] is the abstraction of a hydrogen atom by the initially formed 2-benzophenone radical (A) from the cyclized σ-complex radical (B) to give 1 mol each of benzophenone (2) and 9-fluorenone (4). In order to test this possibility



2,3,4,5,6-pentadeuterio-2′-diazobenzophenone tetrafluoroborate (1-d_5) was prepared and subjected to copper(I) oxide promoted decomposition. The results (Table IV) show that, as expected, essentially the same product composition is obtained using pentadeuterated or nondeuterated diazonium salts. The actual yield of hexadeuterated benzophenone (2-d_6) (determined by mass spectrometry) was on the order of 2% of the overall yield in each case. The proposed pathway, involving the collision of two transient radicals, therefore accounts for *ca.* 20% of the benzophenone in 0.25 *M* H_2SO_4 and for *ca.* 10% of the benzophenone in 0.5 *M* H_2SO_4.

The involvement of water as a hydrogen source, either directly or *via* abstraction from 2-hydroxybenzophenone (3), had also been considered; it had been rejected because no deuterium-containing benzophenone was obtained when the reaction was conducted in D_2O.[5] Under our reaction conditions, however, 10% of the benzophenone was monodeuterated when the copper(I) oxide promoted decomposition of 1 was carried out in 0.5 *M* D_2SO_4–D_2O solution (Table V).[17] This deuteration pathway must involve water directly because no o-hydroxybenzophenone (3) is obtained in any of these reactions. Since homolytic cleavage of the H–O–H bond with subsequent addition to a carbon atom is an energetically unfavorable process,[19] reduction may involve the hydrolysis of an organocopper. It has been demonstrated that arylcoppers are produced in copper-promoted aryldiazonium ion decompositions[20] and this possibility would also be consistent with the observed formation of 2,2′-dibenzoylbiphenyl,[2] which is an expected product from an arylcopper.[21] On the other hand, rather special conditions are required for the production of arylcoppers from diazonium ions[20] and therefore an alternative pathway should be considered.

In order to avoid the formation of the high-energy species OH·, a hydrogen atom may be transferred from the aquated coordination sphere of the copper(I) ion to the benzophenone radical (A) *via* a bridged intermediate. Such hydrogen atom transfers are weldocumented in reactions between inorganic ions.[22]

$$\mathrm{Ar}\cdot + \mathrm{Cu(H_2O)_n}^{+} \longrightarrow [\mathrm{Ar}\cdot\cdots\mathrm{H}\cdots\overset{\mathrm{H}}{\mathrm{O}}\cdots\mathrm{Cu(H_2O)_{n-1}}]^{+} \longrightarrow \mathrm{ArH} + \mathrm{Cu(OH)(H_2O)_{n-1}}^{+}$$

Since the two hydrogen sources identified so far, namely, H abstraction from a cyclized radical B and from water, apparently account for a maximum of 30% of the benzophenone formed, and since no other hydrogen sources seemed to be available, the possible operation of an isotope effect was considered. Thus, if an isotope effect were present in the hydrogen atom abstraction *via* each pathway and if the pathways were of comparable energy, isotopic substitution in either case would divert the reaction to the alternative path. The results of carrying out the decomposition of pentadeuteriodiazobenzophenone tetrafluoroborate (1-d_5) in 0.5 *M* D_2SO_4–D_2O support this hypothesis; the overall yield of benzophenone was 14.5% and 87% of it was hexadeuterated.

Assessment of the magnitude of the deuterium isotope effects in these steps is rather difficult. There are no reported values for the isotope effect associated with the abstraction of a hydrogen atom from the aquation sphere of metal ions. The deuterium isotope effect for the abstraction of a hydrogen atom from phenol has been reported to be 1.32.[23] If a calculation is carried out using this value for the scission of the O–H bond, a value of 2.3 is obtained for k_H/k_D in the hydrogen abstraction from B (see Appendix for calculation). This value is lower than that of 4, commonly associated with isotope effects in C–H bond breaking by an aryl radical.[6] However, B is a reactive intermedi-

Table IV
Product Composition and Extent of Deuteration in the Copper(I) Oxide Promoted Reaction of Pentadeuterated 2-Diazobenzophenone Tetrafluoroborate (1-d_5)[a]

Diazonium tetrafluoroborate	Conditions	Product yields, %[b,c] Benzophenone (2)	2-Hydroxybenzophenone (3)	9-Fluorenone (4)	% deuteration of benzophenone d_5[f]	d_6[g]
1[d]	0.5 *N* H_2SO_4	11.4	*e*	51.4		
1-d_5[h]	0.5 *N* H_2SO_4	11.4	1.0	43.2	81.4	18.6
1[d]	1.0 *N* H_2SO_4	22.7	*e*	38.4		
1-d_5[h]	1.0 *N* H_2SO_4	20.9	*e*	30.0	91.3	8.7

[a] Reaction of 0.6 mmol of diazonium tetrafluoroborate and 0.42 mmol of copper(I) oxide (99+% pure) in 30 ml volume. [b] The yields were determined by vpc analysis *vs.* hexadecane as the added internal standard. [c] The balance of the reaction was 2,2′-dibenzoylbiphenyl; overall yields were 85–100%. [d] 2-Diazobenzophenone tetrafluoroborate. [e] Present but less than 1% of the overall reaction. [f] 2,3,4,5,6-Pentadeuteriobenzophenone. [g] 2,2′,3,4,5,6-Hexadeuteriobenzophenone. [h] 2,3,4,5,6-Pentadeuterio-2′-diazobenzophenone tetrafluoroborate.

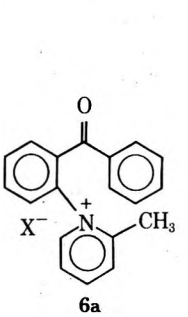
Table V
Decomposition of Undeuterated and Pentadeuterated 2-Diazobenzophenone Tetrafluoroborate (1 and 1-d_5) in Heavy Water[a]

No.	Diazonium tetrafluoroborate	Conditions	Product yields, %[b,c] Benzophenone (2)	2-Hydroxybenzophenone (3)	9-Fluorenone (4)	% deuteration of benzophenone d_0[f]	d_1[g]
1	1[d]	1.0 *N* D_2SO_4–D_2O	11.9	*e*	46.5	89.3	10.7
2	1[d]	1.0 *N* H_2SO_4–H_2O	22.7	*e*	38.4		
						d_5[i]	d_6[j]
3	1-d_5[h]	1.0 *N* H_2SO_4–H_2O	20.9	*e*	30.0	91.3	8.7
4	1-d_5[h]	1.0 *N* H_2SO_4–25% D_2O				84.0	16.0
5	1-d_5[h]	1.0 *N* H_2SO_4–50% D_2O	11.5	*e*	46.4	68.6	31.4
6	1-d_5[h]	1.0 *N* H_2SO_4–75% D_2O				56.0	44.0
7	1-d_5[h]	1.0 *N* D_2SO_4–100% D_2O	14.5	*e*	43.8	13.0	87.0

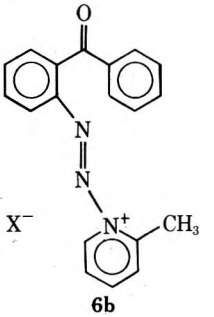
[a] Reaction of 0.6 mmol of 2-diazonium tetrafluoroborate and 0.42 mmol of copper(I) oxide (99+% pure) in 30 ml volume. [b] The yields were determined by vpc analysis *vs.* hexadecane as the added internal standard. [c] The balance of the reaction was 2,2′-dibenzoylbiphenyl; overall yields were 85–100%. [d] 2-Diazobenophenone tetrafluoroborate. [e] Present but less than 1% of the overall reaction. [f] Undeuterated benzophenone. [g] 2-Deuteriobenzophenone. [h] 2,3,4,5,6-Pentadeuterio-2′-diazobenzophenone tetrafluoroborate. [i] 2,3,4,5,6-Pentadeuteriobenzophenone. [j] 2,2′,3,4,5,6-Hexadeuteriobenzophenone.

ate with excess energy and may therefore suffer a smaller isotope effect. In fact, abstraction of a hydrogen atom from B is somewhat analogous to the dehydrogenation of an arylcyclohexadienyl radical in free-radical arylation reactions and can thus be assumed to be rather small.[24] In the extreme case, there might be no isotope effect on this step ($k_H/k_D = 1$). If this assumption is made, an isotope effect of *ca.* 3 is obtained for the abstraction of a hydrogen atom from the aquation sphere of Cu(I) (see Appendix for calculation). It should be emphasized that both sets of values for the isotope effects are extremely rough. However, the last set ($k_H/k_D = 1$ for abstraction from B and $k_H/k_D = 3$ for abstraction from water) is more consistent with the results in Table V. Thus, the small decrease in the yield of **2** in the reaction of 1-d_5 as compared with **1** (no. 2 and 3) supports a very small kinetic isotope effect for abstraction from B. The changes in the yield of **2** due to reaction in deuterated solvent are more difficult to relate to the primary isotope effect, owing to the possible operation of secondary and solvent isotope effects and differences in pH. It is clear, however, that the results are in the right direction, since the observed decrease in benzophenone (**2**) production (no. 1 *vs.* 2 and 4 *vs.* 7) cannot be associated with decreased acidity (Table III) and suggests a kinetic isotope effect >1.

Formation of an Unresolved Product. In the course of the amine–copper(I) perchlorate promoted decompositions, it was noted that the total product yields decreased strikingly with added amine. Since all the components in the organic layer were identified (as **2**, **3**, **4**, and **5**), it was postulated that a water-soluble material must comprise the balance of the product. In view of the unknown material's water solubility, it was assumed to be ionic and since its formation seemed to depend on the presence of excess 2-picoline, two possibilities could be those shown below. The



6a



6b

phenyl analog of **6a** has been postulated by Nesmeyanov[25] and the phenyl analog of **6b** by Abramovitch;[26] however, in neither case were the compounds actually isolated from the decomposition of a diazonium salt.

In order to distinguish between the postulated structures **6a** and **6b**, nitrogen evolution measurements were taken.[27] The total organic products only accounted for 52.8% of the starting material when the tris(2-picoline)copper(I) perchlorate promoted reaction of **1** was carried out in the presence of 3 mmol excess 2-picoline; in the absence of 2-picoline the total of recovered organic products was essentially 100%. If, therefore, structure **6b** were formed, the reaction in the presence of excess 2-picoline should evolve only one-half the moles of nitrogen that would be evolved in the same reaction in the absence of excess 2-picoline. The results of nitrogen evolution measurements in the reaction of

0.6 mmol of 2-diazobenzophenone tetrafluoroborate (1) with 1.0 mmol of tris(2-picoline)copper(I) perchlorate in 30 ml of water in the presence of 3.0 mmol of 2-picoline (0.58 mmol of nitrogen) were the same as those without the added 2-picoline (0.61 mmol of nitrogen) and both are in excellent agreement with the calculated amount of nitrogen that should have been evolved (0.60 mmol). Since nitrogen evolution from the diazonium salt was quantitative under conditions where the organic products accounted for only 52.8% of the product and since structure **6b** should retain nitrogen, it was concluded that **6b** was most probably not the structure of the salt formed.

The reaction in the presence of excess 2-picoline was repeated. The organic products were removed by extraction with methylene chloride and the copper salts were precipitated by dioxane and removed by filtration. The solvent was then evaporated, leaving an oil which showed intense infrared absorptions around 1100 cm^{-1} (BF_4^- and ClO_4^-) along with strong bands at 1640 and 1740 cm^{-1}. Inasmuch as the carbonyl absorption of benzophenone is at 1650 cm^- structure **6a** for this oil was possible.

A dinitrophenylhydrazone (DNPH) derivative of the oil was prepared and the infrared spectrum was taken and compared with that of the DNPH derivative of authentic benzophenone. The derivative of the unknown no longer exhibited absorptions in the 1100-cm^{-1} region or at 1740 cm^{-1}. Its infrared spectrum differed from that of the DNPH of benzophenone only in that two bands, at 1140 and 1370 cm^{-1}, attributable to 2-picoline, were present. The absence of the bands due to tetrafluoroborate or perchlorate anion may be due to exchange with chloride ion during preparation of the DNPH derivative. Alternatively, arylation of the 2-picoline may have occurred during derivatization, along the lines proposed by Abramovitch.[26]

If indeed an ammonium salt like **6a** is formed in the presence of excess 2-picoline, it might account for the significant yield of 2-hydroxybenzophenone (**3**) observed in these reactions. It might well be that such a salt would be slowly decomposed by water to give the phenol.

The reasons for the extensive formation of the ammonium salt in reactions with 2-picoline is not known. Possibly the rather serious steric congestion in the tris(amine)copper(I) salts retards the copper(I)-promoted decomposition sufficiently to allow competing reactions of this type to become important.

Conclusions

The use of ligands capable of hydrogen atom donation in amine–copper(I) perchlorate promoted aryldiazonium ion decompositions leads to the formation of reduction products. The effective hydrogen donor is evidently the triligated copper(I) cation for the tetra- and tricoordinated complexes and the diligated species for the dicoordinated complexes. In the presence of excess ligand a relatively stable ammonium salt is formed, apparently by attack of the amine on the incipient aryl cation.

Therefore, the complexes of choice for carrying out copper(I)-promoted aryldiazonium salt decompositions in neutral water are tetrakis(pyridine)- and tetrakis(quinoline)copper(I) perchlorate with no excess ligand present.

In strong acid, reduction products can be formed by H atom transfer from the aquated coordination sphere of copper(I) *via* a bridged intermediate.

Experimental Section

Physical Measurements. Infrared spectra in the wavenumber range 4000–600 cm^{-1} were obtained with a Perkin-Elmer Model 521 spectrophotometer using potassium bromide pellets.

pH measurements were read with a Beckman Model 76 expanded-scale pH meter. The meter was standardized with buffer solutions.

Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6 mass spectrometer. For determinations of deuterium incorporation the spectra at 16 eV were recorded on the strip chart. For undeuterated materials the agreement between the experimental value of the (M + 1) peak and the value calculated from natural isotopic abundances was better than 1%.

Gas chromatographic analysis was performed as described previously.[2]

Preparation and Decomposition of 2-Diazobenzophenone Tetrafluoroborate. The procedures followed were as previously described.[2]

Copper(I) Oxide. The material designated 99+% pure (Alfa Inorganics) was kept in a nitrogen-filled drybox until used.

Amine–Copper (I) Perchlorates. The preparation of these salts has been described previously.[28]

Nitrogen Evolution Measurements. The procedure described by Siggia for nitrogen measurement was followed.[27]

The nitrogen evolved from the following reactions was measured: reaction 1, 0.6 mmol of 2-diazobenzophenone tetrafluoroborate and 1.0 mmol of tris(2-picoline)copper(I) perchlorate in 30 ml of water; reaction 2, 0.6 mmol of 2-diazobenzophenone tetrafluoroborate with 3 mmol of 2-picoline and 1.0 mmol of tris(2-picoline)copper(I)perchlorate in 30 ml of water.

First two control reactions were run.

A stirred solution of diazonium salt with (or without) 2-picoline in a flask equipped with a solid addition funnel for the copper(I) catalyst was connected to a 100-ml nitrogen measurement apparatus (nitrometer) containing a 50% potassium hydroxide solution (71.5 g of potassium hydroxide per 100 ml of water). Carbon dioxide was passed through the apparatus to flush out the air; it was continuously passed through until the bubbles reached a minimum size in the nitrometer. A blank was run on the carbon dioxide to correct the volume readings for the diazonium salt for a given time interval.

In an actual determination, the air was swept out of the apparatus. The inert gas was removed from the nitrometer and tris(2-picoline)copper(I) perchlorate was added to the solution of 2-diazobenzophenone tetrafluoroborate with (or without) 2-picoline, and the time was noted. The reaction mixture was stirred for 15 min. The carbon dioxide flow was continued throughout this period. The volume of the gas collected was read, the leveling bulb on the nitrometer being used to set the pressure of the gas in the nitrometer equal to atmospheric pressure. The temperature, barometric pressure, and time were noted. The volume of gas collected was corrected for the blank determination made on carbon dioxide. The volume was also corrected for the vapor pressure of the potassium hydroxide solution.

The volume of nitrogen collected was 25.2 ml for reaction 1 and 23.0 ml for reaction 2. The corresponding carbon dioxide blanks were 5.3 and 4.4 ml.

The calculation of the moles of nitrogen collected was as follows. The volume was corrected by subtracting out the CO_2 volume and the pressure was corrected by subtracting out the vapor pressure of 50% aqueous KOH. The volume was then corrected to STP and the number of moles of nitrogen was calculated: reaction 1 gave 0.61 mol of nitrogen; reaction 2 gave 0.58 mol of nitrogen.

Attempted Characterization of an Unresolved Product. The tris(2-picoline)copper(I) perchlorate promoted decomposition of 2-diazobenzophenone tetrafluoroborate in the presence of excess 2-picoline was carried out by the usual procedure.[2] The solution was extracted three times with 150 ml of methylene chloride. To the aqueous layer was then added *ca.* 50 ml of dioxane, whereupon a light blue precipitate formed. The solution was filtered and then evaporated carefully to a few milliliters. Addition of a small volume of CCl_4 caused the separation of an oil, which was separated and placed in a vacuum oven overnight at 105°. An infrared spectrum of the oil showed strong bands at 1740, 1640, and 1100 cm^{-1}.

In a separate isolation experiment the oil was subjected to DNPH derivation.[29] The resulting solid had mp 124°. The infrared spectrum indicated no BF bands.

2,3,4,5,6-Pentadeuterio-2′-aminobenzophenone. A modification of of the procedure employed by Huisgen and Zahler[30] for the preparation of 2-(o-aminobenzoyl)naphthalene was used.

To 3 g (0.12 g-atom) of Mg wire in 10 ml of anhydrous ether, 15.2 (0.097 mol) of bromobenzene-d_5 (Norell Chemical) in 100 ml of ether was added dropwise over a period of 1 hr. After an additional 1 hr the Grignard reaction was allowed to cool to room temperature.

The phenylmagnesium bromide-d_5 was then filtered through glass wool to remove the unreacted magnesium wire and added dropwise over a period of 1 hr to a solution of 15.6 g (0.097 mol) of acetylanthranil[31] in 150 ml of ether at 0°. After the solution was evaporated to *ca.* 20 ml, 150 ml of ethanol and 40 ml of concentrated hydrochloric acid were added and the mixture was refluxed for 2 hr. The water layer was then neutralized with concentrated ammonium hydroxide, whereupon yellow crystals of 2-aminobenzoyl-d_5-benzene appeared. The material was recrystallized from hot ethanol, mp 107° (reported for 2-aminobenzophenone, mp 106–110°).[33]

1,2-Di(2-pyridyl)ethane. The procedure of Campbell and Teague was followed to yield 20% of a solid, mp 49–50° (reported mp 49.5–50.5°).[9]

Acknowledgment. One of us (A.H.L.) gratefully acknowledges helpful discussions with Professor I. A. Cohen.

Appendix

Numerical Solution of the Simultaneous Equations for Formation of Metal Complexes. The formation reactions can be written

$$M + L \overset{\beta_1}{\rightleftharpoons} ML$$
$$M + 2L \overset{\beta_2}{\rightleftharpoons} ML_2$$
$$M + nL \overset{\beta_n}{\rightleftharpoons} ML_n$$

with associated formation constants

$$\beta_i = (ML)/(M)(L)^i \quad (1)$$

The associated equations for conservation of mass are

$$(M)_T = (M) + (ML) + (ML_2) + \ldots + (ML_n) \quad (2)$$

and

$$(L)_T = (L) + (ML) + 2(ML)_2 + \ldots + n(ML_n) \quad (3)$$

By combining the equilibrium equations with the conservation equations a single equation in (L) is obtained.

$$0 = -(L)_T + (L) + (M)_T \frac{\beta_1(L) + 2\beta_2(L)^2 + 3\beta_3(L)^3 + 4\beta_4(L)^4}{1 + \beta_1(L) + \beta_2(L)^2 + \beta_3(L)^3 + \beta_4(L)^4} \quad (4)$$

A numerical solution to eq 4 was obtained using an algorithm based on Newton's approximation.[34] The solution was required to satisfy eq 4 within an amount $(L)_T/10^5$. For the iterative algorithm to converge to a solution a careful choice of an initial approximation for (L) is required. The following choices were found suitable.

If the ligand is present in stoichiometric amounts or more, then take

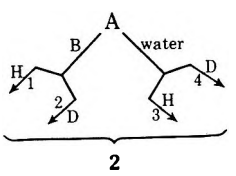
$$(L)_{initial} = (L)_T - N(M)_T$$

otherwise take

$$(L)_{initial} = (L)_T/500$$

With these choices a numerical solution was obtained in all cases for less than 20 iterations. It was verified that the solution was independent of the $(L)_{initial}$ for all cases where the algorithm converged.

Calculation of Isotope Effects. Consider the formation of **2** *via* pathways 1–4. The rate law for the formation of **2**



2

by reaction with B is

$$\frac{d[2]}{dt} = k[A][B]$$

The rate law for the formation of **2** by reaction with water is

$$\frac{d[2]}{dt} = k[A][aq]^n$$

In the reaction of **1** in protiated water (no. 2 in Table V) **2** is formed according to the expression

$$\frac{d[2]}{dt} = k_1[A][B] + k_3[A][aq]^n \quad (i)$$

The formation of **2**-d_6 in the reaction of **1**-d_5 (no. 3) in protiated water is

$$\frac{d[2\text{-}d_6]}{dt} = k_2[A][B] \quad (ii)$$

The formation of **2**-d_1 in the reaction of **1** (no. 1) in deuterated water is

$$\frac{d[2\text{-}d_1]}{dt} = k_4[A][aq]^n \quad (iii)$$

Combining ii and iii

$$\frac{d[2\text{-}d_6]}{d[2\text{-}d_1]} = \frac{k_2[B]}{k_4[aq]^n}$$

$$\frac{k_2[B]}{k_4[aq]^n} = \frac{\text{yield of } 2\text{-}d_6}{\text{yield of } 2\text{-}d_1} = \frac{1.8}{1.3} = 1.4$$

$$k_2[B] = 1.4k_4[aq]^n \quad (iv)$$

In the reaction of **1**-d_5 in deuterated water (no. 7) **2**-d_6 is formed according to

$$\frac{d[2\text{-}d_6]}{dt} = k_2[A][B] + k_4[A][aq]^n \quad (v)$$

Combining iv and v

$$\frac{d[2\text{-}d_6]}{dt} = 2.4k_4[A][aq]^n$$

$$2.4k_4[A][aq]^n = \text{yield of } 2\text{-}d_6 = 14.5 \times 87 = 12.6$$

$$k_4[A][aq]^n = \frac{12.6}{2.4} = 5.3$$

$$k_2[A][B] = 12.6 - 5.3 = 7.3$$

Defining

$$\frac{k_1}{k_2} = a = \text{isotope effect on abstraction from B}$$

$$\frac{k_3}{k_4} = b = \text{isotope effect on abstraction from aq}$$

expression i becomes

$$ak_2[A][B] + bk_4[A][aq]^n = \frac{d[2]}{dt} = \text{yield of } 2 = 22.7$$

$$7.3a + 5.3b = 22.7$$

Table VI
Calculated Equilibrium Concentrations *vs.* Benzophenone Yield for Tetrakis(4-picoline)copper(I) Perchlorate, L_4CuClO_4[a,b]

Concn, *M*								Yield of benzophenone (2), %[c]
Total ligand × 10^2	Total metal × 10^2	Free ligand × 10^2	Free metal × 10^9	LCu × 10^4	L_2Cu × 10^2	L_3Cu × 10^3	L_4Cu × 10^3	
12.0	3.00	5.43	27.8	6.80	2.36	5.00	0.705	7.4
18.6	3.00	11.3	5.15	2.62	1.89	8.35	2.45	15.4
22.0	3.00	14.4	2.83	1.83	1.69	9.44	3.53	18.0
25.0	3.00	17.1	1.81	1.39	1.52	10.1	4.51	21.3
46.0	3.00	36.7	0.203	0.336	0.789	11.3	10.8	24.4

[a] Reference 12. [b] Equilibrium constants used were[11] $[CuL]/[Cu][L] = 4.5 \times 10^5$, $[CuL_2]/[Cu][L] = 6.4 \times 10^2$, $[CuL_3]/[CuL_2][L] = 3.9$, $[CuL_4]/[CuL_3][L] = 2.6$. [c] Determined by vpc analysis *vs.* hexadecane as the added internal standard.

Table VII
Calculated Equilibrium Concentrations *vs.* Benzophenone Yield for Tris(2-picoline)copper(I) Perchlorate, L_3CuClO_4[a,b]

Concn, *M*							Yield of benzophenone (2), %[c]
Total ligand × 10^2	Total metal × 10^2	Free ligand × 10^2	Free metal × 10^9	LCu × 10^4	L_2Cu × 10^2	L_3Cu × 10^3	
9.00	3.00	2.96	54.6	40.4	2.15	4.45	1.8
14.0	3.00	7.19	81.6	14.7	1.90	9.55	3.0
25.0	3.00	17.4	9.76	4.25	1.33	16.3	4.4
32.0	3.00	24.2	4.21	2.54	1.11	18.7	6.0
45.0	3.00	36.9	1.37	1.26	0.835	21.5	9.1
65.0	3.00	56.6	0.418	0.592	0.603	23.9	10.6

[a] Reference 12. [b] Equilibrium constants used were[11] $[CuL]/[Cu][L] = 2.5 \times 10^5$, $[CuL_2]/[CuL][L] = 1.8 \times 10^2$, $[CuL_3]/[CuL_2][L] = 7$. [c] Determined by vpc analysis *vs.* hexadecane as the added internal standard.

Table VIII
Calculated Equilibrium Concentrations *vs.* Benzophenone Yield for Bis(γ-collidine)copper(I) Perchlorate, L_2CuClO_4[a,b]

Concn, *M*						Yield of benzophenone (2), %[d]
Total ligand × 10^2	Total metal × 10^2	Free ligand × 10^2	Free metal × 10^9	LCu × 10^4	L_2Cu × 10^2	
6.00	3.00	0.212	114	21.2	2.79	10.3
7.00	3.00	1.04	5.01	4.56	2.95	12.8
12.7	3.00	6.71	0.123	0.720	2.99	27.7
14.7	3.00	8.71	0.0733	0.5555	3.00	31.5
16.7	3.00	10.7	0.0485	0.452	3.00	30.8
23.7	3.00	17.7	0.0177	0.273	3.00	25.3

[a] Reference 12. [b] Equilibrium constants used were[c] $[CuL]/[Cu][L] = 8.7 \times 10^6$, $[CuL_2]/[CuL][L] = 6.2 \times 10^3$. [c] Approximated using the relationships $\log K_1 = apK_a + b$ and $(K_1/K_2)_{\gamma\text{-collidine}} = (K_1/K_2)_{2\text{-picoline}}$. [d] Determined by vpc analysis *vs.* hexadecane as the added internal standard.

Table IX
Calculated Equilibrium Coxcentrations *vs.* Benzophenone Yield for Bis(2,6-lutidine)copper(I) Perchlorate, L_2CuClO_4[a,b]

Concn, *M*						Yield of benzophenone (2), %[d]
Total ligand × 10^2	Total metal × 10^2	Free ligand × 10^2	Free metal × 10^9	LCu × 10^4	L_2Cu × 10^2	
6.00	3.00	0.587	1000	58.7	2.41	4.1
7.70	3.00	1.91	109	20.9	2.79	9.0
9.40	3.00	3.52	33.3	11.7	2.88	11.3
12.8	3.00	6.86	8.92	6.12	2.94	15.0
17.7	3.00	11.7	3.07	3.61	2.96	22.5
26.4	3.00	20.4	1.02	2.08	2.98	23.4
36.0	3.00	30.0	0.474	1.42	2.99	28.6
43.0	3.00	37.0	0.312	1.15	2.99	18.2

[a] Reference 12. [b] Equilibrium constants used were[c] $[CuL]/[Cu][L] = 1 \times 10^6$, $[CuL_2]/[CuL][L] = 7 \times 10^2$. [c] Approximated using the relationships $\log K = apK_a + b$ and $(K_1/K_2)_{2,6\text{-lutidine}} = (K_1/K_2)_{2\text{-picoline}}$. [d] Determined by vpc analysis *vs.* hexadecane as the added internal standard.

If $b = 1.32$ (as is k_H/k_D foPh· + PhOH → PhH + PhO·), then

$$7.3a = 22.7 - (5.3 \times 1.32) = 22.7 - 6 = 16.7$$

$$a = \frac{16.7}{7.3} = 2.3$$

If $a = 1$ (as is k_H/k_D in free-radical arylation) then

$$5.3b = 22.7 - 7.3 = 15.4$$

$$b = \frac{15.4}{5.3} \cong 3$$

Calculated Equilibrium Concentrations *vs.* Benzophenone Yield. See Tables VI–IX.

Registry No.—1, 342-62-1; 2, 119-61-9; 3, 117-99-7; 4, 486-25-9; 5, 24018-00-6.

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Formation of Nitrate Esters in Thallium(III) Nitrate Oxidation of Alkenes[1]

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Received March 5, 1974

The oxidation of alkenes with $Tl(NO_3)_3 \cdot 3H_2O$ (TTN) in methanol is known to lead to the formation of dimethoxy and carbonyl compounds. However, examination of the oxidation of 1-decene, 2,3-dimethyl-2-butene, and *cis*- and *trans*-stilbene indicates that methoxy nitrates and dinitrates are also formed. A net trans addition is observed in the formation of dimethoxy, methoxy nitrate, and dinitrate products from *cis*- and *trans*-stilbene.

In the course of a kinetic study[2] of the reaction of alkenes with thallium(III) nitrate (TTN) in methanol it became desirable to investigate the products formed. The oxidation of aliphatic alkenes with TTN has been reported to lead to the formation of ketones and glycol dimethyl ethers.[3] The reaction of cyclic alkenes with TTN leads to the formation of ring-contracted carbonyl compounds.[4] The formation of glycol mononitrate esters (5–15%) believed to arise from a minor side reaction was reported in a footnote[5] by Taylor and McKillop in the latter study.[4] However, no further details of the identity of the products were given. As a result of our study we now report that the formation of nitrate esters from the reaction of TTN with alkenes may be a more general process than previously suspected.

Results

The reaction of 1-decene (I), 2,3-dimethyl-2-butene (VI), and *trans*- and *cis*-stilbene (XI and XVI) with TTN in methanol was investigated in detail. Other alkenes such as *cis*-3-hexene, cyclohexene, and 1-buten-3-ol also yield nitrate esters as verified by the presence of ir bands at 1640, 1280, and 870–840 cm^{-1}. These alkenes were not as amenable to product analysis as the four compounds chosen. Each mixture of products was isolated, dissolved in carbon tetrachloride, and examined by pmr. The products were identified by comparison with the pmr of authentic samples prepared by independent methods. Where possible an individual component was isolated and compared spectroscopically with an authentic sample. The yield of each component in the mixture was determined from the area of readily identifiable resonances in the pmr. Attempted analysis of the product mixture by gc on a number of columns was unsuccessful. The instability of nitrate esters on the columns at the temperatures employed precluded this analytical method.

1-Decene (I). Reaction of I in methanol with TTN at 0° leads to the formation of 1,2-dimethoxydecane (II, 33–42%), 2-decanone (III, 34–40%), and 2-methoxy-1-decyl nitrate (IV, 23–27%).

$$\underset{\text{I}}{C_8H_{17}CH{=}CH_2} \xrightarrow[CH_3OH,\,0^\circ]{TTN} \underset{\text{II}}{C_8H_{17}CH(OCH_3)CH_2(OCH_3)} + \underset{\text{III}}{C_8H_{17}COCH_3} + \underset{\text{IV}}{C_8H_{17}CH(OCH_3)CH_2(ONO_2)}$$

Two methoxy singlets at δ 3.26 and 3.30 establish the presence of II in the reaction mixture. An authentic sample of II was prepared by the acid opening of 1,2-epoxydecane in methanol, followed by reaction of the resultant mixture of methoxy alcohols with diazomethane. The pmr of III has been previously reported[6] and is distinguished by a methyl singlet at δ 2.04. Authentic IV was obtained by the nitration of 2-methoxy-1-decanol. Although the protons on the carbon bearing the nitrate group in IV are the AB portion of an ABX spin system, they appear as a doublet at δ 4.35. 2-Methoxy-1-decyl nitrate was isolated from the reaction mixture by eluting the products through a silica gel column (100–200 mesh, 300 × 20 mm) with 400 ml of pentane fol-

lowed by 250 ml of benzene. The nitrate ester eluted in the early benzene fractions and exhibited an identical ir and pmr with the independently synthesized sample. The isomeric 1-methoxy-2-decyl nitrate (V) was obtained by nitration of 1-methoxy-2-decanol and the protons on the nitrate carbon appear as a complex multiplet centered at δ 5.04. The pmr spectrum of the TTN reaction mixture exhibited none of the spectral characteristics of 1-methoxy-2-decyl nitrate.

$$C_8H_{17}CH(ONO_2)CH_2(OCH_3)$$
V

The typical work-up procedure for TTN oxidations employed by Taylor and McKillop involves the removal of thallium(I) nitrate by filtration and then shaking the filtrate with 2 *N* sulfuric acid for 5 min.[3] Our procedure eliminated the use of sulfuric acid. Water was added to the methanol solution after filtration of the thallium(I) nitrate. The resultant aqueous solution was extracted with ether. In order to test the stability of IV under acidic conditions, 0.38 g (16.3 mmol) of IV was dissolved in 25 ml of methanol and stirred for 20 hr with an equal volume of 6 *N* H_2SO_4 at room temperature. Compound IV was isolated unchanged under these conditions.

2,3-Dimethyl-2-butene (VI). The reaction of VI in methanol at 0° with TTN leads to the formation of 3,3-dimethyl-2-butanone (VII, 3%), 2,3-dimethoxy-2,3-dimethylbutane (VIII, 45%), 2,3-dimethyl-3-methoxy-2-butyl nitrate (IX, 34%), and 2,3-dimethyl-2,3-butanediol dinitrate (X, 18%).

$$(CH_3)_2C{=}C(CH_3)_2 \xrightarrow[CH_3OH,\,0°]{TTN}$$
VI

$$(CH_3)_3CCO(CH_3) + (CH_3)_2C(OCH_3)C(CH_3)_2(OCH_3) +$$
VII VIII

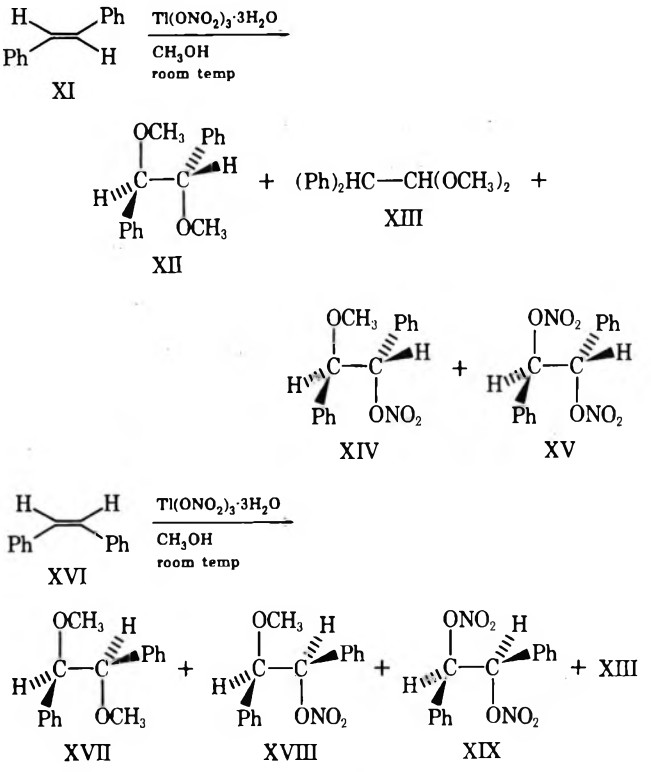
$$(CH_3)_2C(OCH_3)C(CH_3)_2(ONO_2) + (CH_3)_2C(ONO_2)C(CH_3)_2(ONO_2)$$
IX X

The presence of VII and VIII in the product mixture was determined by comparison with their previously reported spectra.[7,8] Compound IX was independently synthesized by the acid opening of 2,3-dimethyl-2,3-epoxybutane followed by nitration of the 2,3-dimethyl-3-methoxy-2-butanol which is formed. The methoxy singlet at δ 3.21 and the two methyl singlets at δ 1.20 and 1.59 established the presence of IX in the reaction mixture. Compound X was synthesized by nitration of 2,3-dimethyl-2,3-butanediol, and its methyl groups appeared as a singlet at δ 1.70. The dinitrate was isolated by eluting the reaction mixture through a silica gel column (100–200 mesh, 12 × 200 mm) with pentane and appeared in the first fractions as a solid (mp 62–63°) which was identical with the authentic sample.

***trans*-Stilbene (XI) and *cis*-Stilbene (XVI).** The reaction of XI and XVI with TTN in methanol (Scheme I) was carried out at room temperature owing to the limited solubility of these compounds in the solvent. The reaction of XI led to the formation of *meso*-1,2-dimethoxy-1,2-diphenylethane (XII, 20–25%), diphenylethanal dimethyl acetal (XIII, 36–47%), *erythro*-1,2-diphenyl-2-methoxy-1-ethyl nitrate (XIV, 33–36%), and *meso*-1,2-diphenyl-1,2-ethanediol dinitrate (XV, 0–3%).

The reaction of XVI leads to the formation of *dl*-1,2-dimethoxy-1,2-diphenylethane (XVII, 31%), *threo*-1,2-diphenyl-2-methoxy-1-ethyl nitrate (XVIII, 29–33%), XIII (30–35%), and *dl*-1,2-diphenyl-1,2-ethanediol dinitrate (XIX, 5–6%).

Scheme I



Authentic XIV and XVIII were prepared by the acid opening of *trans*- and *cis*-stilbene oxide, respectively, followed by nitration of the specific diastereomeric 1,2-diphenyl-2-methoxy-1-ethanol which is formed in each reaction. The stereochemistry of XIV was further verified by its reaction with $LiAlH_4$[9] to form *erythro*-1,2-diphenyl-2-methoxy-1-ethanol (XX), mp 101–102.5° (lit.[10] mp 100–102°). Compound XX was then treated with CH_3I–Ag_2O to form *meso*-1,2-dimethoxy-1,2-diphenylethane (XII), mp 137–139° (lit.[10] mp 140–142°). This sequence of reactions firmly established the stereochemistry of XIV and indirectly the stereochemistry of XVIII. The methoxy signal in XIV appears at δ 3.20, while H(1) and H(2) appear as doublets at δ 5.83 and 4.44, respectively ($J_{H(1),H(2)}$ = 5.5 Hz). The methoxy signal of XVIII appears at δ 3.26 and H(1) and H(2) appear as doublets at δ 5.87 and 4.36 ($J_{H(1),H(2)}$ = 8.0 Hz).

Reaction of *dl*-1,2-diphenyl-1,2-ethanediol (XXI) with CH_3I–Ag_2O yields XVII. The isomeric *meso*-1,2-dimethoxy-1,2-diphenylethane was available from the structure proof of XIV. The methoxy protons of XII and XVII appear at δ 3.06 and 3.23, respectively, while the methine protons appear at δ 4.08 and 4.21.

Reaction of *meso*-1,2-dibromo-1,2-diphenylethane with silver nitrate and acetic acid gave XV, while XIX was prepared by nitrating XXI. The methine signals in XV and XIX appear at δ 6.08 and 6.00, respectively.

Stirring diphenylethanal with methanol and 3 drops of concentrated HCl for 3 days leads to formation of XIII. The methoxy signal appears at δ 3.17 while the methine protons are doublets at δ 4.83 and 4.12 (J = 8.0 Hz).

The pmr signals of XVII, XVIII, and XIX could not be detected in the product mixture from *trans*-stilbene, while the signals of XII, XIV, and XV could not be detected among the products from *cis*-stilbene.

Discussion

The reaction of 1-decene with TTN and methanol at room temperature has previously been reported[2] to yield II

and III in 52 and 28% yields without mention of what constituted the other 20% of the product. In the present study at 0°, II and III were formed in 33–42 and 34–40% yields with a third product, positively identified as IV= AT 23–27% yield. The presence of this nitrate ester and all other nitrate esters reported in this study were readily established by ir. The pmr of the mixture gave conclusive proof that the only nitrate ester formed is 2-methoxy-1-decyl nitrate (IV).

All products of the oxidation of 1-decene by TTN may be derived from a single oxythallation adduct XXII, which

$$C_8H_{17}CH(OCH_3)CH_2Tl(ONO_2)_2$$

XXII

results from initial attack of TTN at the primary carbon while the nucleophilic solvent attacks the secondary carbon, which may develop some carbonium ion character. A 1,2-hydride shift in the dethallation reaction can occur as thallium(I) nitrate departs. Nucleophilic attack of methanol at the carbon bearing the methoxyl group leads to the dimethyl ketal and subsequently to 2-decanone as a result of the aqueous work-up procedure. The formation of III and IV could be envisaged to occur by loss of thallium(I) nitrate accompanied by nucleophilic attack by either methanol or nitrate ion. Either of the nucleophiles may be present in the coordination sphere of thallium.

When 2,3-dimethyl-2-butene is treated under identical conditions there is a decrease in the amount of ketone formed compared to the reaction of 1-decene. This may be due to the migratory aptitudes of hydrogen and methyl. An increase in the amount of methoxy nitrate formed from 2,3-dimethyl-2-butene relative to 1-decene is noted and in addition 2,3-dimethyl-2,3-butanediol dinitrate is also formed. The increase in the yield of methoxy nitrate is probably due to the greater stability and hence selectivity of the tertiary carbonium ion formed as thallium(I) nitrate leaves. This would allow the nitrate ion to compete with the methanol in attacking the cationic center.

The reaction of *cis*- and *trans*-stilbene with TTN in methanol was carried out in order to determine the stereochemistry of the reaction. *cis*- and *trans*-stilbene each form one methoxy nitrate and one dimethoxy product which is the result of net trans addition. This result could be rationalized by assuming that as the TTN attacks one end of the double bond the methanol attacks the developing positive charge on the adjacent carbon trans to the thallium (see Scheme II). As the thallium dissociates there is participation by the adjacent phenyl group stabilizing the intermediate. Attack by methanol at the carbon bearing the methoxy group, accompanied by phenyl migration, leads to formation of diphenylethanal dimethyl acetal (path A). Diphenylethanal was not observed in the pmr of the reaction mixture. Attack by methanol or nitrate ion at the carbon which bore the thallium leads to formation of XII and XIV with net trans stereochemistry. Alternatively the attacking nitrate ion may arise from the coordination sphere of the departing thallium.

The dinitrates, XV and XIX, are also formed with net trans addition. Again as TTN attacks the molecule, the developing positive center is attacked in a trans fashion by a nitrate group (either nitrate ion in solution or from another TTN molecule). Phenyl participation as thallium leaves as previously described and attack by methanol or nitrate ion would lead to formation of the dinitrate or the methoxy nitrate with net trans stereochemistry.

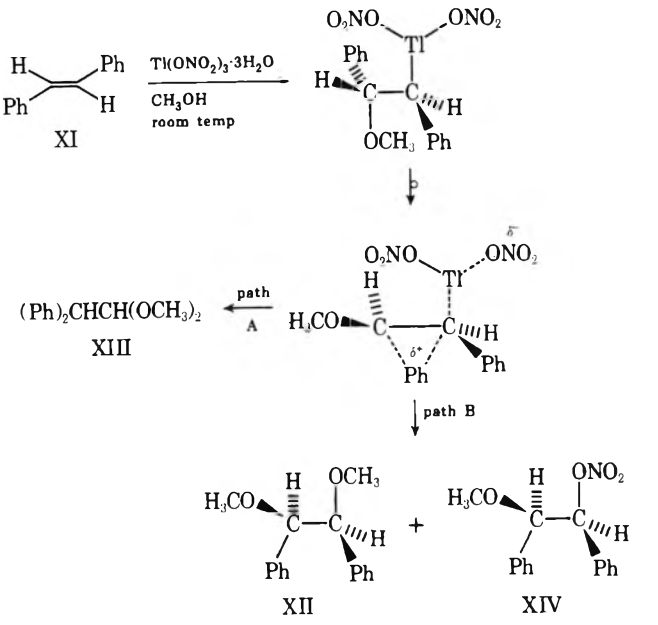
The formation of dinitrates seems to be dependent upon the stability of the carbonium ion that is formed as TTN attacks. Thus dinitrates are observed from the reaction of 2,3-dimethyl-2-butene (X) and *cis*- and *trans*-stilbene (XIX and XV) but they were not observed in the reaction of 1-decene.

Table I
Oxidation Products of Stilbene

Product	Yield, % Shearer and Wright[a] *cis*-	Shearer and Wright[a] *trans*-	Present study *cis*-	Present study *trans*-
XII	2 (2)	22 (28)		20–25
XIII	39 (41)	21 (27)	35–30	47–36
XIV		34 (42)		33–36
XV				0–3
XVII	17 (18)	2 (3)	31	
XVIII	38 (40)		29–33	
XIX			5–6	

[a] Yields normalized to exclude recovered starting material appear in parentheses.

Scheme II



Shearer and Wright[10] studied the reaction of *cis*- and *trans*-stilbene with mercury(II) nitrate in methanol. Their results are listed in Table I. A comparison with the present study indicates that reaction with mercury(II) nitrate leads to formation of products in similar yields. The major difference is the presence of dimethoxy product which results from overall cis addition and the absence of dinitrates (XV and XIX).

Summary. TTN oxidation of *cis*- and *trans*-stilbene, 2,3-dimethyl-2-butene, and 1-decene lead to the formation of methoxy nitrate esters and in two cases dinitrate esters. Studies with *cis*- and *trans*-stilbene indicate that product formation occurs with net trans stereochemistry.

Experimental Section

All melting points are uncorrected and were obtained on a Thomas-Hoover capillary melting point apparatus. Infrared spectra were obtained on a Perkin-Elmer Infracord spectrophotometer and proton magnetic resonance spectra were recorded with a Varian A-60A spectrometer. Preparative gc work was carried out on an Aerograph A-90-P instrument equipped with a thermal conductivity detector.

Reaction of 1-Decene and 2,3-Dimethyl-2-butene with TTN in Methanol. In a typical experiment 18 mmol of the alkene was dissolved in 25 ml of absolute methanol and stirred at 0°. After slow addition of 22 mmol of $Tl(NO_3)_3 \cdot 3H_2O$ in 50 ml of absolute methanol, the reaction mixture was stirred for an additional 1 hr at 0°. The solution was filtered to remove thallium(I) nitrate, dis-

solved in 150 ml of H_2O, and extracted with ether. The extracts were washed with H_2O and saturated NaCl solution and dried ($MgSO_4$). After filtration and removal of solvent the mixture of products was dissolved in CCl_4 and examined by ir and pmr.

Reaction of *cis*- and *trans*-Stilbene with TTN in Methanol. Because of the limited solubility of *trans*-stilbene in methanol, the stilbene reactions were carried out at room temperature. In a typical experiment, 8.0 mmol of TTN dissolved in 50 ml of absolute methanol was added to a solution of 2.8–5.6 mmol of alkene in 80 ml of absolute methanol at room temperature. This solution was stirred for 24–72 hr and then worked up as previously described.

Preparation of 1-Methoxy-2-decanol and 2-Methoxy-1-decanol. To a solution of 23 g (0.113 mol) of 85% *m*-chloroperbenzoic acid (MCPBA) in 200 ml of $CHCl_3$ was slowly added 14 g (0.10 mol) of 1-decene dissolved in 50 ml of $CHCl_3$. After an initial warming, the solution cooled to room temperature and was stirred for 4 hr. The solution was filtered, washed with 10% aqueous KOH, water, and saturated NaCl solution, and dried ($MgSO_4$). Evaporation of the solvent gave 1,2-epoxydecane, which was allowed to react without further purification. To a stirred solution of 3.00 g (19.2 mmol) of 1,2-epoxydecane in 25 ml of absolute methanol was added 2 drops of concentrated H_2SO_4.[12] After 15 min the solution was added to 75 ml of H_2O and extracted with ether. Ether extracts were combined, washed with H_2O, and dried ($MgSO_4$). Evaporation of the filtered solution yielded a mixture of 1-methoxy-2-decanol and 2-methoxy-1-decanol. The isomers were separated by preparative gc (10 ft × 0.25 in., 25% DEGS on Chromosorb 60/80).

Preparation of 2-Methoxy-1-decyl Nitrate (IV). A 0.50-g (2.7 mmol) sample of 2-methoxy-1-decanol was added dropwise to a stirred solution of 12 ml of fuming nitric acid and 24 ml of acetic anhydride at 0°. After stirring for 10 min at 0° the solution was poured on 75 ml of cracked ice and extracted with ether. The ether solution was washed with H_2O and dried ($MgSO_4$). After filtration, the solvent was evaporated to yield 0.23 g (37%) of IV, without any evidence of unreacted starting material, as a slightly yellow liquid: ir (neat) 2910, 1630, 1460, 1270, 1110, and 855 cm^{-1}; pmr (CCl_4) δ 4.35 (d, 2, H_1), 3.35 (s, 3, OCH_3; m, 1, H_2), 1.30 (br s, 14, alkyl), and 0.89 (m, 3, H_{10}).

Anal. Calcd for $C_{11}H_{23}NO_4$: C, 56.63; H, 9.94; N, 6.00. Found: C, 56.67; H, 10.34; N, 6.46.

Preparation of 1-Methoxy-2-decyl Nitrate (V). The same procedure as described for the preparation of IV was followed using 0.50 g (2.7 mmol) of 1-methoxy-2-decanol. This yielded 0.28 g (45%) of V, without any evidence of unreacted starting material, as a slightly yellow liquid: ir (neat) 2910, 1630, 1470, 1270, 1120, 855, and 800 cm^{-1}; pmr (CCl_4) δ 5.04 (m, 1, H_2), 3.44 (d, 2, H_1), 3.30 (s, 3, OCH_3), 1.34 (br s, 14, alkyl), and 0.89 (m, 3, H_{10}).

Anal. Calcd for $C_{11}H_{23}NO_4$: C, 56.63; H, 9.94; N, 6.00. Found: C, 56.59; H, 10.24; N, 6.42.

Preparation of 1,2-Dimethoxydecane (II). A mixture of 3.00 g (16.0 mmol) of 1-methoxy-2-decanol and 2-methoxy-1-decanol was dissolved in 30 ml of ether with 7 drops of BF_3-OEt_2 at 0°. Diazomethane in ether was decanted into the alcohol solution and allowed to react for 2 hr at room temperature. The solution was cooled to 0° and excess diazomethane was destroyed by cautious addition of formic acid. The ether solution was extracted with saturated bicarbonate, H_2O, and saturated NaCl solution and dried ($MgSO_4$). The sample isolated after filtration and evaporation of the solvent was eluted through an alumina column (200 × 10 mm, activity 1, 80–200 mesh) with pentane to yield II as a clear liquid: ir (neat) 2930, 1460, and 1100 cm^{-1}; pmr (CCl_4) δ 3.30 (s, 3, OCH_3), 3.26 (s, 3, OCH_3), 3.28 (m, 3, H_1 and H_2), 1.30 (br s, 14, alkyl), and 0.90 (m, 3, H_{10}).

Anal. Calcd for $C_{12}H_{26}O_2$: C, 71.23; H, 12.95. Found: C, 70.86; H, 13.21.

Preparation of 2,3-Dimethyl-3-methoxy-2-butyl Nitrate (IX). 2,3-Dimethyl-3-methoxy-2-butanol was obtained from VI by following the reaction sequence to obtain the methoxy alcohol mixture from 1-decene. Nitration of 2,3-dimethyl-3-methoxy-2-butanol by previously described procedures yielded a sample of IX as a clear liquid: ir (neat) 2940, 1620, 1470, 1370, 1290, 1120, 1070, and 880 cm^{-1}; pmr (CCl_4) δ 3.21 (s, 1, OCH_3), 1.59 (s, 2), and 1.20 (s, 2).

Anal. Calcd for $C_7H_{15}NO_4$: C, 47.45; H, 8.53; N, 7.90. Found: C, 47.14; H, 8.90; N. 7.83.

Preparation of 2,3-Dimethyl-2,3-butanediol Dinitrate (X). 2,3-Dimethyl-2,3-butanediol hexahydrate was prepared by the bimolecular reduction of acetone with magnesium amalgam.[13] Nitration of 1.00 g (4.4 mmol) of the diol by previously described procedures led to the formation of 0.81 g (89%) of X as crystalline needles: mp 62–63°; ir (CCl_4) 3000, 1630, 1460, 1380, 1280, 1120, 920, and 850 cm^{-1}; pmr (CCl_4) δ 1.70 (s).

Preparation of *erythro*-1,2-Diphenyl-2-methoxy-1-ethyl Nitrate (XIV). Compound XIV was obtained from *trans*-stilbene by following the same reaction sequence as in preparing IX from 2,3-dimethyl-2-butene. To affirm the stereochemistry 0.59 g (2.2 mmol) of XIV was treated with $LiAlH_4$[9] to yield 0.37 g (72%) of *erythro*-1,2-diphenyl-2-methoxy-1-ethanol, mp 101–102.5° (lit.[10] mp 100–102°). The reaction of 1.00 g (5.1 mmol) of *trans*-stilbene oxide by the described procedure yielded 0.59 g (42%) of XIV as white crystals: mp 88–90° (lit.[10] mp 91.4–92°); ir (CCl_4) 2930, 1640, 1260, 1110, 960, and 845 cm^{-1}; pmr (CCl_4) δ 7.22 (m, 10, aromatic), 5.83 (d, 1, H_1), 4.44 (d, 1, H_2), and 3.20 (s, 3, OCH_3), $J_{H(1),H(2)}$ = 5.5 Hz.

Preparation of *threo*-1,2-Diphenyl-2-methoxy-1-ethyl Nitrate (XVIII). *cis*-Stilbene oxide was prepared from *trans*-stilbene oxide by the method of Berti.[14] Starting with 0.40 g (2.0 mmol) of *cis*-stilbene oxide and following the procedure for the preparation of XIV yielded 0.23 g (45%) of XVIII as white crystals: mp 91–94° (lit.[10] mp 92–93°); ir (CCl_4) 2900, 1640, 1260, 1110, 965, and 860 cm^{-1}; pmr (CCl_4) δ 7.10 (m, 10, aromatic), 5.87 (d, 1, H_1), 4.36 (d, 1, H_2), and 3.26 (s, 3, OCH_3), $J_{H(1),H(2)}$ = 8.0 Hz.

Preparation of *meso*-1,2-Diphenyl-1,2-dimethoxyethane (XII). A solution of 0.33 g (1.4 mmol) of *erythro*-1,2-diphenyl-2-methoxy-1-ethanol in 15 ml of DMF was treated with 2.0 g (8.6 mmol) of Ag_2O and 2 ml (4.6 g, 32 mmol) of CH_3I under the same conditions as the preparation of XVII. This yielded 0.22 g (62%) of XII as white crystals: mp 137–139° (lit.[15] mp 139–141°); ir (KBr) 2880, 1430, 1190, 1170, 1080, 935, 820, 750, and 690 cm^{-1}; pmr (CCl_4) δ 7.18 (br s, 5, aromatic), 4.08 (s, 1, H_1 and H_2), and 3.06 (s, 3, OCH_3).

Preparation of *dl*-1,2-Diphenyl-1,2-dimethoxyethane (XVII). A solution of 0.50 g (2.3 mmol) of *dl*-1,2-diphenyl-1,2-ethanediol in 15 ml of DMF was covered with aluminum foil and 2.5 g (10.8 mmol) of freshly prepared Ag_2O and 4 ml (9.12 g, 64 mmol) of CH_3I were added. This was stirred for 24 hr at room temperature and suction filtered. The filtrate was dissolved in 75 ml of H_2O and extracted with ether. The ether extracts were washed with water and dried ($MgSO_4$). After filtration, evaporation of solvent gave crude product (mp 128–136°). Recrystallization from petroleum ether gave 0.21 g (37%) of XVII as white crystals: mp 90–92° (lit.[15] mp 91–92°); ir (KBr) 2860, 1430, 1190, 1170, 1060, 950, 825, 755, and 690 cm^{-1}; pmr (CCl_4) δ 7.00 (m, 5, aromatic), 4.21 (s, 1, H_1 and H_2), and 3.23 (s, 3, OCH_3).

Preparation of *meso*-1,2-Diphenyl-1,2-ethanediol Dinitrate[11] (XV). To a solution of 3.40 g (10 mmol) of *meso*-1,2-dibromo-1,2-diphenylethane[16] in 100 ml of refluxing glacial acetic acid was slowly added a solution of 4.10 g (24.0 mmol) of $AgNO_3$ in 10 ml of HOAc–H_2O (1:1). The solution was refluxed for 15 min and filtered hot, 500 ml of H_2O was added, the solution was cooled, and the crystals were collected. Recrystallization from benzene–petroleum ether (1:1) yielded 1.02 g (34%) of XV as white crystals: mp 145–146° (lit.[11] mp 148.5–149.5°); ir (KBr) 1640, 1260, 1250, 975, 840, 770, 750, and 695 cm^{-1}; pmr (CCl_4) δ 7.29 (m, 5, aromatic) and 6.08 (s, 1, H_1 and H_2).

Preparation of *dl*-1,2-Diphenyl-1,2-ethanediol Dinitrate (XIX). Compound XIX was prepared by the method of Hayward and coworkers.[11] A solution of 0.50 g (2.3 mmol) of *dl*-1,2-diphenyl-1,2-ethanediol[17] was dissolved in a stirred solution of 15 ml of HOAc–H_2O (1:1) at 0°. A 12-ml solution of HOAc–Ac_2O–fuming HNO_3 (1.5:1.5:1.0) was slowly added. The reaction mixture was stirred for 45 min at 0°, added to 100 ml of H_2O, and extracted with ether. The ether solution was washed with H_2O and dried ($MgSO_4$), and evaporation of solvent after filtration gave crude product. Elution through an alumina column (200 × 10 mm, activity 1, 80–200 mesh) with benzene–petroleum ether (1:1) followed by recrystallization from the same solvent yielded 0.38 g (54%) of XIX as white crystals: mp 103–105° (lit.[11] mp 105.5–107.5°); ir (KBr) 1640, 1270, 970, 835, 755, 740, and 695 cm^{-1}; pmr (CCl_4) δ 7.20 (m, 5, aromatic) and 6.00 (s, 1, H_1 and H_2).

Preparation of Diphenylethanal Dimethyl Acetal (XIII). Diphenylethanal (3.00 g, 15.3 mmol) was dissolved in 100 ml of methanol with 1 ml of concentrated HCl and let stand for 72 hr at room temperature with occasional shaking. The solution was then made slightly basic with NaOMe in methanol, concentrated on a steam bath, dissolved in 200 ml of H_2O, and extracted with ether. The ether solution was washed with H_2O and dried ($MgSO_4$), and evaporation of solvent gave a viscous liquid. Distillation yielded 2.82 g (76%) of XIII as a clear, viscous liquid: bp 138° (0.55 mm); ir (neat) 2900, 1480, 1440, 1180, 1110, 1060, 975, 755, 745, and 695

cm^{-1}; pmr (CCl_4) δ 7.14 (m, 10, aromatic), 4.83 [d, 1, $CH(OCH_3)_2$], 4.12 [d, 1, $CH(C_6H_5)_2$], and 3.17 (s, 6, OCH_3), $J_{H(1),H(2)}$ = 8.0 Hz.

Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.18; H, 7.33.

Registry No.—I, 872-05-9; II, 30390-81-9; IV, 51936-02-8; V, 51936-03-9; VI, 563-79-1; IX, 51936-04-0; X, 51936-05-1; XI, 103-30-0; XII, 1147-17-7; XIII, 51936-06-2; XIV, 51936-07-3; XV, 3720-11-4; XVI, 645-49-8; XVII, 14156-28-6; XVIII, 51936-08-4; XIX, 3720-10-3; TTN, 13746-98-0; 2-methoxy-1-decanol, 5935-15-9; 1-methoxy-2-decanol, 5935-14-8; 2,3-dimethyl-3-methoxy-2-butanol, 51936-09-5; 2,3-dimethyl-2,3-butanediol, 76-09-5; *erythro*-1,2-diphenyl-2-methoxy-1-ethanol, 6941-71-5; *dl*-1,2-diphenyl-1,2-ethanediol, 655-48-1; *meso*-1,2-dibromo-1,2-diphenylethane, 13027-48-0; diphenylethanal, 947-91-1.

References and Notes

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Evidence Pointing to an Uncharged Homoheteroaromatic System in an Enaminoimine with an N–H–N Bridge

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Received March 12, 1974

Spectral and chemical evidence suggest cyclic delocalization in the ground state of 1,2-di-*tert*-octylamino-3-*tert*-octylimino-1,3-dicyanopropene-1 (7). A monohomopyrazole structure is proposed with a short intramolecular N–H–N bond that bridges the single interruption in the σ framework. This bond is postulated to have a potential with either a symmetrical double well or a central single well. The hydrogen atom is probably located out of the plane of the ring, thus allowing transmittal of conjugation through overlap of p orbitals on the terminal nitrogens. Electron density is expected to be relatively low on these nitrogens and high on the α carbon atoms. It is proposed that the stabilizing effect of the nitrile groups may make such a homoaromatic structure energetically favorable.

Homoaromatic systems are defined as aromatic systems in which part of the σ framework is interrupted.[1] Homoaromatic stabilization is now well recognized for a number of charged species.[2,3] Recently homoaromaticity has for the first time been demonstrated in a neutral hydrocarbon.[4]

In heterocyclics such as pyrrole and pyrazole, aromaticity implies (in a VB representation) the contribution of charge-separated ylide-like structures. This suggests the possible existence of neutral homoaromatic heterocyclic systems.

An unusual type of cyclic delocalization, reminiscent of homoaromaticity, has been proposed before for certain compounds with enaminoimine or aminotroponimine structures. Specific examples are 2-benzylamino-4-benzyliminopentene-2 [**1** ≡ **2a** (or **2b**), R_1 = CH_2Ph; R_2 = CH_3][5a] and 1-methylamino-7-methylimino-1,3,5-cycloheptatriene (**3**).[6] (See Chart I.)

Subsequently, Daltrozzo and Feldmann[5b] have shown that in **1** no unusual cyclic delocalization exists. Instead, very rapid proton exchange occurs between the nitrogen atoms of two tautomeric forms [**2a** ⇌ **2b**, R_1= $PhCH_2$;R_2 = CH_3 (Chart I)].

Furthermore, Müller-Westerhoff[7a] has recently disproven nonclassical aromaticity in 6-aminofulvene-2-aldimines (**4**, Chart I) and has extrapolated this conclusion to the structurally related aminotroponimines (**3**).

He concludes, however, that some interaction between orbitals on the two nitrogens[8] is probable "in spite of" the proton (at very small N–N distance). In essence this amounts to a homoallylic effect. Müller-Westerhoff did not consider a bent N–H–N bridge with the hydrogen out of the plane. However, for effective transmission of conjugation, the overlap must be intermediate between π and σ.[1] That is only possible when the bridging hydrogen is located out of the plane of the ring.[10]

In enaminoimines such as **1** the substituents (methyl or benzyl) on the chelated ring have been shown to be equivalent by nmr spectroscopy.[5,11a,12] Averaging of the environment must therefore be rapid relative to the nmr time scale. This implies that not only fast intramolecular proton transfer occurs but that additionally the ring atoms have to average their positions through a concerted adjustment of bond lengths.

Although these two processes must occur concurrently, and must both be fast, they need not necessarily be synchronized. Proton transfer can probably occur much faster than concerted bond length adjustment because the latter requires rehybridization at the terminal nitrogens as well as movements of the carbon and nitrogen atoms that are large relative to normal vibrational amplitudes.

The N–H–N bond in the enaminoimines may resemble the bridges in the associated imidazoles which have been investigated extensively by Zimmermann.[14] Ultrafast proton transfer—possibly by tunneling—may occur without

Chart I

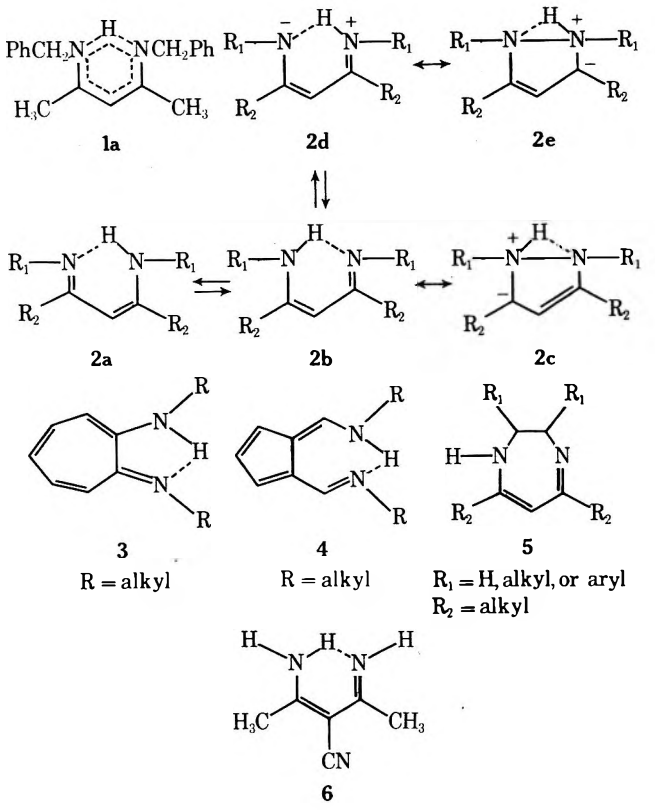
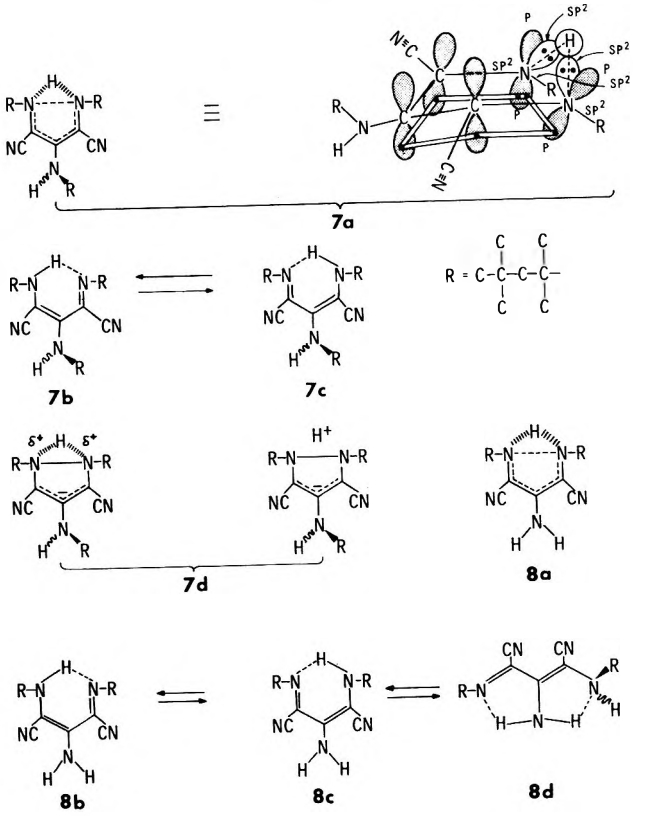


Chart II



adjustment of bond lengths, thus giving rise to rapid interconversion between a nonpolar structure **2b** and a proton-transferred structure **2d.**[15]

Homoallylic overlap between p orbitals on the nitrogens would result in the additional, bridged forms **2c** and **2e.** Owing to the distorted bond lengths, the first of these is probably of high energy and contributes little to the stability of the open nonpolar structure **2b.** The relatively undistorted **2e** may, however, stabilize the open proton-transferred structure **2d** considerably. This should tend to diminish the energy difference between **2b** and **2d** as well as the height of the separating energy barrier. Such conditions are conducive to proton delocalization (tunneling) as demonstrated by Zimmermann for the associated imidazoles.[14a]

Homoallylic interaction could thus account for an anomalously short and possibly strengthened hydrogen bridge in enaminoimines.

In the ylide-like forms **2e** and **2c** a formal positive charge resides on the heteroatom and a negative charge on the α-carbon atom. Therefore, substitution of electron-withdrawing groups on the α-carbon atoms in enaminoimines should increase stabilization. The opposite should be true for electron-donating substituents such as the methyl groups of **1.** Furthermore, certain electron-withdrawing groups may be capable of stabilizing a homoaromatic ground state with all ring atoms in intermediate positions. The amount of energy required to keep the ring atoms in these intermediate positions can be roughly estimated from a comparison with the benzene–cyclohexatriene case. The compression energy of benzene, where six bonds are involved, has been variously estimated at 27–35 kcal.[16] For enaminoimines, where only four bonds are involved, 20 kcal is a rough estimate. If cyclic delocalization is to occur, it must at least account for this amount of resonance energy.

On the basis of spectral and chemical evidence, it is proposed that this requirement may be met for 1,2-di-*tert*-octylamino-3-*tert*-octylimino-1,3-dicyanopropene-1 (**7**)[17] (Chart II). Specifically, the nmr spectrum shows evidence for the presence of a ring current; vibrational spectra indicate molecular symmetry, a high degree of equalization of bond orders in the ground state, and the absence of a mode attributable to the C=N moiety; the uv spectrum shows an anomalous "interaction band;" and protonation occurs on one of the "electron-rich" carbon atoms, bearing the nitrile groups, rather than on a relatively electron-depleted amino or imino nitrogen.

A second compound (**8**) has also been prepared which differs from **7** only through lack of a *tert*-octyl substituent on the central amino group. For **8** all available evidence suggests a classically conjugated enaminoimine structure.

If the transition from homoconjugative interaction—as may occur in **1**—to complete cyclic delocalization—as postulated for **7**—indeed depends upon transmission of electron withdrawal by the nitrile groups (see above), then the lack of homoaromaticity in **8** may be rationalized as follows.

Models of **7** and nmr evidence indicate that the effect of the bulky substituent on the central amino group is to twist the lone electron pair on nitrogen out of conjugation with the unsaturated system in the hydrogen bonded ring and consequently with the vinylic β-nitrile group. However, through the circuitous homoconjugative route, the electron demand of this nitrile group could be satisfied by the α-amino group.

In contrast, the unsubstituted central amino group in **8** can be coplanar with the ring and can provide electron density to the vinylic β-nitrile group. The correspondingly lowered demand for homoconjugative electron supply from the α-amino group may now be insufficient to support homoaromaticity. Moreover, in **8**, hydrogen bond formation between the terminal amino and imino groups (**8b** $\rightleftharpoons$ **8c,** Chart II) must compete with hydrogen bonding between these groups and the central unsubstituted amino group as in **8d** where homoaromaticity is not possible.

Since the cyclic delocalization as in **7a** requires all ring atoms to remain in intermediate positions, the N–H–N

Table I
Nmr Spectrum[a] of 7

Solvent	Temp, °C	NH		CH_2		$C(CH_3)_2$		$C(CH_3)_3$[b]	
		A	B	A	B	A	B	A	B
CCl_4	25	9.88	2.68	1.54	1.79	1.10	1.42	1.05	0.95

[a] In parts per million (δ). [b] The small difference in the positions of the A and B *tert*-butyl signals (A and B labeling as in Figure 1) may be largely of statistical origin. A model (Figure 2) shows that rotation around the single bonds in the *tert*-octyl substituents allows the A *tert*-butyl groups to enter both nitrile-deshielding zones while the B group can enter only one.

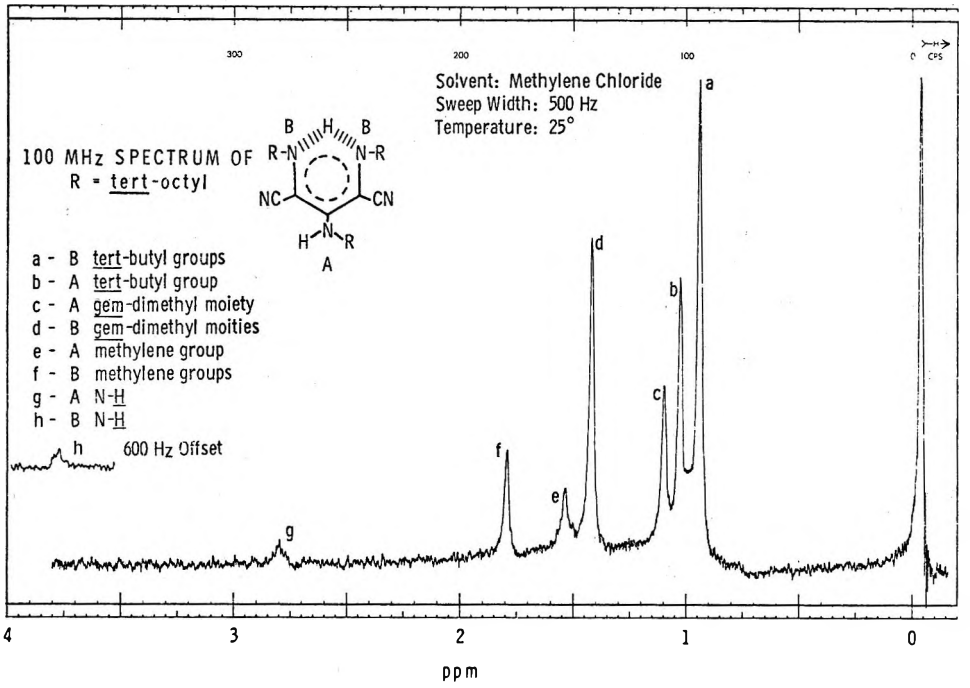


Figure 1.

bridge must be symmetrical with either two equally deep energy wells or a single central well.[18] The nature of this bridge is, however, incidental to its prime function in **7a**. This is to keep the nitrogens in close proximity so as to allow effective p-orbital overlap.

Evidence for the Structures of 7 and 8. Nmr Spectra. Nmr spectra have been reported for a few symmetrically substituted enaminoimines. In each case, the substituents were found to be magnetically equivalent. This indicates proton exchange between the nitrogens, which is fast relative to the nmr time scale.

Examples are the 1,4-diazepines[21a] (**5**), 2-benzylamino-4-benzyliminopentene-2[5] (**1**), and 2-amino-3-cyanopent-2-ene-4-imine[11a] (**6**).

Spectrum of 8.[17] The nmr spectrum in CCl_4 solution (see Experimental Section) is consistent with an equilibrium mixture of two configurational isomers, C and D, in approximately equimolar proportion.[17] The two *tert*-octyl groups are equivalent in C and nonequivalent in D. The equivalence in C is consistent with the presence of an intramolecular hydrogen bond in which very fast tautomeric proton exchange occurs (**8a** or **8b** ⇌ **8c**, Chart II). The nonequivalence in D implies the absence of such exchange. A probable structure for D appears to be **8d**, which is stabilized by two hydrogen bonds. Alternative structures with a single hydrogen bond cannot, however, be ruled out.

Rapid interconversion between different enaminoimine isomers may occur through a tautomeric diimine intermediate, which could be present in a small equilibrium concentration.

Spectrum of 7[17] **(Table I, Figure 1).** The magnetic equivalence of the *tert*-octyl groups on the terminal nitrogen atoms in **7** and an NH resonance far downfield at δ 9.98 ppm can be accounted for in either of two ways.

(1) Rapid tautomerization occurs, involving very fast proton transfer between the terminal nitrogens (**7b** ⇌ **7c**, Chart II).

(2) The heavier ring atoms remain essentially stationary in intermediate positions (**7a**, Chart II).

In either case, it must be assumed that the central amino group is twisted so that its *tert*-octyl substituent remains essentially equidistant from the β-carbon atoms. In case 2, this follows directly drom the implied symmetry. In case 1, the alternative would require improbably fast oscillation of this bulky group.

The *tert*-octyl groups on the terminal nitrogens remain magnetically equivalent even at −80°, but this does not prove cyclic delocalization as in **7a**.[22]

However, the nmr spectrum of **7** strongly suggests the presence of a ring current, which is commonly accepted as a criterion for aromatic character.

Evidence for a Ring Current in 7. Aromatic ring currents give rise to shielding in two conical domes with a common truncated apex that coincides with the ring. Deshielding occurs in the remaining peripheral zone.[23]

The resonances assigned to the methylene and the *gem*-dimethyl groups in the *tert*-octyl substituent on the central (A) amino group of **7** are shifted upfield by about 0.3 ppm relative to the corresponding resonances for the equivalent *tert*-octyl groups on the terminal (B) nitrogens. (See Figure 1 and Table I.) The A amino group is forced "out of conjugation" owing to steric crowding (see above), and its *tert*-octyl substituent is therefore suspended above the plane of the ring, unlike the two *tert*-octyl substituents on the ter-

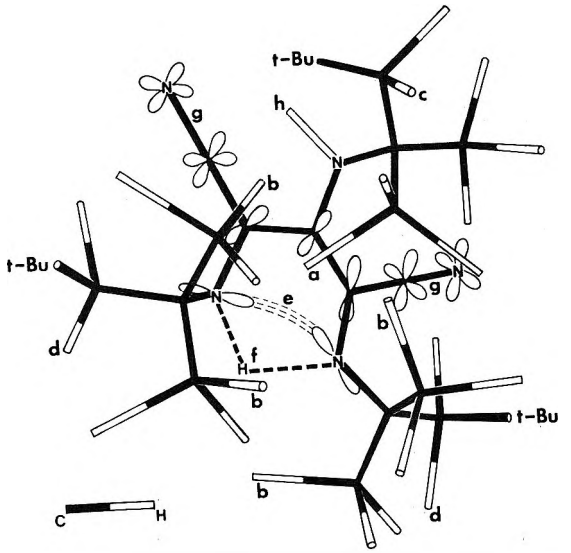
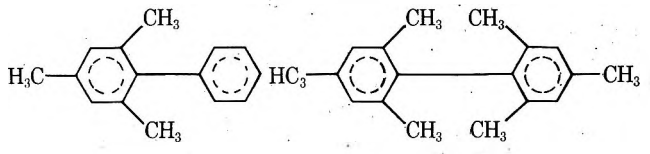


Figure 2.

minal nitrogens, which are more or less confined to that plane (Figure 2). In the A substituent, the methylene group and the two *gem*-dimethyl groups are three bond distances removed from the ring carbon atom and should thus be in the proper position to experience shielding. The magnitude of the observed shift suggests that an aromatic ring current indeed exists. Since at any one time only a single hydrogen can be located in the ring current (see Figure 2), the actual shift per affected hydrogen is greater by a statistical factor which may be as large as 8.

In phenylmesitylene and dimesityl[24] (**9** and **10** below), the o-methyl groups (unlike the *p*-methyl groups) are similarly suspended above and below an aromatic ring at three bond distances. Here, the difference in the shifts of the o-



9 **10**

and *p*-methyl groups is 0.30–0.45 ppm. In these compounds, both *o*-methyl groups are simultaneously located in the shielding cones. In the case of **7**, however, only one A methyl or methylene group at a time is properly oriented to experience shielding so that only an average value is recorded. Allowing for all statistical factors, the shielding observed for **7** appears to be considerably larger than that for the two aromatic model compounds **9** and **10**.

The presence of an aromatic ring current may also account for the relative shielding of the bridging proton (δ 9.88 ppm). For a strongly intramolecularly bonded N–H, this resonance is located at a surprisingly high field.[25] Relative to the corresponding N–H signal for **8**, in which the N–H–N bond is supposedly asymmetrical, the N–H signal for the N–H–N bridge in **7** is shifted downfield by only 2 ppm. Since effective homoaromatic orbital overlap requires that the bridging proton is located out of the plane of the ring (see above), it may be within one of the shielding cones associated with the aromatic ring current. (See Figure 2.)

The ultimate position of the bridge NH resonance in **7** would accordingly be determined by two opposing effects: a downfield shift associated with the symmetry of the N–H–N bridge and an upfield shift due to ring current induced shielding anisotropy.

The anomalous shielding of the proton signals in cyclopropane—with a well-established ring current—has been similarly explained.[27]

Comparison of the Vibrational Spectra of 8 and 7. The nmr evidence shows that **8** occurs in carbon tetrachloride solution as a mixture of two configurations (C and D). In the crystalline state, however, structural uniformity is suggested by the sharp melting point.[28]

Accordingly the configurational mixture in carbon tetrachloride solution shows two ir-active nitrile bands while the configurationally pure crystalline compound (KBr disk) shows a single ir-active nitrile band at 2175 cm^{-1}, which is also strongly Raman active. The Raman spectrum shows an additional band at 2222 cm^{-1}, which is ir inactive. These spectral features are consistent with a single structure with two nonequivalent nitrile groups: An enaminonitrile group (2175 cm^{-1}, strongly ir and Raman active, reported[29] range 2198–2165 cm^{-1}) and a iminonitrile group (2222 cm^{-1}, ir inactive or weakly active and Raman active, reported[30] frequency 2232 cm^{-1}).

Ir spectra of **7**, in carbon tetrachloride or in a potassium bromide disk, are essentially the same, thus pointing to identical configurations in the dissolved and crystalline states. A single ir-active band at 2220 cm^{-1} and a single Raman-active band at 2212 cm^{-1} indicate two equivalent nitrile groups which interact to give two stretching modes: one asymmetric and ir active, the other symmetric and Raman active.

The N–H Stretching Region. In this region, **8** shows several strong and medium bands consistent with the simultaneous presence of a primary and a secondary amino group.

In the same region, **7** shows a very weak split band, centered at 3360 cm^{-1}, and another very weak broad band at 3180 cm^{-1}. These bands shift to 2500 and 2300 cm^{-1} upon deuteration.

The frequency of both bands appears to be too high to be associated with the N–H–N bridge, which according to the nmr evidence (see above) is either symmetrical or exhibits very fast tautomeric proton exchange.

For compounds with demonstrated fast proton exchange in an N–H–N bridge the N–H stretch occurs at exceptionally low frequencies (*below* 3000 cm^{-1}). Examples are **1** with a broad shallow band centered at about 2850 cm^{-1}, shifting to 2260 cm^{-1} upon deuteration,[5a] and the 6-aminofulvene-2-aldimines[7] with a broad band centered at about 2625 cm^{-1}, shifting to about 2000 cm^{-1} upon deuteration.

Several additional N–H stretching modes, shifted to <3000 cm^{-1} owing to N–H–N bridge formation, have been reported.[32]

In the spectrum of **7**, there are no bands between 3000 and 1600 cm^{-1}, which are affected by deuteration, nor does deuteration give rise to an N–D band in the 2220-cm^{-1} region which would be indicative of an N–H mode submerged under the C–H absorption at ~3000 cm^{-1}.

Accordingly, the 3360- and 3180-cm^{-1} bands are best assigned to the unassociated and intermolecularly associated N–H stretching vibrations of the central amino group (reported ranges 3350–3310[33] and 3300–3150 cm^{-1} [34]).

The bridging hydrogen in **7** may give rise to a band below 3000 cm^{-1} which is so broad and shallow that it escapes detection, as is the case for protonated 1,8-bis(dimethylamino)naphthalene.[35]

The 1500–1700-cm^{-1} Region. Enaminoimines are structurally related to three classes of compounds: the ami-

dines, the amides, and their vinylogs the enamino ketones. All three show two bands in the 1500–1700-cm^{-1} region, providing that a single hydrogen is attached to the amino nitrogen as it is in **7** or **8**. In each case the position of the shorter wavelength band is almost unchanged by deuteration. This band represents essentially the C=N or C=O stretch [ν(C=N) or ν(C=O)]. The Raman activity, expected for a double bond stretching mode, has been confirmed for the amides[36] and amidines.[37]

For the latter two classes of compounds the longer wavelength band has been assigned to a mixed vibration with a major contribution from the N–H deformation [δ(N–H)] and a minor one from the C–N stretch [ν(C–N)]. Accordingly the band is deuteration sensitive; also it has been shown to be Raman inactive.[36,37]

The extensively investigated enamino ketones[31] occur as intramolecularly hydrogen bonded s-cis forms and intermolecularly bonded s-trans forms. For these compounds the longer wavelength band (1600–1500 cm^{-1}) has been assigned to a mixed vibration of the delocalized O=C–C=C–NH system with contributions from δ(N–H) and ν(C–N) as well as ν(C=O) and ν(C=C). The deuteration sensitivity of this band is higher (~50 cm^{-1}) for the s-cis than for the s-trans forms (~15 cm^{-1}).[31]

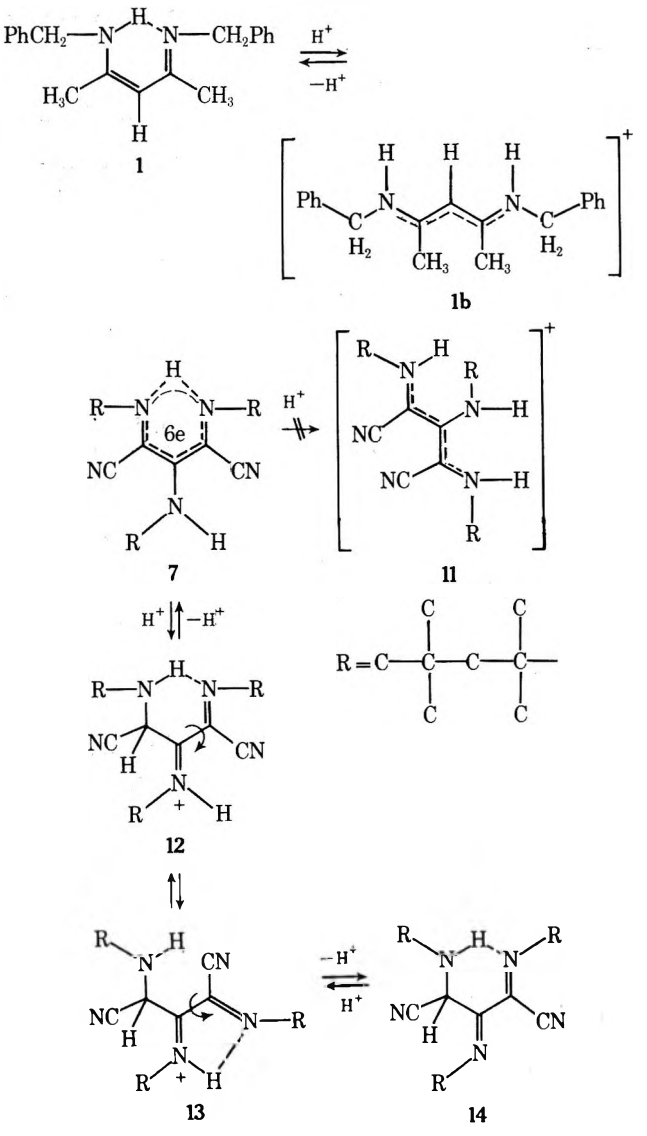
The enamino imines are the vinylogs of the amidines as well as the imino analogs of the enamino ketones. They are therefore expected to conform to the same absorption pattern in the 1500–1700-cm^{-1} region, *i.e.*, a relatively deuteration-insensitive band at higher frequency—designated AVI (amidine vinylog I)—which represents essentially ν(C=N) and a lower frequency AVII band, which is a mixed vibration with contributions from ν(C=N), ν(C=C), ν(C–N), and δ(N–H).[11b] The deuteration sensitivity of this band should be higher for the s-cis than for the s-trans forms, in analogy to the enamino ketones.

These predictions are confirmed by the spectrum of 2-amino-3-cyano-4-iminopentene-2 (**6**),[11b] which is an enamino imine with an intramolecularly hydrogen bonded s-cis configuration. Its spectrum shows an AVI band at 1617 cm^{-1} (shifted to 1600 cm^{-1} upon deuteration) and an AVII band at 1580 cm^{-1} (shifted to 1500 cm^{-1} upon deuteration).[38]

The spectrum of **8**, which is assumed to occur in a single configuration in the crystalline state (see discussion of nitrile region), is also consistent. In a KBr pellet it shows an AVI band at 1592 cm^{-1} (shifted to 1574 cm^{-1} upon deuteration) and an AVII band at 1538 cm^{-1} (shifted to 1535 cm^{-1} upon deuteration). The anomalously small isotope shift of the AVII band suggests an s-trans configuration as in **8d** (Chart II). Both AV bands of **8** are Raman active, consistent with major contributions to both from ν(C=N) and/or ν(C=C).

In this region the ir spectrum of **7**, with bands at 1578 and 1528 cm^{-1}, is superficially similar to that of **8**. However, while both bands of **8** are Raman active, only the second band is Raman active in the case of **7**. This suggests that double bond stretching modes—generally associated with strong Raman activity—make significant contributions to this band only. Upon deuteration this Raman-active band shifts from 1528 to 1472 cm^{-1},[40] indicating considerable participation of δ(N–H). This band is therefore assigned to a mixed vibration of the AVII type. The striking absence of a Raman-active, but deuteration-insensitive, AVI band—specifically assignable to δ(C=N)—may be rationalized by the cyclically delocalized structure **7a**, assuming major contributions to **7a** from **7d**-type forms, which lack the carbon–nitrogen double bond. Structure **7a** could also account for the exceptionally low frequency of the 1528-cm^{-1} band.

Chart III



Assignment of the Raman-inactive 1578-cm^{-1} band of **7** is difficult without additional data.

Ultraviolet Spectra. Uv spectra for several enaminoimines are shown in Table II.

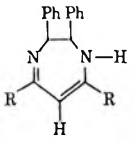
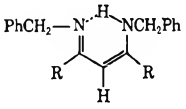
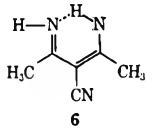
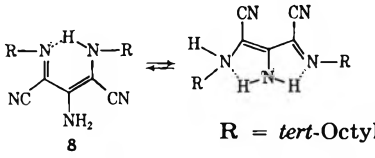
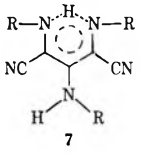
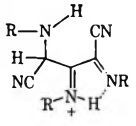
In each case protonation results in a small bathochromic shift of the long-wavelength band and a large increase in ϵ. For the well-documented case of **7**,[5b] this increase has been attributed to conversion of the s-cis free base into the vinylogous amidinium ion **1b** (Chart III) with an extended s-trans configuration.

Protonation of enaminoimines is likely to occur on the imino nitrogen, where the electron density is probably highest owing to resonance (>N–C=C–C=N– ↔ >N$^+$=C–C=C–N–$^-$). This is consistent with the reported alkylation of amidines on the double-bonded nitrogen.[41] The conjugated system is not appreciably affected by protonation on the imino nitrogen. This explains the small difference between uv max of the free base (315 nm) and of the salt (318 nm).

Ultraviolet Spectrum of 8. The uv spectrum of **8** resembles that of the other enaminoimines (Table II). The exceptionally long wavelength of the 400-nm band may be accounted for by the substituents. (An amino substituent on an unsaturated system produces shifts of 65–85 nm.)[42]

The very small wavelength changes upon protonation of **8** suggest that the chromophoric system is not appreciably affected. This is consistent with attachment of the proton

Table II
Ultraviolet Spectra of Enaminoimines and Derived Cations

Compd		Solvent	Uv max, nm	$\epsilon \times 10^{-3}$	Ref
	R = H	Tetrahydrofuran	305, 230	6.08, ~5.6	19a
	Cation	Aqueous HCl (1 *N*)	333		
	R = CH_3	Tetrahydrofuran	302, 230	6.60, ~5.6	19a
	Cation	Aqueous HCl (1 *N*)	327		
	R = H	CCl_4	318	15.0	5b
	Cation?	MeOH	282	38.0	
	R = CH_3 (**1**)	MeOH, MeO^-	318	17.4	5b
	Cation	MeOH	321	41.7	
 **6**	Cation	H_2O	292, 222	11.8, 13.2	12c
		0.001 *N* HCl	300, 222	22.0, 7.9	
 **8**	R = *tert*-Octyl	Isooctane	400, 234	5.59, 8.37	
		MeOH	407, 242	4.10, 7.82	
		Cation (MeOH)	410, 243	1.69, 12.64	
 **7**	R = *tert*-Octyl	Isooctane	416, 281, 237.5	10.09, 3.22, 8.14	
		MeOH	418, 281, 237.5	8.46, 4.72, 7.12	
		CH_3CN	418, 282, 238	9.57, 3.31, 7.83	
	Cation (**13**) (See Chart III)	CH_3CN, H^+	255.0	7.48	

either to the central amino group or to the imino group, as is the case for the other enamino amines. The imino group in 8 should be sufficiently basic for salt formation in spite of the electron-withdrawing nitrile substituents. In this respect 8 is probably comparable to the 1-cyanoformamidines [$R_2NC(CN)=NH$, R = Me, Et] which form stable salts with mineral acids.[43]

Ultraviolet Spectrum of 7. In addition to long- and short-wavelength bands in approximately the same ranges as for 8, the spectrum of 7 shows a band of moderate intensity at an intermediate wavelength (281 nm, ϵ 3220, Table II), which has no counterpart in the spectra of any of the other enamino imines. A similar band, shown by cyclic amino ketones, has been attributed to transannular interaction between N and C=O.[44] There it is probably largely an excited-state phenomenon since in these substances aromatic stabilization as in 7 is impossible.

In the case of 7, however, the insensitivity of the 281-nm band to changes in solvent polarity suggests that more is involved than an excited-state phenomenon. In that case, one would expect a hypsochromic shift in more polar solvents, as occurs for $n \rightarrow \pi^*$ transitions.[45] The band at 281 nm is therefore tentatively assigned to an electronic transition of the cyclically delocalized system.

Protonation of 7. Chemical Evidence for Cyclic Delocalization. In sharp contrast to the behavior of the enaminoimine 1, which is partially protonated[5b] *even in neutral methanol*, addition of a small amount of acetic acid to solutions of 7 does not affect the spectrum. This difference is striking, although decreased basicity of 7 is expected in view of the electron-withdrawing nitrile substituents. Addition of the equivalent amount of methanesulfonic acid, however, results in protonation, as evidenced by the rapid[46] disappearance of all three bands, characteristic of the free base (Table II).

The originally yellow solution becomes at first brownish red, and the spectrum (CH_3CN) of the protonated species consist of two new bands, uv max 247 nm (ϵ 16,000) and 510 (1780). During the next few minutes, the intensity of the bands at 247 and 510 nm diminishes rapidly, and the solution becomes colorless. Simultaneously, a new band emerges, uv max 255 nm (ϵ 7944).

The disappearance of both long-wavelength bands of the free base (418.0 and 282 nm) suggests shortening of the chromophoric system which can be accounted for by protonation on carbon. Accordingly, it is proposed that the initial band at 247 nm is due to the s-trans immonium ion **12** (Chart III). The subsequent shift of the 247-nm band to 255 nm is associated with a decrease in ϵ_{max}. Since such a decrease is indicative of a trans–cis isomerization,[5b] the 255-nm band is assigned to the s-cis ion **13**.[47] Examination of the products supports these assumptions.

From the solution of protonated 7 the salt 13 CH_3SO_3H was isolated; it had uv max (MeOH) 255 nm (ϵ 7480). Treatment of this salt with base gave the conjugated diimine **14**.

In the presence of a catalytic amount of acetic acid, 14 reverts quantitatively to 7.

The structures assigned to 13 and 14 are based on elemental analysis and spectral data. (See Experimental Section)[49]

The immonium ion **13**, resulting from protonation on carbon, appears to be the thermodynamically determined product of protonation of 7, which itself is the most stable species under essentially neutral conditions.

The anomalous protonation behavior of 7 argues against

the classical enamino imine structure **7b**. In accordance with the protonation of 8 (see above) this structure is expected to protonate on the imino nitrogen (to give **11**, Chart III) or on the central amino group, but not on carbon.

The central amino group is the more likely site, since it should be more basic than the corresponding group in **8**. In **7b** the additional *tert*-octyl substituent should twist the electron pair on nitrogen out of conjugation with the ring and with the β-nitrile group. This should result in diminished electron withdrawal.

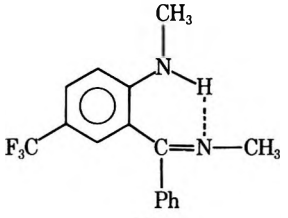
In either case structure **7b** fails to account for the striking changes observed upon protonation of **7**. The wavelength changes due to protonation of **7b** are expected to be minor, as is the case for **8** and the other enaminoimines (Table II).

Protonation of **7** on carbon in preference to the three available sites on nitrogen becomes understandable if **7** has the alternative homoheteroaromatic structure **7a**. This structure implies transfer of electron density from the terminal nitrogens to the α-carbon atoms and the nitrile nitrogens. Accordingly, kinetically controlled protonation on these carbon atoms becomes a possibility. This is not without precedent and actually may be the rule for five-membered hetero(N) aromatics, since protonation of alkylpyrroles has been reported to occur exclusively on the carbon atoms α to nitrogen.[52]

Alternatively, initial protonation of **7a** may occur on a nitrile nitrogen or on the central amino group. In both cases, the ion **12** could result from a fast subsequent proton shift.[53] Protonation of the central amino group may occur without disturbing the homoaromatic ring if it is twisted out of conjugation with the π system. The driving force for the subsequent proton shift could be provided by high electron density on the β-carbon atoms.

A single instance was found in the literature of a neutral heterocyclic system for which spectral anomalies suggest possible homoaromaticity similar to **7a**.

The atypical enaminoimine structure in **15** is fused to an aromatic ring and occurs in an anti (phenyl) configuration [ν(NH) 3570 cm^{-1}] and in an intramolecularly hydrogen bonded syn (phenyl) configuration [ν(NH) 3010 cm^{-1}].[54]



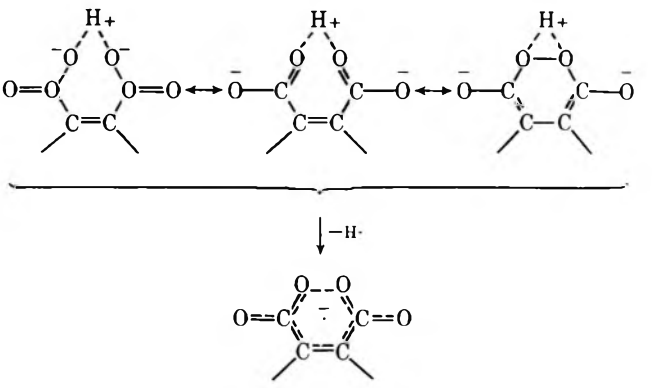
15

The syn isomer has uv max 240 nm (ϵ 30,700), 273–278 (8200), and 358 (6500). The anti isomer has uv max 256 nm (ϵ 24,300). The authors ascribe the anomalous spectrum of the syn form to "expansion of the conjugated system through hydrogen bridge formation."

Clear implications for a broader family of compounds do not yet exist. Cyclic delocalization may be contingent upon stringent structural requirements. As an example a classical structure is indicated for **8** in spite of its close similarity to **7**.

Cyclic delocalization may, however, occur in some structures shown to have symmetrical intramolecular hydrogen bridges which characteristically are anomalously strong and short. Possible examples are the monoanions of maleic[56a] and phthalic acid[56b] and the biochemically important dianion of *cis*-aconitic acid.[56c] The acid maleate anion has, in the crystalline state, C_s rather than C_{2v} symmetry,[56d] suggesting an O–H–O bridge that is bent out of the plane[57] and may allow the necessary overlap of the p orbitals on oxygen.

Upon X-ray irradiation of the crystal, this ion loses the bridging hydrogen with formation of an extremely stable symmetrical anion radical, for which a cyclically delocalized semiquinone-type structure has been proposed,[58] *e.g.*



Experimental Section

Equipment. The following instruments were used: a Perkin-Elmer 621 double beam grating ir spectrometer, a Laser-Raman Carey 91 spectrometer, and a Varian HA-100 nmr spectrometer.

Materials. The preparation and physical properties of 1,2-di-*tert*-octylamino-3-*tert*-octylimino-1,3-dicyanopropene-1 (**7**) and of 1-*tert*-octylamino-2-amino-3-*tert*-octylimino-1,3-dicyanopropene-1 (**8**) are presented in ref 17. The nmr data of **8** are repeated below, since they are relevant to the above discussion, but are not tabulated.

Nmr Spectrum of 8. Nmr (CCl_4) δ 1.017 [2 $C(CH_3)_2$ of C + $C(CH_3)_3$ of D],[59] 1.100 [$C(CH_3)_3$ of D], total 18 H; 1.386 [$C(CH_3)_2$ of D], 1.474 [2 $(CC(CH_3)_2$ of C], 1.586 [$C(CH_3)_2$ of D], total 12 H; 1.693 (CH_2 of D), 1.860 (2 CH_2 of C), 1.920 (CH_2 of D), total 4 H; 3.636, 4.800, 7.650 ppm (NH_2 of C + D and NH of C + D), total 3 H.

Methanesulfonic Acid Salt of 7 (13). To a solution of 0.25 g (5.2×10^{-4} mol) of **7** in 5 ml of ether was added a solution of 0.05 g (5.2×10^{-4} mol) of methanesulfonic acid in 5 ml of ether. After 1 hr at −10°, a crystalline precipitate had formed. The crystals were collected by filtration and redissolved in 1 ml of chloroform, and ether was added dropwise until incipient crystallization occurred. After 1 hr at −10°, filtration gave 0.18 g of the methanesulfonic acid salt: mp 118.5–120° dec; uv max (MeOH) 255 nm (log ϵ 3.87); nmr ($CDCl_3$) δ 0.97, 1.02, 1.07 [27 H total, 3 $C(CH_3)_3$]; 1.60 w, 1.67 s, 1.93 w, 2.03 s [two unresolved multiplets, 24 H total, 3 CH_2 + 3 $C(CH_3)_2$]; 2.40 (1 H, NH); 2.74 (3 H, $CH_3SO_3^-$); 5.83 (1 H, CH); 8.00 ppm (1 H, NH).

Anal. Calcd for $C_{30}H_{57}N_5SO_3$: C, 63.44; H, 10.14; N, 12.33; S, 5.64. Found: C, 63.01; H, 10.39; N, 12.26; S, 5.25.

1-*tert*-Octylamino-2,3-di-*tert*-octylimino-1,3-dicyanopropane (14). A 5-g quantity of **13** was dispersed in 30 ml of ether and shaken with cold 25% aqueous KOH. The solid disappeared, and the ether layer became light yellow. The aqueous layer was discarded, the ether layer was dried over magnesium sulfate, and the ether was evaporated *in vacuo*. The residue was twice recrystallized from warm (50°) hexane: yield 3.2 g of almost colorlees crystals of **14**; mp 91.5–93°; uv max (isooctane) 216.0, 247.5, 316.7 nm (log ϵ 4.05, 3.88, 1.73); ir ($CHCl_3$) 3230 w (NH), 2180, 2215 vw (C≡N), 1685 w, 1645 s (N=C–C=N); nmr ($CDCl_3$) 0.90 [18 H, 2 $C(CH_3)_3$], 1.22, 1.37, and 3.10, 3.25 [2 H (heterosteric), CH_2], 1.73, 1.66 [2 H (heterosteric), CH_2], 1.42, 1.48, 1.51 (double area), 1.57, 1.60 [18 H, six heterosteric CH_3, 3 $C(CH_3)_2$], 5.01 [1 H, CH], 7.64 ppm [1 H, NH, disappears upon deuteration]; mass spectrum (70 eV) *m/e* 471 (M^+); mol wt 469 (Thermonam).

Anal. Calcd for $C_{29}H_{53}N_5$: C, 73.70; H, 11.33; N, 14.95. Found: C, 73.37; H, 11.49; N, 14.96.

Rearrangement of 14 to Give 7. A 4.0-g quantity of **14** was dissolved in 2 ml of ether. Upon addition of 0.5 ml of acetic acid, the light-yellow solution became deep orange. After 1 hr at room temperature, the solvents were evaporated *in vacuo*.

The residue was purified by three crystallizations from pentane at −30°, using decolorizing carbon the first time: yield 2.8 g of **7**,

identified by ir spectrum and mixture melting point determination.

Acknowledgment. For helpful suggestions, I am indebted to Dr. L. W. Rosenthal and Dr. V. P. Kurkov, who proofread the manuscript, and to Dr. R. M. Bly, who helped interpret the ir, Raman, and nmr spectra.

Registry No.—**7**, 40127-68-2; **8**, 40127-66-0; **13**, 51934-35-1; **14**, 51934-36-2.

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Mechanism of the Basic Methanolysis of Benzanilides

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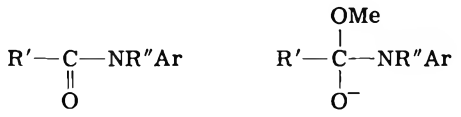
Received March 12, 1974

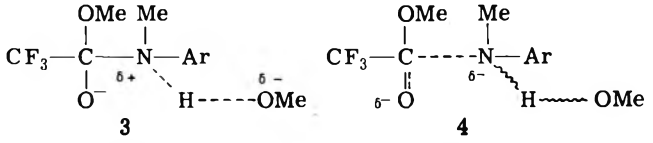
The rate constants for the basic methanolysis of a series of benzanilides (PhCONMeAr), unlike those for the corresponding acetanilides, give a linear Hammett plot. One mechanism operates throughout and is not affected by a change in the acyl aryl substituent. The results are consistent with rate-determining breakdown of the tetrahedral intermediate *via* a transition state involving solvent-assisted C–N bond cleavage.

There is considerable current interest[1] in the details of the basic hydrolysis and alcoholysis of amides. One characteristic feature that has emerged is that, for simple acyclic anilides (1, R′ = H,[1] CH_3,[2,3] CF_3[4]), the Hammett



1 2

plot for aryl-substituted compounds is curved (the apparent ρ value increases with an increase in the electron-withdrawing power of the substituent). This has been interpreted[4] as being due to a change in the mechanism for the rate-determining breakdown of the intermediate (2, for methanolysis) with change in the aryl substituent. Examples of the two extreme transition states are illustrated in 3 and 4.

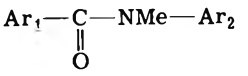


3 4

poor leaving group — ρ = 0 (ref 4)

good leaving group — ρ = 2.9 (ref 4)

We decided to investigate the analogous reaction of *N*-methylbenzanilides (5),[5] since it was reasoned that the



5a, Ar_1 = Ph; Ar_2 variable
b, Ar_1 variable; Ar_2 = p-$NO_2C_6H_4$
c, Ar_1 variable; Ar_2 = Ph

substituent dependence of Ar_1 on rate would vary according to the mechanism of the reaction, determined by the nature of Ar_2. This would then provide another diagnostic probe for investigating such mechanistic changes. The existing data[6,7] on benzanilide reactivity were insufficient to provide the required information and, as they were derived from reaction of the NH compounds, were presumably also complicated by conjugate base formation. We report here a detailed study of substituent effects on the basic methanolysis of *N*-methylbenzanilides where we have found in fact that the complexities evident in the acetanilide system do not occur.

Results and Discussion

Three series (5a–c) of substituted *N*-methylbenzanilides were prepared and their rates of basic methanolysis were measured by a standard spectrophotometric method under pseudo-first-order conditions. The complete kinetic results are given in Table I.

The original aim of the product was voided when the results of series 5a were obtained. Surprisingly, these data give a linear Hammett plot (using σ^- values for p-NO_2 and p-CO_2Me substituents) with a ρ_2 value of 2.5 (373°K). Thus, unlike for the acetanilides, this reaction proceeds *via* the same rate-determining transition state irrespective of the substituent. The change of acyl substituent from alkyl to phenyl is sufficient to overcome any effect of substituent in Ar_2 on the mechanism.

The question then arose as to whether changes in Ar_1 could cause a change in mechanism in a series in which the substituent in Ar_2 was kept constant. Results from series 5b and 5c showed that this is not the case. Again the Hammett plots for the data from each series are linear (σ value for NO_2 substituents), indicating the occurrence of one common mechanism. The agreement of the ρ_1 values [1.73 (339°K) and 1.76 (373°K), respectively] is probably fortuitous because of the different temperatures involved. However, from the linear plots and similar ρ values, one can conclude that the reaction proceeds by the same mechanism through essentially the same transition state for the complete reactivity range from 5b (Ar_1 = m-$NO_2C_6H_4$; Ar_2 = p-$NO_2C_6H_4$) to 5c (Ar_1 = p-$MeOC_6H_4$; Ar_2 = Ph). The change of acyl substituent from alkyl (acetanilides) to aryl produces a far greater effect on the mechanism than does any variation in the aryl group.

All the results are consistent with a common mechanism proceeding *via* a transition state analogous to 4, *i.e.*, solvent-assisted C–N bond cleavage. The ρ_2 value for series 5a is very similar to that found[4] by Schowen for the trifluoroacetanilide reaction proceeding through this transition state and the lower, but appreciable, ρ_1 values in 5b and 5c are consistent with this mechanism.

The alternative extreme mechanism involving breakdown of the tetrahedral intermediate, *viz.*, rate-determining protonation of the nitrogen, 3, is not compatible with the results. Reaction *via* this transition state has been shown[4] to have a low ρ_2 value and ρ_1 would also be expected to be much smaller for protonation at the distant nitrogen than was experimentally observed. For example, ρ = 1.05 (298°K) for the dissociation of substituted benzylammonium ions.[8] In addition, the large rate enhancement observed at both ends of the reactivity scale on changing the solvent to 80% DMSO–methanol (a factor of 454 at 286.5°K for $PhCONMeC_6H_4NO_2$-p and 330 at 373°K for PhCONMePh) is consistent with reaction by way of 4 but not 3 (in which a negligible solvent effect occurs).[9]

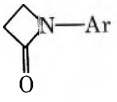
The unlikely possibility that the rate-determining step has changed from breakdown to formation of the tetrahedral intermediate is readily discounted. In such a situation ρ_1 would be expected to be greater than ρ_2. This is found in the $B_{Ac}2$ mechanism of ester hydrolysis. For example, the hydrolysis of Ar_1COOEt and CH_3COOAr_2 in aqueous acetone at 273°K give[10] ρ_1 = 2.6 and ρ_2 = 1.65. Anilide hydrolysis studies[1,2,11] have established that the ρ_2 value for hydroxide attack on the carbonyl group is

Table I
Kinetic Data for the Basic Methanolysis (MeO^- = 5 × 10^{-3} to 0.1 *M*) of Some *N*-Methylbenzanilides[a] ($XC_6H_4CONMeC_6H_4Y$) and *N*-Arylazetidinones[a]

Registry no.	Series	X	Y	Analyt. λ, nm	Temp, °K	$10^3 k_2$, M^{-1} sec^{-1}
33675-68-2	**5a**	H	*p*-MeO	232	373	0.16
1934-92-5	**5a,c**	H	H	233	373	0.32
51774-34-6	**5a**	H	*p*-Br	309[b]	373	2.09
51774-35-7	**5a**	H	*m*-Br	302[b]	373	4.09
51774-36-8	**5a**	H	*p*-CO_2Me	304	373	29.6
51774-37-9	**5a**	H	*m*-NO_2	230	373	61.0
33672-82-1	**5a**	H	*p*-NO_2	385	373	525[c]
51774-38-0	**5b**	*p*-MeO	*p*-NO_2	385	339	28.0
51774-39-1	**5b**	*p*-Me	*p*-NO_2	385	339	39.5
	5b	H	*p*-NO_2	385	339	62.1
51774-40-4	**5b**	*p*-Cl	*p*-NO_2	385	339	201
51774-41-5	**5b**	*m*-Cl	*p*-NO_2	385	339	320
51774-42-6	**5b**	*m*-NO_2	*p*-NO_2	385	339	1310
33672-81-0	**5c**	*p*-MeO	H	254	373	0.19
51774-43-7	**5c**	*m*-Cl	H	238	373	2.10
51774-44-8	**5c**	*m*-NO_2	H	248	373	8.6
961-61-5	**5c**	*p*-NO_2	H	250	373	10.8
5099-95-6	**6**	H		250	304	2.65
38560-29-1	**6**	*m*-NO_2		390	304	85.5
19018-01-0	**6**	*p*-NO_2		380	304	427

[a] Substrate ~1 × 10^{-4} *M*. [b] Substrate ~5 × 10^{-4} *M*. [c] By extrapolation, 7.00 (310°K), 16.3 (321°K), 62.1 (339°K); E_a = 15.7 kcal mol^{-1}; ΔS_{298}^* = −20 eu.

~1.3. We have briefly examined methanolysis in one model amide system to confirm the expected lower susceptibility to *N*-aryl substituents in this mechanism. Recent work[12] has shown that, because of a rate-enhancing relief of steric strain in the breakdown of the intermediate, the hydrolysis of *N*-arylazetidinones (**6**) proceeds by



6

rate-determining hydroxide attack. We have measured the rates of basic methanolysis of three of these compounds. The results are given in Table I, and the Hammett plot (using σ^- for *p*-NO_2) gives ρ_2 = 1.7 (304°K). This is somewhat greater than that found[12] for hydrolysis (1.25) but is much less than ρ for the benzanilide reaction (especially when the temperature difference is considered).

There seems no doubt then that the mechanism of *N*-methylbenzanilide methanolysis proceeds by rate-determining breakdown of the tetrahedral intermediate *via* a transition state analogous to **4**.

The occurrence of linear (benzanilides) *vs.* nonlinear (acetanilides) Hammett plots clearly illustrates that the transition state is determined by the acyl substituent as well as by the leaving group. The effect of an aryl group on the acyl carbon is to give a pseudo-improvement in the leaving group nature of the amine. This presumably comes about because the aryl substituent can conjugate with the developing carbonyl bond. This favorable interaction provides additional impetus to C–N bond cleavage and prior protonation is now unnecessary for the poorer leaving groups.

Understandably, σ^- values are needed to correlate the data for the resonance-withdrawing substituents (*p*-NO_2 and *p*-CO_2Me) in Ar_2 in the rate-determining CN cleavage mechanism. It is worthy of note that in this and other studies[1,11,12] it has also been found necessary to use σ^- values to correlate data for methoxide and hydroxide attack on the distant carbonyl group. The same does not apply in the analogous ester reaction[10] and indicates the greater resonance interaction between the carbonyl group and nitrogen of an amide than oxygen of an ester.

Experimental Section

***N*-Methylanilines.** *N*-Methylaniline and *p*-*N*-methylaminobenzoic acid were commercial samples. Esterification of the latter (MeOH–sulfuric acid) gave methyl *p*-*N*-methylaminobenzoate, mp 94–95° (lit.[13] mp 95.5°). *p*-Nitro-*N*-methylaniline, mp 149° (lit.[14] mp 152°), was prepared from methylamine and *p*-chloronitrobenzene. *m*-Bromo-, *p*-bromo-, *p*-methoxy-, and *m*-nitro-*N*-methylaniline were prepared[11,15] from the corresponding acetanilides.

3′- and 4′-Substituted *N*-Methylbenzanilides (5a). These were prepared by reaction of benzoyl chloride with the appropriately substituted *N*-methylaniline under Schotten–Baumann conditions. The products were extracted with ether, washed with water, dried, concentrated, and chromatographed (silica–ethyl acetate). They were then recrystallized or distilled and are described in Table II.

4′-Methoxycarbonyl-*N*-methylbenzanilide was prepared by the same method, but in dry tetrahydrofuran solvent. An attempted synthesis under Schotten–Baumann conditions resulted in hydrolysis of the ester group.

3- and 4-Substituted *N*-Methyl-4′-nitrobenzanilides (5b). These were prepared by reaction of a solution of *N*-methyl-*p*-nitroaniline (7 g, 0.05 mol) in dry tetrahydrofuran (40 ml) with a solution of the substituted benzoyl chloride (0.05 mol) in dry tetrahydrofuran (20 ml). After addition was complete, the mixture was refluxed (1 hr), then cooled and evaporated to dryness. Water was added and the benzanilide was filtered off and recrystallized from ethanol. The products are described in Table II.

3- and 4-Substituted *N*-Methylbenzanilides (5c). These were prepared by reaction of a solution of *N*-methylaniline (0.1 mol) in dry tetrahydrofuran (20 ml) with the substituted benzoyl chloride (0.05 mol) in dry tetrahydrofuran. The mixture was refluxed (1 hr), then cooled and evaporated to dryness. The residue was dissolved in chloroform and washed with 1 *M* hydrochloric acid (3 × 100 ml), 2 *M* sodium hydroxide (3 × 50 ml), and water (2 × 100 ml), then dried and concentrated. The products were recrystallized from ethanol–water and are described in Table II.

***N*-Arylazetidinones (6).** These were prepared as described[12] by Blackburn and Plackett.

Rate Measurements. The methanolysis reactions, which were first order under the conditions used, were followed spectrophotometrically using a Varian-Techtron 635 recording spectrophotometer. Details of concentrations and analytical wavelengths are given in Table I. Reactions in series **6** were carried out in ther-

Table II
Properties of *N*-Methylbenzanilides

Substituents	Mp or bp, °C (mm)	Lit. mp, °C	Formula[a]
4′-NO_2	109	111–112[a]	
4′-NO_2	147.5–148.5		$C_{14}H_{11}ClN_2O_3$
4′-NO_2-4-MeO	74–75		$C_{15}H_{14}N_2O_4$
3,4′-di-NO_2	140–141		$C_{14}H_{11}N_3O_5$
4′-NO_2-4-Cl	90–92		$C_{14}H_{11}ClN_2O_3$
4′-NO_2-4-Me	89–91		$C_{15}H_{14}N_2O_3$
3′-NO_2	102–103		$C_{14}H_{12}N_2O_3$
3′-Br	214–218 (15)		$C_{14}H_{12}BrNO$
4′-Br	72–73	77[b]	
H	55–57	63[a]	
4′-MeO	76–78	79–80[c]	
4′-CO_2Me	63		$C_{16}H_{15}NO_3$
4-NO_2	109–110	110–111[d]	
3-NO_2	107–109	109[e]	
3-Cl	33–35	40[f]	
4-MeO	Oil, tlc pure		$C_{15}H_{15}NO_2$

[a] See ref 14. [b] F. B. Dains and F. Eberly, *J. Amer. Chem. Soc.*, **55**, 3859 (1933). [c] F. W. Bentley and R. A. W. Johnstone, *J. Chem. Soc. B*, 1804 (1971). [d] R. N. Ring, J. G. Sharefkin, and D. Davidson, *J. Org. Chem.*, **27**, 2428 (1962). [e] D. H. Hey and R. A. J. Long, *J. Chem. Soc.*, 4110 (1959). [f] P. Grammaticakis, *Bull. Soc. Chim. Fr.*, 862 (1963). [g] Satisfactory analytical data were obtained for all new compounds listed.

mostatted cuvettes in the spectrophotometer, while sealed ampoules were required for the higher temperature reactions in series 5. First-order rate constants were calculated graphically from plots of log $(D_\infty - D_t)$ *vs.* time. All rate constants listed in Table I are averages of two or more runs, with agreement between runs being within 4%.

Acknowledgment. The authors thank Mr. C. Carolane for synthesizing the three *N*-arylazetidinones.

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Synthetic Reactions by Complex Catalysts. XXXII. Reaction of o-Xylylene Halides with Copper–Isonitrile Complex. o-Xylylene Intermediates

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Received February 6, 1974

The system of o-xylylene halide with Cu(0)–*tert*-butyl isocyanide was subjected to the reaction with an electron-deficient olefin such as acrylate, fumarate, and maleate. In the case of o-xylylene dibromide, tetrahydronaphthalene derivative **3** was produced in a moderate yield. As one of possible mechanisms, an unstable intermediate of o-xylylene (**6**) was proposed. The system of $\alpha,\alpha,\alpha',\alpha'$-tetrabromo-o-xylene with Cu(0)–*tert*-butyl isocyanide reacted with an electron-deficient olefin to produce naphthalene derivatives (**4**). Similarly, the intermediacy of α,α'-dibromo-o-xylylene (**7**) was proposed for the production of 1,4-dibromotetrahydronaphthalene followed by dehydrobromination to the final naphthalene derivative. In the case of o-xylylene dichloride, tetrahydronaphthalene derivative (**3**) as well as the dihydronaphthalene derivative (**5**) were produced, for which two o-xylylene intermediates (**6** and **8**) were presented, respectively. Concerning the formation of **6** and **8**, the effect of substituents in the aromatic ring on the product ratio of **5** to **3** was examined. The ratio of **5** to **3** increases with the increase of σ^+ of the substituent.

Intramolecular dehalogenation of o-xylylene dihalide by means of a transition metal has provided a convenient route[1] leading to the transient formation of a reactive intermediate of o-xylylene. Metallic iron has often been used for this purpose.[2] Roth and Meier[3] succeeded in the isolation of unstable o-xylylene in the form of a stable π complex with iron tricarbonyl in the reaction of o-xylylene dibromide with diiron nonacarbonyl.

The present paper deals with systems in which o-xylylene halides are treated with Cu(0)–*tert*-butyl isocyanide in the presence of an electron-deficient olefin. In the course of our investigations of copper–isonitrile complexes,[4] we found that metallic copper was dissolved in liquid isonitrile under nitrogen to form a soluble complex. The complex exhibited a broad, unresolved esr signal (g value = 2.0041), which was taken to suggest a Cu(0)–isonitrile species. Interestingly, the Cu(0)–isonitrile complex[4] was found to react with the carbon–halogen bond and sometimes the carbon–hydrogen bond to form the organocopper–isonitrile complexes. In these reactions, the oxidative additions of the carbon–halogen bond and of the carbon–hydrogen bond, respectively, onto the Cu(0)–isonitrile complex may probably be assumed. For example, the Cu(0)–isonitrile complex reacts with benzyl halide to give a benzylcopper–

isonitrile complex (1). The formation of 1 was demonstrated by a trapping experiment with allyl bromide to produce 4-phenyl-1-butene (eq 1). On the other hand, the

$$C_6H_5CH_2Cl + Cu^0(RNC)_l \longrightarrow C_6H_5CH_2CuCl(RNC)_m \xrightarrow{CH=CHCH_2Br} C_6H_5CH_2CH_2CH=CH_2 \quad (1)$$

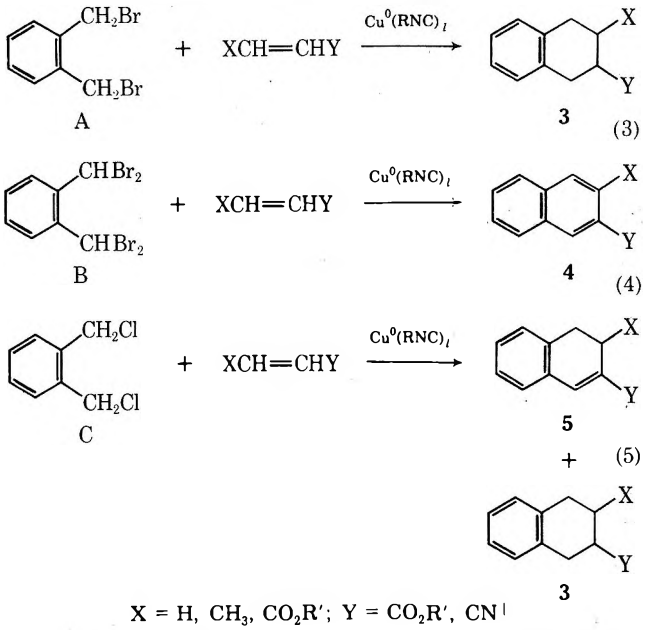
1

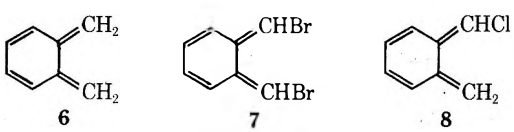
reaction of 1,4-dichloro-2-butene with the Cu(0)–isonitrile complex selectively produced butadiene, in which all attempts to trap an organocopper intermediate (2), however, failed. It implies that 2 rapidly undergoes the 1,4-elimination of copper chloride–isonitrile complex to give butadiene.

$$ClCH_2CH=CHCH_2Cl + Cu^0(RNC)_l \longrightarrow ClCH_2CH=CHCH_2CuCl(RNC)_m \xrightarrow{-CuCl_2(RNC)_n} CH_2=CHCH=CH_2 \quad (2)$$

2

These findings prompted us to investigate the reactions of *o*-xylylene halides with the Cu(0)–isonitrile complex which might lead to the formation of *o*-xylylene intermediate. Now we wish to report that derivatives of tetrahydronaphthalene (3), naphthalene (4), and dihydronaphthalene (5) are produced when o-xylylene dibromide (A), $\alpha,\alpha,\alpha',\alpha'$-tetrabromo-*o*-xylene (B) and *o*-xylylene dichloride (C) are treated with Cu(0)–*tert*-butyl isocyanide in the presence of an electron-deficient olefin, as shown in eq 3–5. It is noteworthy that in the reaction with *o*-xylylene dichloride, the product ratio of 3 to 5 varied by substituents on the aromatic ring, *i.e.*, an electron-withdrawing substituent favors the formation of 5. All these products, 3–5, may be explained in terms of the following *o*-xylylene intermediates 6–8, respectively.

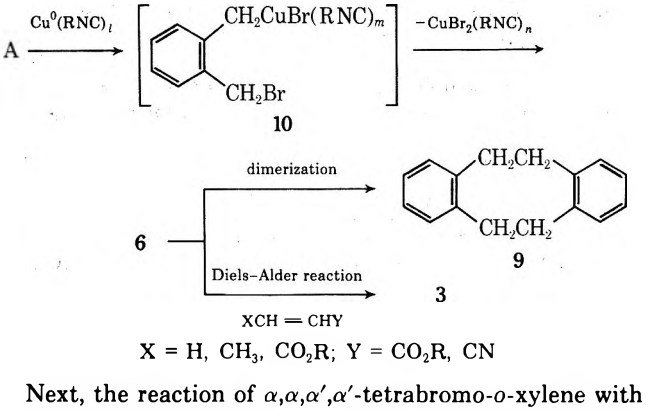




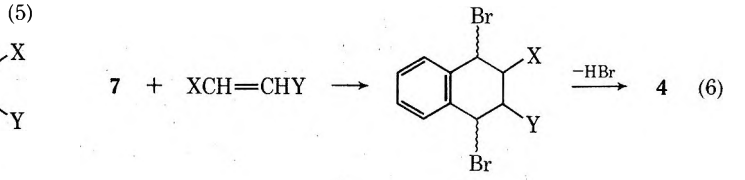
Results and Discussion

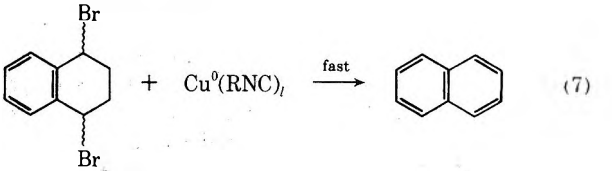
On treating *o*-xylylene dibromide with Cu(0)–*tert*-butyl isocyanide complex, dibenzocyclooctadiene (9) was produced along with a few minor products. However, when this reaction was carried out in the presence of an electron-deficient olefin such as acrylate and fumarate, tetrahydronaphthalene derivatives (3) were selectively produced without being accompanied by 9 (Table I, runs 1–4). The finding may be explained by the formation of a reactive intermediate of *o*-xylylene 6 in the reaction of o-xylylene dibromide with Cu(0)-*tert*-butyl isocyanide as shown in Scheme I. The *o*-xylylene intermediate then reacts with an olefin to produce the final product of tetrahydronaphthalene (3). As to the reactions of *o*-xylylene 6, the dimerization and the Diels–Alder reaction with an electron-deficient olefin have been known.[1,2,5] As a mechanistic alternative to *o*-xylylene intermediate, a stepwise mechanism involving an addition of organocopper (10) to olefin and the subsequent ring closure may also be conceivable. No experimental observation is at hand to exclude this possibility. However, the observation aforementioned that 1,4-dichloro-2-butene undergoes the 1,4-dechlorination by the Cu(0)–isonitrile complex to produce butadiene may be taken to support the o-xylylene mechanism.

Scheme I



Next, the reaction of $\alpha,\alpha,\alpha',\alpha'$-tetrabromo-*o*-xylene with Cu(0)–*tert*-butyl isocyanide complex in the presence of olefin afforded naphthalene derivatives (4) (Table I, runs 5 and 6). Dibromotetrahydronaphthalene derivative (11) was not isolated among the products. By analogy with the case of *o*-xylylene dibromide, an intermediate of α,α'-dibromo-*o*-xylylene (7) may be assumed for this reaction. The subsequent elimination of two molecules of hydrogen bromide from the Diels–Alder adduct (11) leads to the formation of 4. The rapid dehydrobromination of 11 in the present reaction conditions was verified by a reference experiment, in which naphthalene was produced almost exclusively in the reaction of 1,4-dibromotetrahydronaphthalene with Cu(0)–isonitrile complex even in the presence of acrylate (eq 7).





The behavior of o-xylylene dichloride toward Cu(0)–*tert*-butyl isocyanide is complicated a little. The reaction of o-xylylene dichloride with the Cu(0)–isonitrile in the presence of an olefin produced tetrahydronaphthalene derivative (3) as well as dihydronaphthalene derivative (5). For this reaction two o-xylylene intermediates of 6 and 8 may

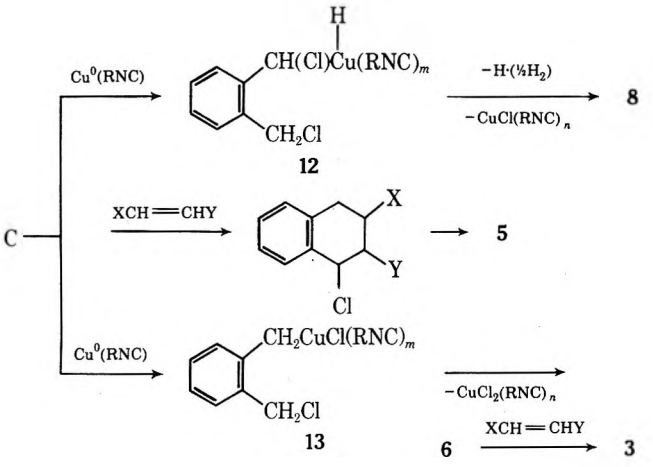
Table I
Reaction of o-Xylylene Halides with Cu(0)–*tert*-Butyl Isocyanide in the Presence of Olefin

No.	o-Xylylene halide[a] (registry no.)	Olefin (registry no.)	Product[b] (%)
1	A (91-13-4)	CH_2=$CHCO_2CH_3$ (96-33-3)	**3i**, X = H; Y = CO_2CH_3 (33)[c]
2	A	CH_2=CHCN (107-13-1)	**3ii**, X = H; Y = CN (25)[c]
3	A	*trans*-$C_2H_5O_2CCH$=$CHCO_2C_2H_5$ (623-91-6)	**3iii**, X = Y = $CO_2C_2H_5$ (53)
4	A	CH_3CH=$CHCO_2C_2H_5$ (10544-63-5)	**3iv**, X = CH_3; Y = $CO_2C_2H_5$ (14)
5	B (13209-15-9)	CH_2=$CHCO_2CH_3$	**4i**, X = H; Y = CO_2CH_3 (60)[d]
6	B	*trans*-$C_2H_5O_2CCH$=$CHCO_2C_2H_5$	**4ii**, X = Y = $CO_2C_2H_5$ (55)[e]
7	C (612-12-4)	CH_2=$CHCO_2CH_3$ (554-12-1)	**3i**, X = H; Y = CO_2CH_3 (36) **5i**, X = H; Y = CO_2CH_3 (35)
8	C	CH_2=CHCN	**3ii**, X = H; Y = CN (15) **5ii**, X = H; Y = CN (14)
9	C	*cis*-$C_2H_5O_2CCH$=$CHCO_2C_2H_5$	**3iii**, X = Y = $CO_2C_2H_5$ (26) **5iii**, X = Y = $CO_2C_2H_5$ (18)
10	C	*trans*-$C_2H_5O_2CCH$=$CHCO_2C_2H_5$	**3iii**, X = Y = $CO_2C_2H_5$ (39) **5iii**, X = Y = $CO_2C_2H_5$ (18)
11	C	CH_3CH=$CHCO_2C_2H_5$	**3iv**, X = CH_3; Y = $CO_2C_2H_5$ (21) **5iv**, X = CH_3; Y = $CO_2C_2H_5$ (5)

[a] A = o-xylylene dibromide, B = o-xylylene tetrabromide, C = o-xylylene dichloride. [b] Satisfactory analytical data were reported for all new compounds listed in the table. [c] Reference 1. [d] M. S. Newman and H. V. Zahn, *J. Amer. Chem. Soc.*, **65**, 1097 (1943). [e] K. Auwers and A. Fruhling, *Justus Liebigs Ann. Chem.*, **422**, 196 (1900).

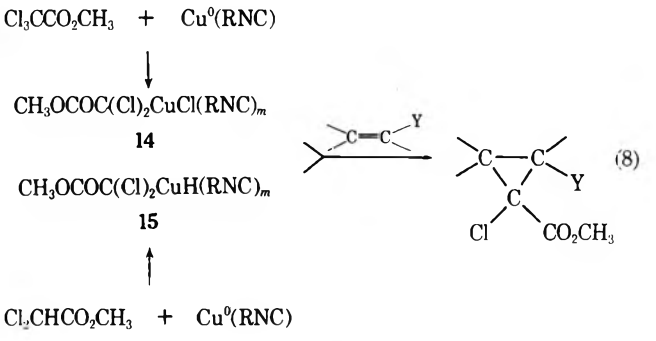
be assumed. Monochloro-o-xylylene intermediate (8) would arise *via* the organocopper–isonitrile complex (**12**) formed by an oxidative addition of the benzylic carbon–hydrogen bond onto the Cu(0)–isonitrile complex, which in turn undergoes the elimination of copper chloride–isonitrile complex (Scheme II). The evolution of hydrogen gas in the

Scheme II



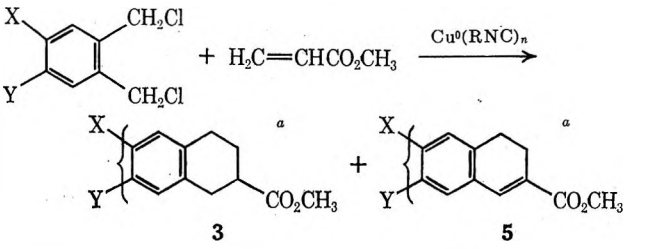
reaction of o-xylylene dichloride with the Cu(0)–isonitrile complex was really observed, which is taken as a support to the intermediacy of copper hydride species (**12**). Concerning Scheme II, we may refer to our previous findings of the reactions of Cu(0)–isonitrile with trichloroacetate and with dichloroacetate in the presence of olefin, both of which produce the same cyclopropane derivative.[4] The transient formations of organocopper–isonitrile complexes, **14** and **15**, both of which contain the Cu–$C(Cl)_2CO_2CH_3$ moiety, have been presented for the reactions. Both the α-carbon–chlorine bond of trichloroacetate and the α-carbon–hydrogen bond of dichloroacetate would be assumed to react with the Cu(0)–isonitrile complex through the fashion of oxidative addition.

The stereochemistry of tetrahydronaphthalene derivative (3) obtained in the reaction of o-xylylene dichloride or



dibromide with 1,2-dicarbethoxyethylene (fumarate and maleate) is worthy of notice. A single product of *trans*-2,3-dicarbethoxytetrahydronaphthalene, irrespective of the starting isomers of 1,2-dicarbethoxyethylene, was detected. In a separate experiment, however, *cis*-2,3-dicarbethoxytetrahydronaphthalene was found to be isomerized rapidly into the trans isomer by Cu(0)–isonitrile complex. Therefore, the product stereochemistry could not be taken as a criterion to determine the reaction mechanism, *i.e.*, the

Table II



X	Y	σ_p^+ of substituent X	Product ratio[b] 3:5
CH_3	CH_3[c]	−0.31	1:0
F	H	−0.07	1:trace
H	H	0	1:1
Cl	H	+0.11	1:1.8

[a] The position of the substituents X, Y in the products was not determined. [b] Yields (**3** + **5**) were 60–70% in all runs. [c] 4,5-Dimethyl-o-xylylene dichloride was used.

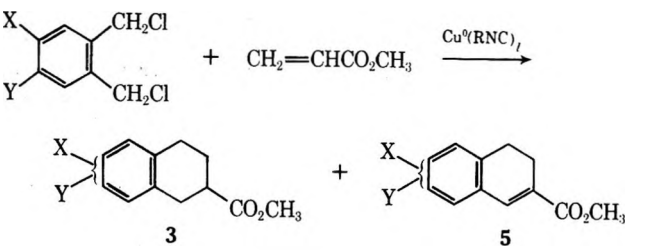
Table III
Characterization of Products[a]

Compd	Ir, cm^{-1}	Nmr, τ[b]	Mass
3i	>3000, 1735, 745	3.02 (4 H, s) 6.36 (3 H, s) 6.88–7.45 (5 H, m) 7.65–8.40 (2 H, m)	
3ii	>3000, 2210, 750	2.98 (4 H, s) 6.90–7.36 (5 H, m) 7.60–8.20 (2 H, m)	
3iii	>3000, 1735, 750	3.01 (4 H, s) 5.87 (4 H, q) 6.75–7.30 (6 H, m) 8.75 (6 H, t)	
3iv	>3000, 1734, 745	3.60 (4 H, s) 5.92 (2 H, q) 6.80–8.10 (6 H, m) 8.76 (3 H, t) 9.00 (3 H, d)	
3v	>3000, 1730, 870	3.14 (2 H, s) 6.30 (3 H, s) 7.00–7.43 (5 H, m) 7.82 (6 H, s) 7.90–8.40 (2 H, m)	218 (M^+) 187 ($-OCH_3$) 159 ($-CO_2CH_3$)
3vi	>3000, 1736, 862, 808	2.82–3.60 (3 H, m) 6.32 (3 H, s) 6.80–7.50 (5 H, m) 7.70–8.40 (2 H, m)	208 (M^+) 177 ($-OCH_3$) 149 ($-CO_2CH_3$)
3vii	>3000, 1738, 860, 805	2.64–3.10 (3 H, m) 6.27 (3 H, s) 6.70–7.40 (5 H, m) 7.72–8.40 (2 H, m)	224 (M^+) 193 ($-OCH_3$) 165 ($-CO_2CH_3$)
4i	>3000, 1710, 785, 770	1.47 (1 H, s) 1.80–2.57 (6 H, m) 6.03 (3 H, s)	
4ii	>3000, 1725, 785, 765	1.30 (2 H, s) 1.50–2.07 (4 H, m) 5.10 (4 H, q) 8.63 (6 H, t)	
5i	>3000, 1710, 1630, 750	2.56 (1 H, s) 2.86 (4 H, s) 6.26 (3 H, s) 6.88–7.66 (4 H, m)	
5iii	>3000, 1740, 1710, 1635, 780	2.52 (1 H, s) 2.87 (4 H, s) 5.77 (2 H, q) 6.02 (2 H, q) 6.68–7.10 (2 H, m) 8.70 (3 H, t) 8.90 (3 H, t)	
5iv	>3000, 1710, 1630, 776	2.60 (1 H, s) 2.60 (4 H, s) 5.75 (2 H, q) 6.75–7.50 (3 H, m) 8.63 (3 H, t) 9.01 (3 H, d)	
5vi	>3000, 1710, 1634, 866, 820		
5vii	>3000, 1710, 1630, 882, 820	2.42–3.00 (4 H, m) 6.20 (3 H, s) 6.95–7.58 (4 H, m)	222 (M^+) 191 ($-OCH_3$) 163 ($-CO_2CH_3$)

[a] Satisfactory analytical data were reported for all new compounds listed in the table. [b] $CDCl_3$ solution (TMS).

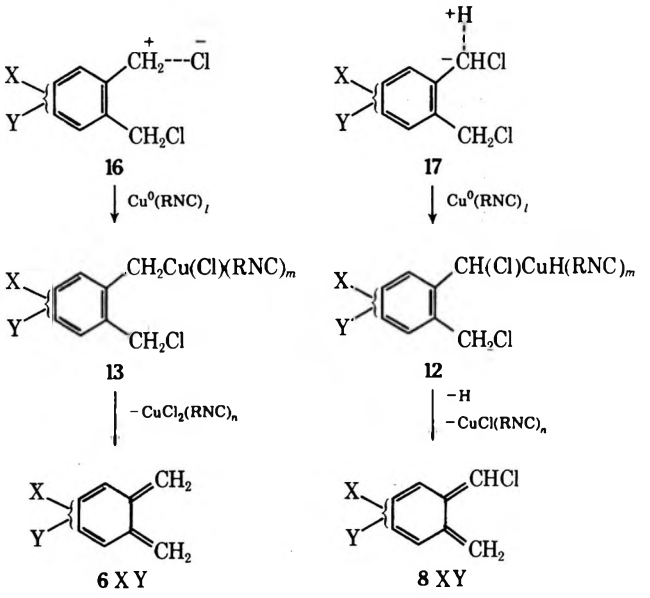
Diels–Alder reaction mechanism or the stepwise reaction mechanism.

Substitution Effect on the Reaction of *o*-Xylylene Dichloride with Cu(0)–Isonitrile Complex. In the reaction of *o*-xylylene dichloride with Cu(0)–*tert*-butyl isocyanide, two products, **3** and **5**, were obtained, for which the respective *o*-xylylene intermediates **6** and **8** were assumed. Concerning the formation of **6** and **8**, the effect of substituent of the benzene ring upon the ratio of **3** and **5** was examined. Table II shows the ratios of the products **3** and **5**, which have been correlated with the σ_p^+ values of the substituents X. The ratio of **5** to **3** increases with the increase



v, X = Y = CH_3
vi, X = F; Y = H
vii, X = Cl; Y = H

of the σ_p^+ value of the substituent. This finding is taken to support the concurrent formation of two organocopper species, **12** and **13**. When the substituent X,Y is an electron-donating one, the oxidative addition of carbon–chlorine bond onto Cu(0)–isonitrile complex may be favored and produces predominantly 6XY. On the other hand, an electron-withdrawing substituent favors the oxidative addition of the polarized carbon–hydrogen bond onto Cu(0)–isonitrile complex, which leads to the formation of 8XY *via* **12**.



Experimental Section

Reagents. *tert*-Butyl isocyanide was prepared according to Ugi's procedure.[6] *o*-Xylylene dichloride was synthesized from the corresponding o-xylene and sulfuryl chloride in the presence of benzoyl peroxide. o-Xylylene dibromide and $\alpha,\alpha,\alpha',\alpha'$-tetrabromo-o-xylene were commercial reagents and were purified by recrystallization before use. 4,5-Dimethyl-o-xylylene dichloride was prepared by chloromethylation[7] of o-xylene and used after recrystallization. 4-Fluoro-o-xylylene dichloride was synthesized from 4-fluoro-*o*-xylene and sulfuryl chloride in the presence of benzoyl peroxide. 4-Fluoro-o-xylene was prepared from xylidine and tetrafluoroboric acid according to Starkey's procedure.[8] 1,4-Dibromotetrahydronaphthalene was prepared by the reaction of tetrahydronaphthalene with *N*-bromosuccinimide.[9] The olefins such as acrylate, acrylonitrile, crotonate, fumarate, and maleate were all commercial reagents and purified by distillation under nitrogen.

Reaction of *o*-Xylylene Dibromide with Cu(0)-*tert*-Butyl Isocyanide Complex in the Presence of Olefin. Under nitrogen to a mixture of 0.64 g (10 mg-atoms) of copper powder, 3.3 g (40 mmol) of *tert*-butyl isocyanide, 1.7 g (10 mmol) of diethyl fumarate, and 5 ml of benzene, 1.3 g (5 mmol) of o-xylylene dibromide in 5 ml of benzene was added at room temperature. The mixture was heated at 80° with stirring under nitrogen for 10 hr. After the reaction mixture was treated with ether to remove copper bromide–*tert*-butyl isocyanide complex, the extract was concentrated and subjected to glpc analysis. *trans*-2,3-Dicarbethoxytetrahydronaphthalene (**3iii**) was obtained in a yield of 53%. The structure of the products was confirmed by elemental analysis and spectral data. The data are shown in Table III.

Other combinations of o-xylylene dibromide and Cu(0)–*tert*-butyl isocyanide complex with methyl acrylate, acrylonitrile, methyl crotonate, and diethyl maleate were carried out according to the procedure mentioned above.

Reaction of *o*-Xylylene Dichloride with Cu(0)-*tert*-Butyl Isocyanide Complex in the Presence of Olefin. Under nitrogen to a mixture of 0.64 g (10 mg-atoms) of copper powder, 3.3 g (40 mmol) of *tert*-butyl isocyanide, 1.7 g (10 mmol) of diethyl fumarate, and 5 ml of benzene, 0.88 g (5 mmol) of o-xylylene dichloride in 5 ml of benzene was added at room temperature. After the reaction mixture was heated at 80° with stirring for 10 hr, the mixture was extracted with ether. The extract was concentrated and subjected to glpc analysis. *trans*-2,3-Dicarbethoxytetrahydronaphthalene (**3iii**) and 2,3-dicarbethoxy-3,4-dihydronaphthalene (**5iii**) were isolated in yields of 39 and 18%, respectively.

In the reaction of *o*-xylylene dichloride and Cu(0)–*tert*-butyl isocyanide complex in the presence of acrylonitrile, two products, tetrahydronaphthalene derivative (**3ii**) and dihydronaphthalene derivative (**5ii**) could not be separated by glpc analysis. After the mixture of two products was hydrolyzed with aqueous sodium hydroxide, acidified with sulfuric acid, and then esterified with diazomethane, the mixture was analyzed by glpc. 2-Carbomethoxytetrahydronaphthalene (**3i**) and 2-carbomethoxy-3,4-dihydronaphthalene (**5i**) were isolated.

Other reactions of o-xylylene dichloride with Cu(0)–*tert*-butyl isocyanide complex in the presence of olefin were carried out according to the procedure mentioned above.

Reaction of $\alpha,\alpha,\alpha',\alpha'$-Tetrabromo-*o*-xylene with Cu(0)-*tert*-Butyl Isocyanide Complex in the Presence of Olefin. To a mixture of 0.64 g (10 mg-atoms) of copper powder, 3.3 g (40 mmol) of *tert*-butyl isocyanide, 0.86 g (10 mmol) of methyl acrylate, and 5 ml of benzene, 1.2 g (2.5 mmol) of $\alpha,\alpha,\alpha',\alpha'$-tetrabromo-*o*-xylene in 5 ml of benzene was added dropwise at room temperature under nitrogen. After the reaction mixture was stirred at 80° for 10 hr, the reaction mixture was treated with ether to remove copper bromide–*tert*-butyl isocyanide complex. The extract was concentrated and subjected to glpc analysis. 2-Carbomethoxynaphthalene (**4i**) was isolated in a yield of 60% by preparative glpc.

The reaction of $\alpha,\alpha,\alpha',\alpha'$-tetrabromo-o-xylene and Cu(0)–*tert*-butyl isocyanide complex in the presence of diethyl fumarate was carried out according to the procedure mentioned above.

Reaction of *o*-Xylylene Dichloride Bearing a Substituent on the Benzene Ring with Cu(0)-*tert*-Butyl Isocyanide Complex in the Presence of Methyl Acrylate. To a mixture of 0.64 g (10 mg-atoms) of copper powder, 3.3 g (40 mmol) of *tert*-butyl isocyanide, 0.86 g (10 mmol) of methyl acrylate, and 5 ml of benzene, 1.05 g (5 mmol) of 4-chloro-o-xylylene dichloride in 5 ml of benzene was added with stirring at room temperature. After the reaction mixture was heated at 80° for 10 hr, the mixture was extracted with ether. The extract was concentrated and subjected to glpc analysis. Dihydronaphthalene derivative (**5vii**) and tetrahydronaphthalene derivative (**3vii**) were isolated in the ratio of 1.8:1 in a total yield of 60%.

The reaction of o-xylylene dichloride bearing a substituent on the benzene ring with Cu(0)–*tert*-butyl isocyanide complex was carried out according to the procedure mentioned above.

Registry No.—**3i**, 39246-30-5; **3ii**, 51849-33-3; **3iii**, 51849-34-4; **3iv**, 51849-35-5; **3v**, 51849-36-6; **3vi**, 51849-25-3; **3vii**, 51849-26-4; **4i**, 2459-25-8; **4ii**, 50919-54-5; **5i**, 51849-37-7; **5ii**, 51849-38-8; **5iii**, 28937-23-7; **5iv**, 51849-35-5; **5vi**, 51849-27-5; **5vii**, 51849-28-6; Cu(0)–*tert*-butyl isocyanide, 51898-98-7.

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Photochemistry of 4-Methylverbenene

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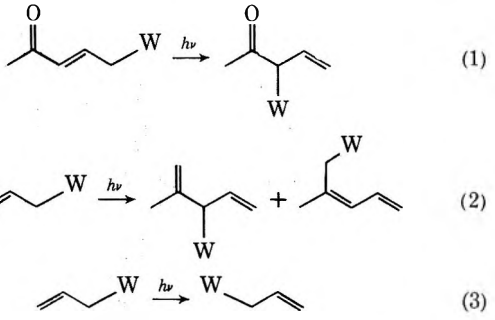
Received March 26, 1974

The photochemistry of 4-methylverbenene (11) has been investigated. Both sensitized and direct irradiation of 11 leads to production of 3-methylenelimonene (12). The mechanism of this process and comparison of the excited-state reactivity of 11 with that of structural and chromophoric analogs are discussed.

The photochemistry of compounds which possess the capability of reacting by [1,*n*]-sigmatropic pathways has received modest attention since the early discovery by Hurst and Whitham[1] of the conversion of verbenone (1) to chrysanthenone (2). In recent years, several excited-state isomerization reactions of this type have been uncovered.[2]

These transformations appear to be part of a general class of reactions in which compounds possessing conjugated-enone and -diene and monoolefin chromophores with substituted alkyl moieties α to the π group rearrange to products having the alkyl substituents 1,3- or 1,5-relocated. In general, the reactions result in the conversion of conjugated enones to β,γ-unsaturated ketones, of 1,3-dienes to 1,4-dienes or rearranged 1,3-dienes, and of monoolefins to their regioisomers, as depicted in a schematic way in eq 1–3.

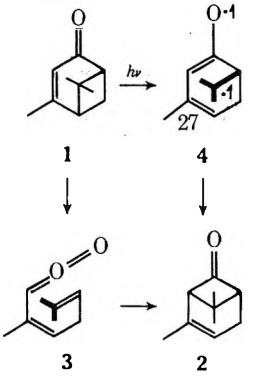


(1)

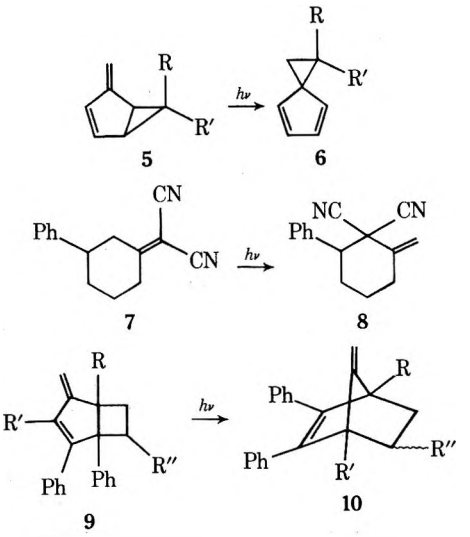
(2)

(3)

However, mechanistic dissimilarities between the reactions appear to preclude their inclusion into one class. Although in a formal sense each transformation could be depicted as a simple 1,3- or 1,5-sigmatropic carbon migration, the evidence suggests that the actual mechanism for isomerization in each case is dependent upon the structure and chromophore within the reactant and the excited-state multiplicity utilized for reaction. Of particular interest are the observations made on the verbenone to chrysanthenone rearrangement. Two competing mechanisms appear to operate, one involving a nonconcerted 1,3-alkyl shift and the other a retro-cycloaddition to the ketene **3** followed by readdition.[6] Both pathways are followed in reaction of triplet excited verbenone[7] and, thus, most probably pass through the triplet diradical **4**.



On the other hand, the stereochemical courses of singlet reactions of the related 3-methylenebicyclo[3.1.0]hexene **5**[9] and olefin **7**[10] suggest mechanisms having two consecutive 1,2-carbon shifts or a concerted 1,3-migration, respectively. Evidence which suggests that the chromophore, *i.e.*, enone *vs.* diene or monoolefin, contained within the reacting system is not solely influential in determining reaction mechanisms is found in the study of the 3-methylenebicyclo[3.2.0]heptenes **9**.[11] Nonconcerted mechanisms in these cases are proposed to account for the absence of stereospecificity in rearrangement.



Thus, with these observations in mind, we have prepared 4-methylverbenene (11, 4-methylene-α-pinene) in order to investigate the photochemistry of a noncarbonyl π analog of verbenone. We now would like to report our results from this study which indicate a departure from the photochemical behavior observed for related systems.

Results

The direct and sensitized photochemistry of 4-methylverbenene (11),[12] prepared by the reaction of verbenone[6] with methylidenetriphenylphosphorane, was investigated in order to determine the nature of the preferred excited state reaction pathways.

Triplet Sensitized Irradiation. Irradiation of a pentane solution of 11 (1.2×10^{-2} *M*), containing benzophenone (0.1 *M*) as a triplet sensitizer,[14] afforded two products, separable from the starting diene and benzophenone by alumina chromatography and glc. The ratio of the two photoproducts was found to be dependent upon the extent of conversion of 11, the minor product being nearly absent at low conversions (*vide infra*). Thus, 4-methylverbenene triplet reacts cleanly to yield only one product. This photoproduct is isomeric with 4-methylverbenene and its proton nmr spectrum is uncharacteristically simple, having 5 vinyl and 11 allylic and methylene protons. Its ultraviolet spectrum (λ_{max} 236 nm), which is quite similar to that of 11, in-

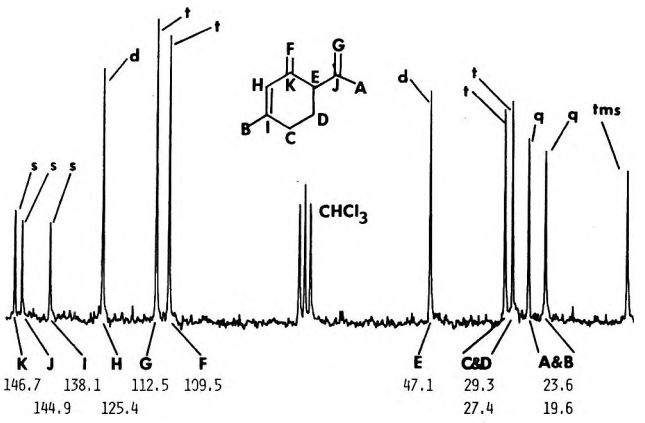
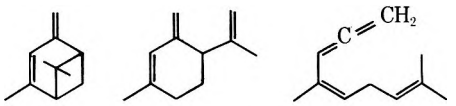


Figure 1. Carbon-13 nmr spectra of 3-methylenelimonene. Chemical shifts are recorded in parts per million relative to tetramethylsilane. The undecoupled spectra derived carbon-proton multiplicities are given along with the carbon assignments.

dicates that the photoproduct contains either a heteroannular conjugated-diene chromophore with one alkyl substituent or a trisubstituted acyclic diene chromophore. Likewise the mass spectrum of the material is nearly identical with that of 4-methylverbenene; both have a molecular ion at *m/e* 148, a base peak at *m/e* 133 (P − 15), and an intense *m/e* peak corresponding to the loss of an uncharged isopropyl group.

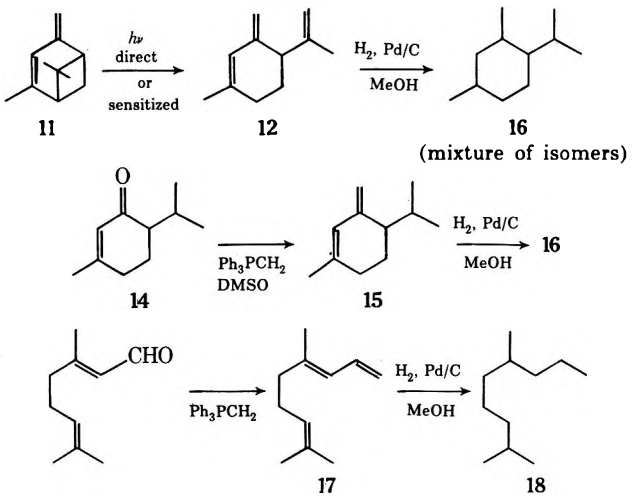
On the basis of this data and the known photochemistry of α-pinene[15] and verbenone, chromophoric and structural analogs of **11**, two structures emerged as likely candidates for the sensitized photoproduct; these were 3-methylenelimonene (**12**) and 4,8-dimethyl-1,2,4,7-nonatetraene (**13**).



11 **12** **13**

Further spectral and chemical data allowed the unambiguous assignment of **12** as the sole triplet photoproduct of 4-methylverbenene. First, the infrared spectrum of this material does not contain the characteristic band for a vinyl allene chromophore near the 1950-cm^{-1} region as would have been expected for **13**.[16,17] More firm support for **12** derives from the hydrogenation and independent synthetic results summarized in Scheme I. Exhaustive cat-

Scheme I



alytic hydrogenation of the photoproduct leads to three gas chromatographically separable products, having molecular weights (by mass spectrum, parent at *m/e* 154, *vide infra*) that indicate the consumption of 3 mol of hydrogen in the production of each. The nature and relative quantities of the three hydrogenation products are insensitive to reaction time, and thus the hydrogenation appears complete. Therefore the photoproduct must be a monocyclic triene as is **12**.

Definitive proof of the hydrogenation product structures derives from their independent synthesis from piperitone (**14**). The sequence involves reaction of **14** with methylidenetriphenylphosphorane, yielding the methylenedihydroterpinene **15**, followed by exhaustive hydrogenation. The gas chromatographic retention times of the synthesized and photoproduct-derived hydrogenation products are identical. The mass spectra of materials from both sources are nearly identical and characteristic of the 1,3-dimethyl-6-isopropylcyclohexanes **16**.[18]

To remove all questions concerning allene **13** as the possible structure for the triplet photoproduct, 2,6-dimethylnonane (**18**)[19] was prepared from citral *via* the triene **17**[20] (see Scheme I). The chromatographic behavior and mass spectrum of 2,6-dimethylnonane were found not to match those of any of the three photoproduct-derived hydrogenation products.

The results summarized above are consistent with the assignment of 3-methylenelimonene (**12**) as the product from the sensitized photolysis of **11**. Owing to its import in the mechanistic interpretation of the photoreaction observed, it was necessary to obtain more firm support for the location of the unsaturation present in the photoproduct skeleton, *i.e.*, to obtain further evidence beyond the nmr and uv spectral data presented above to eliminate the cyclohexadiene **19** and methylenecyclohexene **20**. The C-13

19 **20**

nmr spectrum of the photoproduct is displayed in Figure 1. As expected on the basis of structure **12**, the spectrum contains two methyl and two saturated methylene resonances in the regions predicted from inspection of spectra of model systems, in particular that of 1-methyl-4-isopropyl-3-methylenecyclohexane (**15**). Exceptionally characteristic are the quaternary vinyl carbon resonances at 146.7 and 138.1 ppm (singlets in the undecoupled spectrum) due to carbons K and I, the vinyl methine at 125.4 ppm for carbon H, and the vinyl methylene at 109.5 ppm for carbon F, when compared to the corresponding respective carbon resonances in the model **15**, at 146.4, 137.7, 124.9, and 109.1 ppm. These data well confirm the structure of **12** and together with the other spectral properties rule out **19** and **20**.

Direct Irradiation. Direct irradiation of a degassed pentane solution of 4-methylverbenene (2.6×10^{-2} *M*), using Vycor filtered light, led to production of a complex photomixture containing unreacted **11** and one major product, along with several minor unidentified photoproducts. The major product obtained under these conditions was determined to be 3-methylenelimonene (**12**) on the basis of the equivalence of its spectral and physical parameters with those of material derived from the sensitized photolysis.

Varying Conversion Photolysis. Indirect, but sufficient, proof that the minor photoproduct of the sensitized photolysis originates from a secondary photochemical reaction of the initially formed 3-methylenelimonene comes from varying conversion sensitized runs, the results of which are summarized in Figure 2. Thus, at low conversions

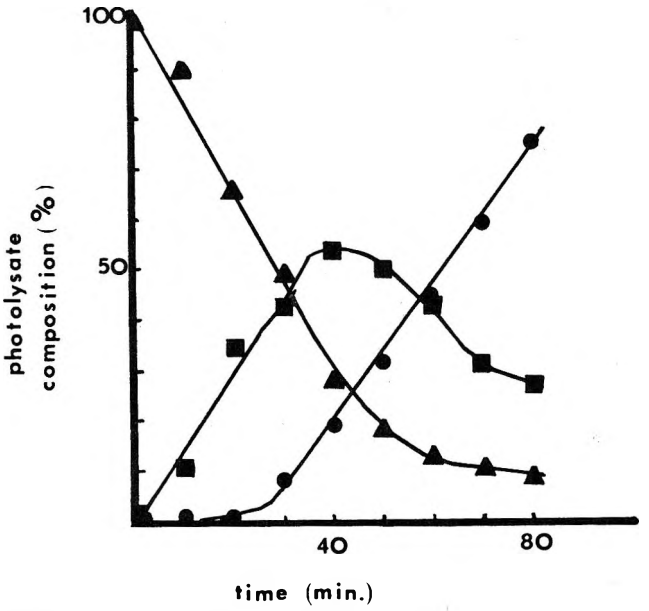


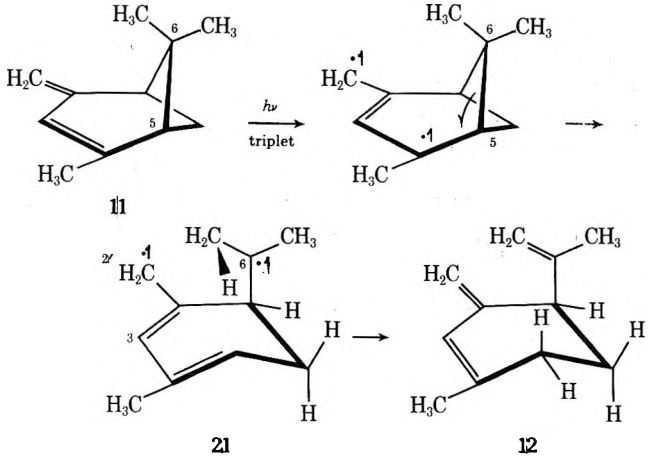
Figure 2. Plot of photolysate composition in benzophenone-sensitized run. The relative percentages of starting 4-methylverbenene (▲), 3-methylenelimonene (■), and the unidentified secondary product (●) are recorded *vs.* the time of irradiation.

12 is the sole photoproduct detected; its yield diminishes simultaneously with build-up of the minor photoproduct.

Discussion

The photochemical rearrangement of 4-methylverbenene (**11**) to 3-methylenelimonene (**12**) represents a novel departure from reaction pathways followed by closely related structural and chromophoric analogs, like verbenone (**1**).[1-6] A plausible mechanism for this unusual, but easily rationalizable, photoisomerization involves a simple nonconcerted process, having as its initial step rupture of the high-energy C-5–C-6 bond with concomitant formation of the highly stabilized diradical **21**. Ensuing transformation of **21** to 3-methylenelimonene (**12**) proceeds *via* an intramolecular disproportionation having transfer of one of the C-6 methyl hydrogens to C-5 of the pentadienyl radical moiety.

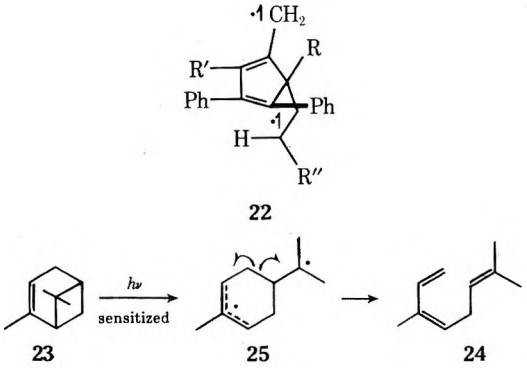
Three important features of the 4-methylverbenene isomerization and its likely mechanism warrant further brief comment. First, the preferred triplet reaction pathway followed by **11** is quite different from those employed in triplet rearrangements of closely related compounds. For example, and in contrast, the familiar verbenone to chrysanthenone transformation has been postulated to involve two mechanistically distinct pathways, both of which pass



through the initially formed diradical **4**, one having ensuing bonding between C-6 and C-3 and the other further collapse to the ketene **3** followed by ground-state cycloaddition (*vide supra*).[6] Indirect support for the diradical nature of one of the two modes utilized by excited verbenone derives from the stereochemical results of Cargill and coworkers[3] from studies of related bicyclic ketones. Loss of stereochemical integrity about the migrating carbon in this case has been logically interpreted in terms of a nonconcerted mechanism. The implication is that the 1,3 carbon shift in the verbenone isomerization follows similar pathways.

In addition, Schuster[8] has shown that rearrangement to chrysantheonone is a triplet reaction of verbenone and has thus concluded that a nonsynchronous mechanism is likely.

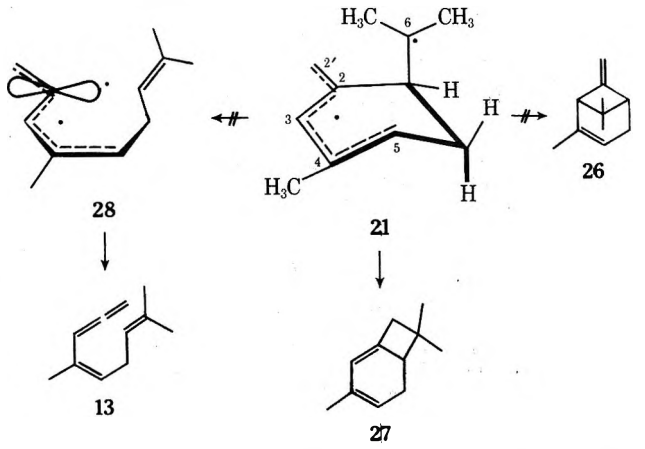
Olefin analogs appear to utilize similar reaction pathways for rearrangement. One of the more characteristic examples is found in the triplet sensitized isomerization of the 3-methylenebicyclodiene **9** to a mixture of 5-endo- and -exo-substituted 7-methylenenorbornenes **10a** and **10b**.[11] Here, as in Cargill's example, the nonstereospecific nature of the rearrangement could be interpreted in terms of a stepwise mechanism *via* the long-lived diradical intermediate **22**. The interesting sensitized conversion of α-pinene (**23**) to *cis*-ocimene (**24**)[15] represents another case in which triplet reaction of a structural analog of **11** appears to rearrange through a diradical resulting from cleavage of the σ bond in conjugation with the excited chromophore. In this example, the diradical, **25**, adopts, preferentially, the familiar cleavage route for further reaction. This pathway is characteristic of those followed by 1,4-diradicals produced in other ways.[21]



It is significant that the triplet conversion of 4-methylverbenene to 3-methylenelimonene is still another example which implicates the intermediacy of initially formed diradicals in rearrangements of systems like those found in eq 1–3 above. In this case, the "diradical detector" is not present as a stereochemical marker, but rather in the familiar disproportionation reaction which hindered free radicals easily and characteristically undergo.[22]

Thus, the major difference between triplet reaction of **11** and those of its carbonyl and olefin analogs appears to result solely from the nature of preferred, low-energy reaction pathways followed by the generated diradical intermediate. The differences and the exclusive adherence to the internal disproportionation route by **11**, however, remain perplexing. The apparent exclusion of alternate reaction modes from the diradical **21**, such as C-3–C-6 bonding leading to 6-methylenechrysanthene (**26**, C-2′–C-6 bonding to the bicyclooctadiene **27**, and C-1–C-2 bond cleavage yielding the divinylallene **13**, may perhaps reflect the odd-electron spin density at the various positions in the pentadienyl radical moiety[23] (weighted at the termini more heavily than at the central atom) and the initially formed conformer of **21**, having the C-6 grouping pseudo-axially disposed

and thus in closer proximity to C-5 than to C-2′. Recombination between C-6 and C-5 would lead to regeneration of the starting verbenene while disproportionation involving the C-5 center results in the production of **12**.[25] Divinylallene **13** production, by a pathway analogous to that followed in the α-pinene to *cis*-ocimene conversion, would require collapse of diradical **21** to the initially nonstabilized diradical **28**, which contains the odd electron at C-2 in an orbital perpendicular to the π system.



In conclusion, 4-methylverbene undergoes a rather unusual triplet reaction which is both specific and deviant from that expected on the basis of the known photochemistry of closely related structural and chromophoric analogs.

Experimental Section

General. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Nmr spectra were recorded on Varian T-60 or HA-100 (proton) and Jeol PS-100 (carbon) spectrometers with tetramethylsilane as the internal standard. Infrared spectra were taken with a Perkin-Elmer 237 spectrophotometer and ultraviolet spectra were measured using a Beckman Acta-III spectrophotometer. Gas chromatographic separations were conducted using a Varian Model 2700 chromatograph and analyses using a Varian Model 940 chromatograph. Mass spectra were obtained using a Varian MAT CH-7 with a gc inlet and a CEC-21-110 mass spectrometer.

4-Methylverbenene (11). An ethereal solution containing 0.067 mol of *n*-butyllithium was added dropwise to a solution of 27.0 g (0.067 mol) of triphenylphosphonium iodide in 120 ml of dimethyl sulfoxide. The resulting mixture was stirred at 20° for 0.5 hr and then heated to reflux while a solution of 7.2 g (0.05 mol) of verbenone in 25 ml of dimethyl sulfoxide was added. After stirring overnight at reflux, the solution was cooled, quenched with water, and extracted with ether. The combined ethereal extracts were dried and concentrated by careful distillation. The precipitated triphenylphosphine oxide was removed from the pot residue by filtration and the filtrate was fractionally distilled, yielding 2.43 g (28.3%) of 4-methylverbenene, bp 45° (3.5 mm) [lit.[13] bp 60° (15 mm)]. The spectral properties of this compound were identical with those reported previously.[13]

Photolyses of 4-Methylverbenene. Sensitized Irradiation. A nitrogen-purged solution of 4-methylverbenene (4.0 m*M*) and benzophenone (126 m*M*) in pentane was irradiated for 10 min using an apparatus consisting of a Hanovia 450-W medium-pressure lamp in a water-cooled quartz immersion well with a Pyrex glass filtr. The photolysate was concentrated carefully to a volume of 50 ml, percolated with pentane through an alumina column (10 × 2 in., Matheson chromatographic grade, 923 80–200 mesh), and concentrated carefully again. Glc analysis (10 ft × 0.25 in. column, packed with 4% SE-30 on ABS Anakromb, 120°, 120 ml/min) indicated the presence of the following: unreacted 4-methylverbenene (69.2%), a major photoproduct (11.8%), and a high-boiling material (19%). The major photoproduct, later identified as 3-methylenelimonene (**12**), was isolated by preparative glc (retention time 13 min, using the same conditions) as a clear liquid having the following spectral properties: proton nmr (CCl_4) δ 1.8 (br s, 6 H, methyls), 2.1 (m, 5 H, methylenes and methine), 4.8 (m, 4 H, vinyl methylenes), 5.9 (s, 1 H, vinyl); carbon-13 nmr, see Figure 1; ir (liquid film) 6.1, 6.25, 7.0, 7.3, and 11.4 μ; uv (acetonitrile) 236 nm (ϵ 14,200); mass spectrum *m/e* (rel intensity based upon base peak at *m/e* 133) 148 (47), 133 (100), 105 (51), 91 (55), 28 (66).

Anal. Calcd for $C_{11}H_{16}$: C, 89.19; H, 10.81. Found: C, 89.33; H, 10.96.

Varying Conversion Sensitized Photolyses. A nitrogen-purged solution of 4-methylverbenene (15.6 m*M*) and benzophenone (31.5 m*M*) in pentane was used employing the immersion apparatus described above. At 10-min intervals, 2-ml aliquots were removed from the photolysis mixture and analyzed by glc (10 ft × 0.125 in., 1.5% OV-101 on 100/20 Varoport 30, 60°, 13 ml/min flow rate). The data obtained are plotted in Figure 2.

Direct Irradiation. Direct irradiations of 4-methylverbenene were conducted on 26 m*M*, degassed and nitrogen purged, pentane solutions in sealed quartz tubes mounted adjacent to the quartz immersion well containing a Vycor glass filter. The solutions were irradiated for 0.75 hr. The photolysate, after removal from the tubes, was concentrated by careful distillation and analyzed by glc using the conditions described above. A typical photolysis yielded a photolysate containing unreacted 4-methylverbenene (27.5%), and the identical major (20.4%) and many minor photoproducts as obtained in the sensitized reaction.

Hydrogenation of the Major Photoproduct. Hydrogenation of 40 mg of the major photoproduct, derived from both the direct and sensitized photolyses, was conducted by bubbling hydrogen through a suspension of pre-hydrogen-saturated 5% palladium on charcoal (5 mg) and the photoproduct in 5.0 ml of absolute methanol for 8 hr. The solution was filtered and analyzed by glc (10 ft × 0.125 in., 1.5% OV-101 on 100/20 Varaport 30, 60°, 13 ml/min flow rate). Three components with retention times of 3, 6, and 7 min were detected. The gc–mass spectral analyses indicated that they were isomeric and corresponded to products resulting from the absorption of 3 mol of hydrogen. Later comparison of the mass spectra of the hydrogenation products with those of independently synthesized material showed thatthey are the isomeric 1-isopropyl-2,4-dimethylcyclohexanes.

To ensure that catalyzed isomerization of the photoproduct had not occurred during the course of the hydrogenation, a solution of the catalyst and photoproduct in methanol was stirred in the absence of hydrogen for 8 hr. Glc analysis of the filtered solution showed that only nonisomerized photoproduct remained.

2,6-Dimethylnonane. Hydrogenation of 4,8-dimenthyl-1,3,7-nonatriene[19] prepared by the Wittig reaction of methylidenetriphenylphosphorane with citral, was carried out, using 5% palladium on charcoal in absolute methanol, as described above. Glc analysis of the product mixture showed one component (retention time 6 min on 10 ft × 0.125 in., 1.5% OV-101 on 100/20 Varaport 30, 60°, 13 ml/min flow rate) identified as 2,6-dimenthylnonane.[19] The mass spectral fragmentation pattern of this compound was as follows: *m/e* (rel intensity based upon base peak at *m/e* 71) 156 (2), 141 (3), 71 (100), 70 (65), 57 (93), 56 (34), and 55 (46).

1-Methyl-4-isopropyl-3-methylenecyclohexene. To a solution of methylidenetriphenylphosphorane, prepared from 65 mmol of *n*-butyllithium and 26.5 g (65 mmol) of methyltriphenylphosphoniumiodide in 200 ml of dimethyl sulfoxide, was added 5.0 g (32 mmol) of piperitone (K and K Laboratories) in 10 ml of dimethyl sulfoxide. The resulting solution was refluxed for 12 hr, cooled, quenched with water, and extracted with pentane. The combined pentane extracts were dried, concentrated to 25 ml by fractional distillation, and percolated with pentane through an alumina column (10 ft × 2 in., Matheson chromatographic grade 923, 80–200 mesh). The pentane was again removed by distillation and the pot residue was further purified by preparative glc (10 ft × 0.25 in., 4% SE-30 on ABS Anakromb, 120°, 90°, 100 ml/min flow rate). The compound having a 20-min retention time was shown to be 1-methyl-4-isopropyl-3-methylenecyclohexene (0.3 g, 6%) on the basis of the following spectral properties: proton nmr ($CDCl_3$) δ 1.0 (d, 6 H, methyls), 1.8 (br s, 3 H, vinyl methyl), 2.1 (m, 6 H, saturated CH and CH_2's), 4.7 (d, 2 H, vinyl methylenes), 5.9 (s, 1 H, vinyl); uv (acetonitrile) 236 nm (ϵ 15,200); ir 6.15, 6.3, 7.3, 7.4, 11.5 μ.

Anal. Calcd for $C_{11}H_{18}$: C, 87.93; H, 12.07. Found: C, 87.87; H, 11.91.

Isomeric 1-Isopropyl-2,4-dimethylcyclohexanes. Hydrogenation of 40 mg (0.27 mmol) of 1-methyl-4-isopropyl-3-methylenecyclohexene in 10 ml of absolute methanol containing 5 mg of 5% palladium on charcoal was carried out by bubbling hydrogen through the suspension for 2 hr. The solution was filtered and analyzed by glc (same conditions as above). Three components of re-

tention times 6, 8, and 10 min were detected. Gc-mass spectral analysis of the first component showed that it was identical with the hydrogenated photoproducts. The other two components were identified as products of partial hydrogenation.

Acknowledgment. Grateful acknowledgment is made to the Robert A. Welch Foundation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Environmental Quality Program of Texas A&M University for generous support of this research. The authors would like to express their appreciation to Dr. Robert Stipanovic for many helpful discussions and for recording the gc–mass spectra.

Registry No.—**1,** 80-57-9; **11,** 51911-75-2; **12,** 51911-77-4; **14,** 89-81-6; **15,** 51911-80-9; **16,** 51911-81-0; **17,** 51911-82-1; **18,** 17302-28-2.

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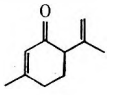
(25) Disproportionation of delocalized radicals is known to be less efficient than in localized tertiary radical systems.[26] However, in this system only one of the two radical centers is delocalized and the competing combination process leads to starting material. It should be noted that small



i

quantities of isopiperitenone (i) formed on photolysis of verbenone[6] probably results from disproportionation of the intermediate diradical **4** by pathway analogous to the production of **12.**
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Oxazolines. IX. Synthesis of Homologated Acetic Acids and Esters

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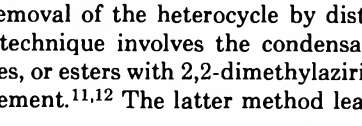
Received April 16, 1974

The lithio salt of 2,4,4-trimethyl-2-oxazoline (**1a**) reacts with alkyl halides affording the 2-alkyloxazolines **3** which may be hydrolyzed to homologated acetic acids. Dialkylation leads to α,α-dialkylacetic acids **5.** Alternatively, the alkylated oxazolines may be directly transformed into esters derived from the use of an appropriate alcoholic solvent. The lithio oxazolines also add smoothly to carbonyl compounds producing, after hydrolysis, α,β-unsaturated acids (**25**) or esters (**26**). Under certain conditions, the formation of β-hydroxy esters (**27**) is allowed, thus providing a convenient alternative to the Reformatsky reaction. The scope and limitations of this novel approach to alkylated acetic acids are also described.

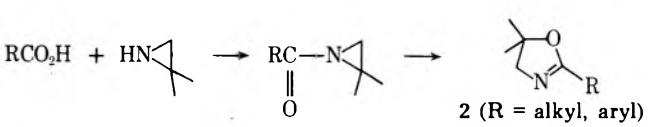
The recent surge of techniques developed for homologation of acetic acids has advanced synthetic methodology considerably. When one recalls that the only generally useful routes available prior to 1967 were the classical malonic and acetoacetic ester syntheses, these new methods involving alkali metalated acetic acids and esters,[3,5,6,8] organocopper derivatives,[7] and organoboranes[4] have all demonstrated that they are more versatile or superior in many respects. Thus, electrophiles may now be directly introduced onto $-CH_2CO_2R(H)$ or $RCHCO_2R(H)$ affording alkylated or dialkylated acetic acids or esters.

In 1970 a preliminary account appeared[9a] which described the potential utility of the simple 2-oxazoline **1** as a precursor to homologated acetic acids and esters. A more complete description of this method and its scope is now presented. Furthermore, the oxazoline precursor may also provide a useful alternative to the Reformatsky reaction (β-hydroxy esters) and, as described in the accompanying paper,[9b] to a variety of butyrolactones.

The requisite 2-oxazolines (**1**) are readily prepared by treating 2-amino-2-methyl-1-propanol with carboxylic acids and removal of the heterocycle by distillation.[10] An alternative technique involves the condensation of acids, acid chlorides, or esters with 2,2-dimethylaziridine followed by rearrangement.[11,12] The latter method leads to the iso-

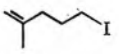


1 (R = alkyl, aryl)



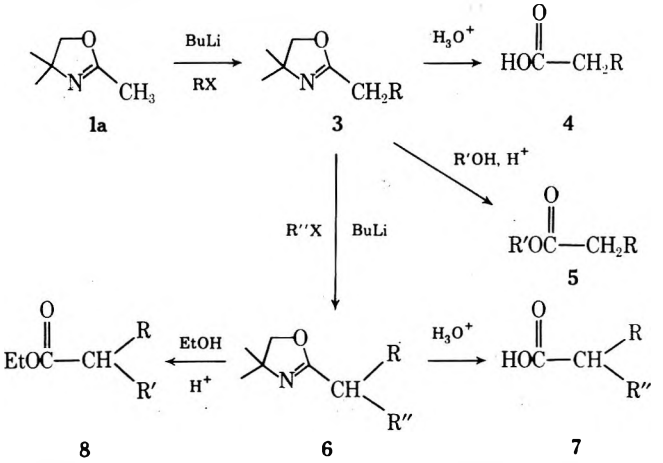
2 (R = alkyl, aryl)

Table I
Formation of Alkylated Acetic Acids and Esters from 2-Oxazolines

RX	R″X	% acid 4	% ester 5 (R′)	% acid 7	% ester 8
n-BuBr		80	84 (Et)		
$PhCH_2Cl$		95	98 (Et)		
			95 (Me)		
			99 (*i*-Pr)		
			85 (*sec*-Bu)		
			0.5 (*t*-Bu)		
$CH_2=C(Br)-CH_2Br$			86 (Et)		
$CH_2=CHCH_2Cl$		77	96 (Et)		
			95 (*i*-Pr)		
			94 (Et)		
$PhCH_2Cl$	MeI			89	80
$PhCH_2Cl$	$CH_2=CHCH_2Cl$			84	88
$PhCH_2Cl$	*n*-BuI			77	83

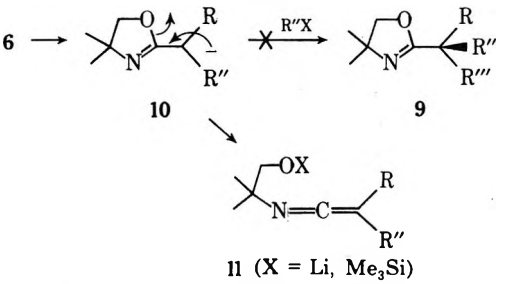
meric 2-oxazoline (2) which also serves as a precursor to homologated acetic and benzoic acids.[12b]

Reaction of Lithio Oxazoline with Alkyl Halides. Homologated Acetic Acids and Esters. Treatment of the 2-methyloxazoline **1a** with *n*-butyllithium at −78° in THF produces, within a few minutes, the lithio oxazoline as a yellow suspension, which was then alkylated with a variety of alkyl halides, furnishing the elaborated oxazoline **3**. In all cases 2–7% of dialkylated oxazoline **6** (R = R″) accompanied the major product. The removal of the dialkyloxazoline did not present any serious experimental difficulty, since direct acid hydrolysis gave the homologated carboxylic acid **4**, which was then purified by distillation (Table I). However, if a subsequent alkylation was carried out using a different alkyl halide, it was necessary to first purify **3** by distillation. Repeating the metalation of **3** with *n*-butyllithium and a second equivalent of alkyl halide produced the dialkylated oxazoline **6**, which was smoothly cleaved to the α,α-dialkylcarboxylic acid **7**.

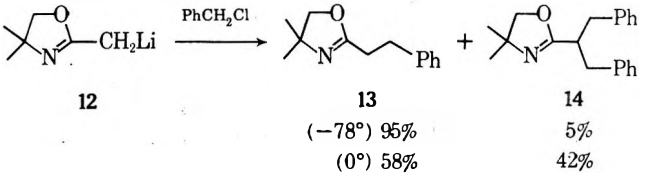


Of further value in this scheme was the fact that the elaborated oxazolines **3** and **6** could be converted directly to their corresponding esters **5** and **8** by performing the cleavage in an alcohol containing 5–10% sulfuric acid. Methyl, ethyl, isopropyl, and *sec*-butyl esters are formed in excellent yields, whereas the *tert*-butyl esters virtually resist formation (Table I).

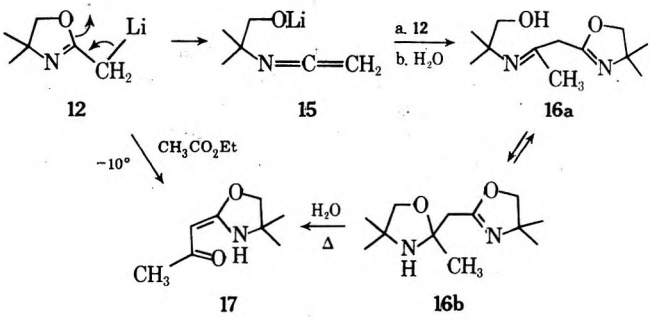
Attempts to alkylate oxazolines **6** to their trialkylated derivative **9** were not successful owing mainly to the fact that the tertiary proton is not removed by the base (*n*-butyllithium, *tert*-butyllithium, or lithium diisopropylamide) until the solution is warmed to approximately 20°. At this temperature, the anion **10** is not stable and rapidly rearranges to the ketenimine **11** (X = Li). The latter was successfully trapped as its trimethylsilyl derivative **11** (X = Me_3Si).[13b] This behavior is similar to that of tertiary anions derived from dihydro-1,3-oxazines.[13a]



A study to evaluate the stability of the primary and secondary carbanions derived from the 2-alkyloxazolines was also performed. When the anion **12** was alkylated with benzyl chloride (1.0 equiv) at −78° the ratio of monoalkylated derivative **13** to dialkylated derivative **14** was 95:5 with an overall yield of 93%. However, when alkylation was per-

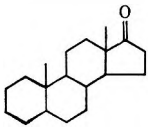
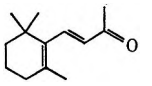
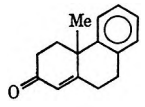


formed at −10 to 0°, the ratio of **13** to **14** was 58:42 in an overall yield of 45%. If the anion **12** was allowed to warm to room temperature in the absence of an external electrophile, there was obtained after aqueous quenching the dimer **16** (**a** and **b**). The latter tautomers were presumably formed



via the transient ketenimine **15** and rapid sequential reaction with unrearranged **12**.[14] Isolation of **16** could be readily achieved by distillation below 100°, whereas heating above 150° resulted in thermal reversion of **16** to starting 2-methyloxazoline **1a**. On the other hand, heating an aqueous suspension of **16** led to removal of the oxazolidine moi-

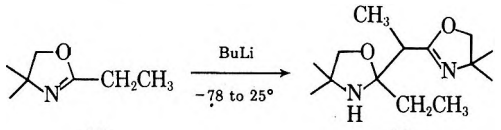
Table II
Unsaturated and β-Hydroxy Acids and Esters from 1a

Carbonyl	% acid (25)	% ester (26)	% hydroxy ester (27)
Acetone			55
3-Heptanone		80[a]	91
Cyclohexanone	84	88	
Cycloheptanone	90[c]	69[b]	80[d]
n-Heptaldehyde			74
	96		
		68[e]	
		78[f]	

[a] Contained 54% of β,γ isomer. [b] Contained 78% β,γ isomer. [c] Mp 75–78°, mixture contains 60–70% β,γ isomer. [d] β-Hydroxy acid obtained from alkaline cleavage of methiodide salt. [e] Contained >90% β,γ-retro ester: W. Oroshnik, G. Karmas, and A. D. Mebane, *J. Amer. Chem. Soc.*, **74**, 3807 (1952). [f] Contains β,γ,δ,ε-unsaturated ester.

ety and provided the vinylogous amide **17** which contains ~10% of the β-keto-2-oxazoline. Structure proof for **17** was gathered by its synthesis *via* an alternate route. Addition of ethyl acetate to the lithio oxazoline furnished **17**, which was identical with the sample obtained from hydrolysis of **16**.

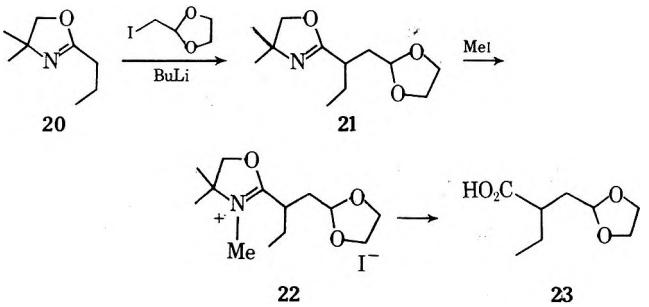
In a similar fashion the 2-ethyloxazoline **18**, when treated with *n*-butyllithium at −78° and then allowed to warm to ambient, gave the dimer **19** after quenching. Thus, pri-



18 **19**

mary, secondary, and tertiary lithio carbanions of oxazolines all appear to have one trait in common: they are unstable at or near room temperature and rearrange to ketenimines. The primary and secondary carbanions ultimately lead to dimers, whereas the tertiary carbanions may be too bulky to dimerize. This behavior, since it was also observed in the dihydro-1,3-oxazines,[13] may be a general property of cyclic imino ethers and thio ethers.

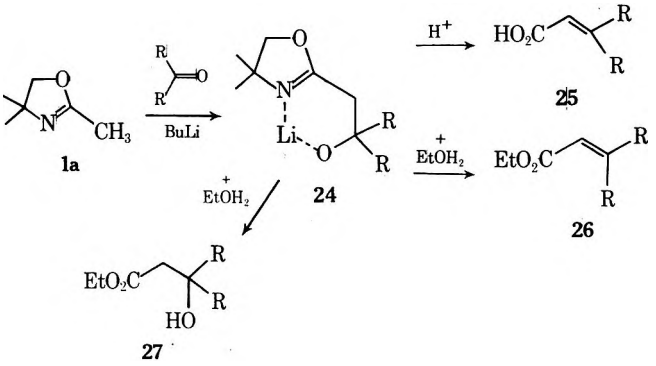
In cases where the elaborated oxazoline carries acid-sensitive groups, it was found feasible to perform the cleavage to carboxylic acids under alkaline conditions. Thus, the 2-(*n*-propyl)oxazoline **20** (obtained from *n*-butyric acid and 2-amino-2-methyl-1-propanol) was converted to the dioxalane derivative **21** using *n*-butyllithium and the dioxalane of iodoacetaldehyde. Treatment with methyl iodide fur-



20 **21** **22** **23**

nished the methiodide salt **22** which was transformed quantitatively to the dioxalane acid **23** by stirring in aqueous sodium hydroxide at room temperature. This alkaline release of the carboxylic acids was found to be general for a number of elaborated oxazoline methiode salts and should provide additional latitude in the preparation of substituted aliphatic carboxylic acids. In a subsequent report,[12b] the utility of the oxazoline as a masking group for preconstructed carboxylic acids and the eventual alkylation to homologated derivatives will be described.

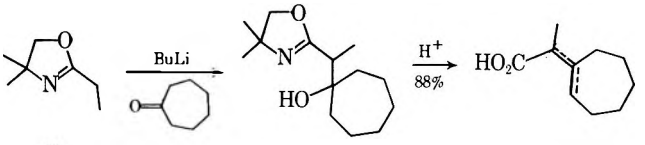
Reaction of Lithio Oxazolines with Carbonyl Compounds. Unsaturated and β-Hydroxy Acids and Esters. The 2-methyloxazoline **1a** was found to react *via* its lithio salt with a variety of carbonyl compounds, leading to the adducts **24** in high yield. Acidic hydrolysis provided the unsaturated carboxylic acids **25**, whereas acidic ethanolysis afforded the corresponding unsaturated esters **26**. In all



1a **24** **25** **26** **27**

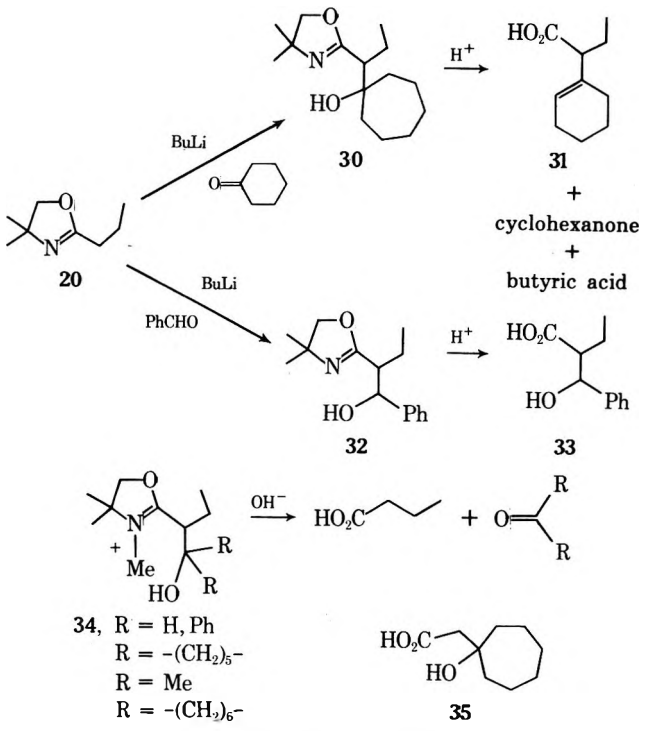
cases, a thermodynamic mixture of unsaturated acids and esters was formed containing various amounts of the β,γ isomers (Table II). By employing lower concentrations of sulfuric acid in the ethanol, the cleavage of the oxazoline adduct **24** leads to the β-hydroxy esters in good yield, thus introducing a viable alternative to the Reformatsky reaction (Table II).[15]

When the oxazoline contained a 2-alkyl group other than methyl, α-alkyl derivatives may be obtained. For example, the 2-ethyloxazoline **18** was alkylated with cycloheptanone, affording a high yield of the adduct **28**. Hydrolysis in aqueous acid provided the 2-cycloheptylidinepropionic acid **29**,

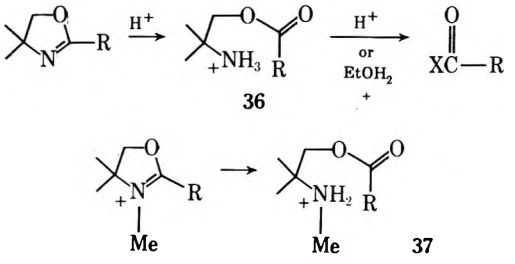


18 **28** **29** (α,β 21%) (β,γ 79%)

which existed mainly as the β,γ isomer. This result, however, was not general with other ketones. Repeating this sequence using cyclohexanone gave much lower yields (25–50%) of the corresponding cyclohexylidine acid. In order to assess the nature of this alkylation in more general terms, a study was performed on the 2-(*n*-propyl)oxazoline **20**. Although reaction of the lithio salt of **20** with carbonyl compounds proceeded in high yield to **30** and **32**, hydrolysis to the respective esters **31** and **33** took place in poor to moderate yields, the main products being reversion to the starting carbonyl compounds and butyric acid. This behavior has been noted previously on the facile reversion of α-alkyl-β-hydroxy acids and esters to their carbonyl precursors.[16,17] When the hydrolysis was carried out on the *N*-methyl salts of **30** and **32** (*e.g.*, **34**), complete reversion occurred to the starting carbonyl and butyric acid. Only in the case of the cycloheptanone adduct was the β-hydroxy acid **35** obtained (55%, see Table II) *via* alkaline hydrolysis.



The mechanism of oxazoline hydrolysis has been studied extensively[17] and found to proceed to the amino ester salts in acidic medium but undergoes more complicated reactions above pH 5. The reversion of the β-hydroxy oxazolines **28, 30, 32,** and **34** must have therefore taken place through their amino ester derivatives (*i.e.*, **36** and **37**), in a manner similar to the reversion in simple esters.



Thus, β-hydroxy esters and acids containing an α-alkyl substituent are formed in less than satisfactory yields under acidic cleavage conditions, and virtually not at all under alkaline conditions.

Experimental Section[18]

Butyllithium was obtained from Lithium Corp., Bessemer City, N. C. The infrared spectra were taken on a Perkin-Elmer 257 grating instrument and the nmr spectra were taken on a Varian T-60. Mass spectra were taken on a AEI-MS-9 or MS-12 instrument at 70 eV.

2,4,4-Trimethyl-2-oxazoline (1a). The procedure was essentially that of Allen and Ginos.[10] Thirty grams (0.50 mol) of glacial acetic acid was added with stirring to 44.5 g (0.50 mol) of 2-amino-2-methyl-1-propanol. The mixture was heated and the temperature (pot) rose to 120° and then slowly declined to 110°. The mixture was distilled azeotropically at 98–110° through a 6-in. Vigreux column into 200 ml of hexane. The upper hexane layer was separated and the water layer was extracted repeatedly with hexane. The combined hexane extracts were dried ($MgSO_4$) and evaporated to yield 41.3 g (73%). The material was pure enough to use (>99%), but was fractionated (bp 75°) to yield a colorless oil which formed a yellow picrate: mp 162–164°; tlc (ether–silica gel) showed one spot, R_f 0.37; ir (film) 1670 cm^{-1} (C=N); nmr ($CDCl_3$) δ 3.82 (s, 2), 1.82 (s, 3), 1.20 (s, 6).

2-(*n*-Propyl)-4,4-dimethyl-2-oxazoline (20) was prepared in 88% yield from *n*-butyric acid as described above: bp 152°; ir (film) 1650 cm^{-1}; nmr ($CDCl_3$) δ 3.82, 2.10, 1.57, 1.11, 0.85; tlc (silica gel–ether) R_f 0.50.

General Method for Alkylation of Lithio Oxazolines. 2-(Phenethyl)-4,4-dimethyl-2-oxazolines (13). 2,4,4-Trimethyl-2-oxazoline (5.0 g, 0.044 mol) in 40 ml of dry THF under nitrogen was cooled to −78° (Dry Ice–acetone bath) and 41 ml of 1.22 *M* *n*-butyllithium in pentane–hexane was added with a syringe through a rubber septum. There was an immediate precipitation of the yellow anion, and benzyl chloride (6.2 g, 0.049 mol) in 20 ml of dry THF was added over a 10-min period. The Dry Ice–acetone bath was removed and the mixture was allowed to return to room temperature and then poured into 100 ml of cold water. The water was made acidic with HCl and extracted with ether. The acid portion was then neutralized with 40% NaOH with cooling and extracted with ether. The ether was dried ($MgSO_4$) and evaporated to yield 8.80 g (99%) of a yellow oil: bp 168° (20 mm); ir (film) 1660 cm^{-1}; nmr (CCl_4) δ 7.18 (br s, 5), 3.82 (s, 2), 2.82 (t, 2), 2.32 (t, 2), 1.20 (s, 6). The sample was sufficiently pure (95–97%) for hydrolysis or alcoholysis.

General Method for Hydrolysis to Carboxylic Acids. 3-Phenylpropionic Acid. The alkylated oxazoline from above was dissolved in 40 ml of 3 *N* hydrochloric acid and heated to reflux for 15–20 min. The oily layer was taken up in chloroform or dichloromethane, dried ($MgSO_4$), and concentrated to give the carboxylic acid (80%). The product was >95% pure prior to distillation. If the carboxylic acid was solid, it was removed by filtration, washed and dried.

General Method for Alcoholysis of Oxazolines. 3-Phenylpropionic Esters (5). Twenty millimoles of 2-phenethyl-4,4-dimethyl-2-oxazoline was heated to reflux (15 hr) in 100 ml of 95% alcoholic sulfuric acid (prepared by mixing 50 ml of alcohol, 4 ml of concentrated sulfuric acid, and 5 ml of water and bringing the total volume to 100 ml with additional alcohol). After cooling, the solution was concentrated to *ca.* 25 ml and poured into 200 ml of ether. The ethereal solution was washed with saturated brine until no further solid material separated and was then dried (K_2CO_3) and concentrated. The purity was checked by vpc.

Methyl ester: 95% yield (95% purity).

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.17; H, 7.32. Found: C, 73.39; H, 7.51.

Ethyl ester: 99% yield (98% purity).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.22; H, 7.87.

Isopropyl ester: 99% yield (96–98% purity).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 75.00; H, 8.33. Found: C, 74.77; H. 8.47.

***sec*-Butyl ester:** 85% yield (95–98% purity).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.73; H, 8.74. Found: C, 75.57; H, 8.53.

Ethyl 2-Methyl-3-phenylpropionate. General Procedure for Alkylation of a Secondary Carbanion and Conversion to Ethyl Ester (3 to 8). Five grams (25 mmol) of **3** (R = benzyl) was dissolved in 40 ml of dry THF and cooled to −78° under a dry nitrogen atmosphere. To the magnetically stirred solution was added 11 ml (27 mmol) of *n*-butyllithium in hexane. The solution immediately assumed a deep red color and was stirred for an additional 30 min to ensure complete anion formation. Methyl iodide (7.00 g, 49 mmol) in 20 ml of THF was added in a dropwise manner and the resulting solution (yellow) was stirred at −78° for 30 min and then allowed to warm to room temperature. The mixture was poured into 100 ml of cold saturated brine and extracted with three 100-ml portions of ether. The ether extract was dried ($MgSO_4$) and evaporated to yield 4.79 g (91%) of **6** (R = $PhCH_2$; R″ = Me). The crude material was used without further purification in the next step.

Oxazoline **6** (4.68 g, 0.022 mol) was dissolved in 60 ml of ethanolic sulfuric acid and heated to reflux for 16 hr. The mixture was cooled to room temperature, poured into 100 ml of cold saturated brine and extracted with three 100-ml portions of ether. Pentane (100 ml) was added to the ether extract and the cloudy solution was washed successively with saturated brine, 10% bicarbonate, and saturated brine. After drying and concentration, 3.32 g (80%) of the ester **8** was obtained, bp 76–79° (0.75 mm),[19] ir (film) 1730 cm^{-1}.

2-Ethyl-3-(2-dioxalanyl)propionic Acid (23). General Method for Alkaline Cleavage. Thirty grams (0.210 mol) of propyloxazoline **20** was magnetically stirred in 80 ml of dry tetrahydrofuran at −78°. To this solution 133.2 ml (0.231 mol, 1.80 *M*) of *n*-butyllithium (hexane) was added dropwise. The yellow solution was stirred for 30 min before 53.93 g (0.252 mol) of 2-iodoacetaldehyde ethylene acetal[20] was added dropwise. The mixture was stirred for 30 min at −78° and then allowed to slowly reach room

temperature. The mixture was poured into 300 ml of saturated brine and extracted with ether. The ethereal solution was dried (Na_2SO_4) and concentrated. Distillation of the residue gave 33.2 g (65%) of **21**: bp 92° (0.25 mm); ir (film) 1675 cm^{-1}; nmr (CCl_4) δ 0.9 (t, 3), 1.20 (s, 6), 1.35–2.65 (m, 5), 3.65–4.00 (m, 6), 4.80 (d of d, 1).

The oxazoline was converted to the methiodide salt by stirring in excess methyl iodide overnight at room temperature and evaporating the volatiles *in vacuo*. The methiodide **22** was recrystallized from acetonitrile–ether, mp 119–120°.

The oxazoline methiodide **22** (8.6 g, 23.3 mmol) was added to 50 ml of 1 *N* sodium hydroxide and the mixture was stirred for 15 hr at room temperature. The solution was acidified with 10% hydrochloric acid (pH 2) and extracted with ether. The extracts were dried (Na_2SO_4) and concentrated to leave an oil: bp 115–118 (0.4 mm), 3.9 g (94%) of the β-dioxalane acid **23**; ir (film) 1700, 1740, 3000 cm^{-1}; nmr ($CDCl_3$) δ 0.95 (t, 3), 1.18–2.75 (m, 5), 3.80 (m, 4), 4.95 (t, 1), 8.60 (s, 1, exchangeable with D_2O).

Anal. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.27; H, 8.21.

General Method for Preparation of β-Hydroxy Esters. Ethyl (3-Hydroxy-3-*n*-propyl)caproate (27, R = *n*-Propyl). A solution of oxazoline **1a** (6 g) in dry tetrahydrofuran (20 ml) was treated dropwise with stirring under nitrogen with *n*-butyllithium (29.4 ml, 2.25 *M*) at −78°. The resulting yellow suspension was stirred for 30 min and then a solution of 4-heptanone (7.55 g) in tetrahydrofuran (10 ml) was added over a 15-min period. The green solution was allowed to warm gradually to room temperature and then poured into 100 ml of ice–water, neutralized with 9 *N* hydrochloric acid, and extracted with ether. The aqueous solution was carefully neutralized with 40% sodium hydroxide and the oil was removed by ether extraction. Drying (Na_2SO_4) and concentration left the colorless hydroxy oxazoline in high purity: ir (film) 1670, 3400 cm^{-1}; nmr (CCl_4) δ 4.2 (s, 1, exchangeable with D_2O), 3.92 (s, 2), 2.30 (s, 2), 0.6–1.7 (m, 20).

A solution of the hydroxy oxazoline above (5.15 g) in 1.5 *N* ethanolic sulfuric acid (50 ml, prepared by diluting 2 ml of concentrated sulfuric acid to 50 ml with absolute ethanol) was heated at reflux for 18 hr. On cooling, the solution was poured into 300 ml of ether and extracted with saturated brine to remove the amino alcohol. The ethereal solution was dried and concentrated to give the hydroxy ester: 4.3 g (91%); ir (film) 1740, 3515 cm^{-1}; nmr ($CDCl_3$) δ 0.68–1.5 (m, 17), 2.48 (s, 2), 3.90 (s, 1, exchangeable with D_2O), 4.18 (q, 2).

Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.43; H, 11.02.

General Method for Preparation of Unsaturated Acids. $\Delta^{17,20}$-Allopregn-21-oic Acid (25). The general method for alkylation of the lithio oxazoline with a carbonyl compound as given above was employed using androstan-17-one (0.327 g, 0.98 mmol). Work-up yielded 457 mg (96%) of a crystalline compound: mp 158–159° (petroleum ether); ir (Nujol) 1650, 3300 cm^{-1}; nmr ($CDCl_3$) δ 3.90 (s, 2), 2.40 (s, 2), 1.21 (s, 6), 0.86 (s, 3), 0.75 (s, 3), and the usual broad signals of the steroidal skeleton.

A solution of 71 mg of the steroid oxazoline in 20 ml of 3 *N* hydrochloric acid containing sufficient ethanol to effect solution was heated to reflux for 15–20 min. The cloudy solution, after cooling, was extracted with chloroform–ether (1:1) and dried ($MgSO_4$). The residue after evaporation was a crystalline solid, mp 250–252° (lit.[21] mp 242–244°), obtained in 97% yield.

General Method for Preparation of Unsaturated Esters. β-Ionylidene Acetic Esters (26). The lithium salt of oxazoline **1a** (5.0 g, 44 mmol) was alkylated with β-ionone (9.6 g, 50 mmol) in the manner described above and gave 9.8 g (73%) of a viscous yellow oil, single spot on tlc, R_f 0.72 (ether), ir (film) 1650, 3350 cm^{-1}. The crude oxazoline–β-ionone adduct (9.5 g) was hydrolyzed in ethanolic sulfuric acid (10% concentrated sulfuric in 95% ethanol) by heating under reflux for 7 hr and gave 8.8 g (93%) of an equal mixture of β-ionylidene ester and *retro*-β-ionylidene ester:[22] ir (film) 1735 (unconjugated C=O) and 1710 cm^{-1} (conjugated C=O); nmr spectrum ($CDCl_3$) showed a ~1:1 mixture of the two isomers; λ_{max} 292 nm (EtOH). The mixture was purified by passing through Woelm Grade I neutral alumina with ether and gave ~90% of the retro isomer, rearrangement to the latter taking place during chromatography.

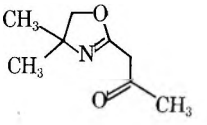
Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.50; H, 9.89.

Unsaturated Acids from 2-Ethyl-2-oxazoline (18). 2-Cycloheptylidenepropionic Acid and Its Endo Isomer (29). The lithio salt of 2-ethyl-2-oxazoline **18** was alkylated with 1.0 equiv of cycloheptanone in the usual fashion (THF, −78°) to give the adduct **28** in 67% yield, ir (film) 1650, 3400 cm^{-1}. The product was hydrolyzed in 40 ml of 3 *N* hydrochloric acid by heating for 20 min. The solution was saturated with salt and extracted with chloroform, dried, and concentrated. The unsaturated acid (96%) was obtained as an oil, R_f 0.83 (ether). It was found convenient to convert the acids to their ethyl esters for vpc analysis. This was done by successive treatment with thionyl chloride and ethanol. Vpc (Chromosorb P, 10% SE-30) at 180° showed the esters to be a 79:21 mixture of endo and exo double-bond isomers, ir (film) 1710, 1740 cm^{-1}.

Dimerization of 2,4,4-Trimethyl-2-oxazoline (1a) to 16b. The anion **1a**, prepared in the usual manner (BuLi, THF, −78°), was allowed to warm to room temperature (18 hr). The resulting brown mixture was poured into saturated brine and extracted several times with ether. Evaporation of the dried extracts left a dark-colored oil, 3.3 g (66%), which was distilled: bp 64–67° (0.25 mm); *m/e* 226; nmr ($CDCl_3$) δ 1.29 (s, 12), 1.40 (s, 3), 2.47 (s, 2), 2.7 (br s, exchangeable with D_2O), 3.52 (d of d, 2), 3.90 (s, 2).

Anal. Calcd for $C_{12}H_{22}N_2O_2$: C, 63.69; H, 9.80. Found: C, 62.66; H, 10.06.

Hydrolysis of Dimer to 17. The dimer **16b** (0.913 g) was dissolved in 10 ml of water and heated on a hot plate at 60° for 2 hr. The solution was cooled and extracted with ether. The dried (K_2CO_3) extracts were concentrated to give a solid: 0.401 g (70%); mp 124–126°; nmr ($CDCl_3$) δ 1.42 (s, 6), 2.01 (s, 3), 4.05 (s, 2), 4.83 (s, 1), 8.85 (br, 1, exchangeable with D_2O). These nmr signals integrated to ~90% of the indicated values while weak signals were observable as singlets at δ 1.3, 2.2, 3.4, and 4.0 which are consistent with the structure below.



Alternatively, **17** was prepared by treating the lithio oxazoline **12** with 1.0 equiv of ethyl acetate at −78°. This was performed *via* inverse addition as follows.

The lithio oxazoline (22 mmol) was prepared in the usual manner and transferred using a cold syringe to a solution of ethyl acetate (3.9 g, 44 mmol) in 10 ml of tetrahydrofuran cooled to −10°. The yellow color of the anion solution was immediately discharged and the solution was allowed to warm to room temperature and stirred for 30 min. Quenching in water, followed by ether extraction, gave, after concentration, a semisolid material. Washing with pentane resulted in crystallization of **17**, mp 123–126°. The pentane solution was evaporated, leaving an oil which was shown to be the β-keto-2-oxazoline. The latter, on standing in air, crystallized and the total yield of crystalline material was 2.91 g (85%). This material was identical with that obtained by hydrolysis of **16b**.

Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.86; H, 8.42; N, 9.23.

Dimerization of 2-Ethyl-4,4-dimethyl-2-oxazoline (18) to 19. A solution of 5.6 g (44 mmol) of **18** in 30 ml of tetrahydrofuran was treated with *n*-BuLi (30 ml, 1.59 *M*) at −78° and then allowed to warm to room temperature. Work-up, as in the case of **16b**, gave an oil which could not be distilled owing to heat sensitivity. Elution through silica gel with ether gave an oil, 5.0 g (92%), ir (film) 1645, 3230 cm^{-1}.

Anal. Calcd for $C_{14}H_{26}N_2O_2$: C, 66.11; H, 10.30; N, 11.01. Found: C, 66.39; H, 10.58; N, 11.10.

Acknowledgment. The authors are grateful to the National Institutes of Health, the National Science Foundation, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

Registry No.—**1a**, 1772-43-6; **1a** picrate, 51869-42-2; **3** (R = $PhCH_2$), 13608-28-1; **5** (R = $PhCH_2$; R′ = Me), 103-25-3; **5** (R = $PhCH_2$; R′ = Et), 2021-28-5; **5** (R = $PhCH_2$; R = *i*-Pr), 22767-95-9; **5** (R = $PhCH_2$; R′ = *sec*-Bu), 51869-23-9; **6** (R = $PhCH_2$; R″ = Me), 51869-24-0; **8** (R = $PhCH_2$; R″ = Me), 34666-01-8; **16b**, 51911-66-1; **17**, 51869-25-1; **18**, 5146-88-3; **19**, 51869-26-2; **20**, 4271-19-6; **21**, 51869-27-3; **22**, 51869-28-4; **23**, 39008-00-9; **27** (R = *n*-Pr), 10297-62-8; **28**, 51869-17-1; **29** (α,β), 51869-18-2; **29** (β,γ), 51869-19-3; acetic acid, 64-19-7; 2-amino-2-methyl-1-propanol, 124-68-5; butyric acid, 107-92-6; 2-(2-hydroxy-2-propylpentyl)-4,4-dimethyl-2-oxazoline, 51869-20-6; $\Delta^{17,20}$-allopregn-21-oic acid, 51869-29-5; androstan-17-one, 963-74-6; β-ionone, 14901-07-6;

4,4-dimethyl-2-oxazoline–β-ionone adduct, 51869-21-7; ethyl β-ionylideneacetate, 5452-61-9; ethyl *retro*-β-ionylideneacetate, 51869-22-8; 2-(2-ketopropyl)-4,4-dimethyloxazolidine, 32385-89-0.

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Oxazolines. X. Synthesis of γ-Butyrolactones

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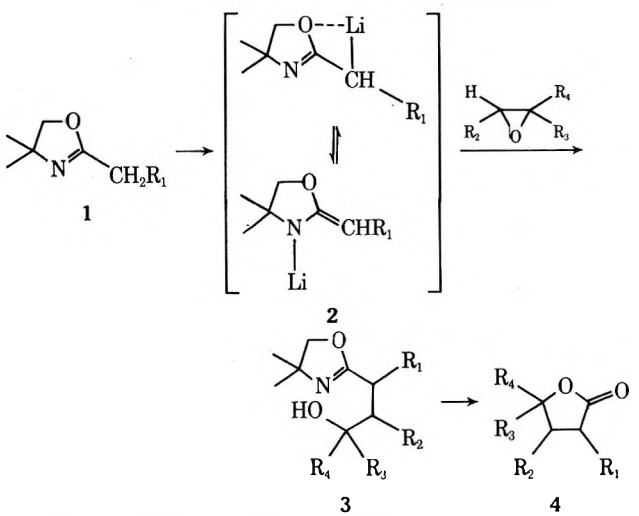
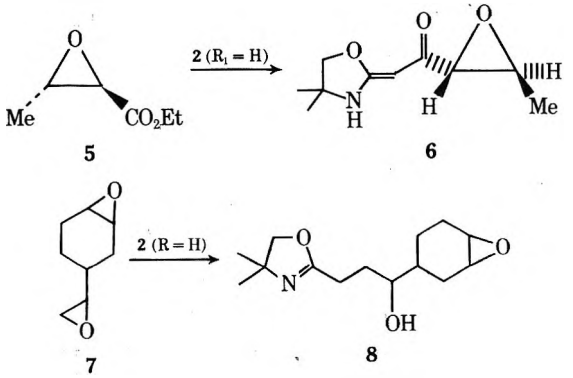
Received April 16, 1974

A variety of butyrolactones (**4**), substituted in the α, β, and/or γ positions with alkyl groups, is described. The approach originates from the lithio salt of 2,4,4-trimethyl-2-oxazoline (**1**, R = H) and higher 2-alkyl homologs (**1**, R = alkyl) which readily reacts with epoxides at low temperature to produce the 2-(β-hydroxyalkyl)oxazolines **3**. Hydrolysis of the latter leads to the butyrolactones **4** in good overall yields. Several examples in which the epoxide is part of a polyfunctional molecule are given to indicate the selectivity of the lithio oxazoline.

In the previous article[1] a series of homologated acetic acids were prepared by treating the lithio salt of 2-substituted 4,4-dimethyl-2-oxazolines **2** with a variety of alkyl halides and carbonyl compounds. Further work on this useful heterocyclic system (**1**) has revealed that its lithio salt **2** may also react with epoxides at low temperature, resulting in the hydroxypropyloxazolines **3**. Hydrolysis of the latter produces a variety of γ-butyrolactones **4** possessing substituents at either the α, β, or γ positions (Table I). Although a

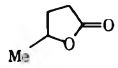
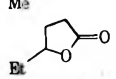
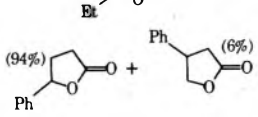
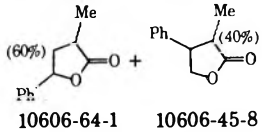
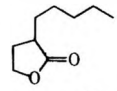
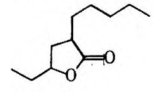
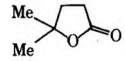
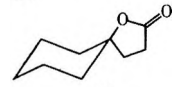
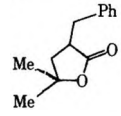
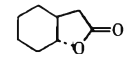
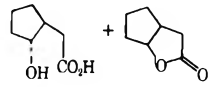
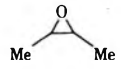
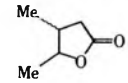
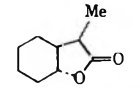
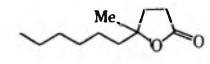


number of epoxides gave good yields of lactones, others proved to be resistant to alkylation. For example, 1,2-disubstituted epoxides (entries 13, 14, and 15) gave little or no ring-opened products except for cyclohexene and cyclopentene oxides. For the latter case, the lactone (entry 12) was poorly formed, since this would necessitate a trans-fused product which involves considerable strain. However, the trans hydroxy acid was the major product formed. The extent to which 1,2 disubstitution prevents epoxide ring opening was clearly seen when the epoxy ester **5** was treated at −78° with the lithio oxazoline. Reaction occurred solely at the carbonyl carbon to give **6** in 87% yield. Al-



though tautomers were expected, the product was found to be entirely **6**, which appeared as a crystalline material. Other organometallics were reported to react with **5** to give ring-opened products[2] with varying degrees of selectivity. On the other hand, α-cyano epoxides were found to react with organolithium reagents exclusively at the cyano group.[3,4] When the bis epoxide **7** was subjected to the lithio oxazoline at −60°, the adduct **8** was isolated in 70% yield.

Table I
γ-Butyrolactones from Epoxides and Lithio Oxazolines

Entry	1, R_1	Registry no.	Epoxide[a]	Registry no.	% 3[b]	Registry no.	Lactone 4	Registry no.	Overall yield, %[c]
1	H	1772-43-6		75-21-8	~100	51849-54-8		96-48-0	75[d]
2	H			75-56-9	80	51849-55-9		108-29-2	72[d]
3	H			106-88-7	85	51849-56-0		695-06-7	85[d]
4	H			96-09-3	~100	51849-57-1 51849-58-2	 1008-76-0 1008-73-7		89
5	Me	5146-88-3			80	51849-59-3 51849-60-6	 10606-64-1 10606-45-8		65
6	*n*-Amyl	51849-53-7			~100	51849-61-7		51849-71-9	72
7	*n*-Amyl				95	51849-62-8		51849-72-0	76
8	H			1558-30-5	99	51849-63-9		3123-97-5	72[d]
9	H			185-70-6	80	51849-64-0		699-61-6	56[e]
10	$PhCH_2$	13608-28-1			~100	51849-65-1		51849-73-1	70
11	H			286-20-4	83	51849-66-2		27345-71-7	65
12	H			285-67-6	95[h]	51849-67-3	 51849-74-2 (80–85%) 5745-61-9 (15–20%)		30[f]
13	H			286-62-4	~0				
14	H		 (cis or trans)	1758-33-4 (cis) 21490-63-1 (trans)	10–30	51849-68-4	 (50 : 50 mixture)	10150-95-5 (cis) 10150-96-6 (trans)	16[d]
15	H			23024-54-6	~0[f]				
16	Me				14	51849-69-5		2205-25-6	9[e]
17	H			6924-86-3	82	51849-70-8		7011-83-8	70

[a] 1.1 equiv of epoxide added at −78° and slowly allowed to rise to room temperature. For entries 9, 11, 12, and 17, the epoxide was added at −45°, stirred for 4–5 hr, and then allowed to warm slowly to room temperature. [b] Crude yield, used in subsequent step without purification. [c] Based on starting oxazoline; products were checked for purity by vpc after bulb-to-bulb distillation. Purity in all cases was >95%. [d] Hydrolysis of **3** performed in acidic ethanol. Yields were ~30% lower when hydrolysis was done in aqueous acid. [e] Hydrolysis in wet benzene–toluenesulfonic acid. [f] Epoxide was recovered in >80% yield. [g] The lithio salt **2** (R_1 = H) was complexed with 1.0 equiv of *N,N,N′,N′*-tetramethylethylenediamine prior to addition of styrene oxide. [h] 2.0 equiv of **1** (R_1 = H) employed.

Thus, the low-temperature alkylation of the lithio oxazolines proceeds with considerable selectivity, the predominant factor being the steric environment of the epoxide carbons. However, steric bulk on the lithio oxazoline was

also seen to affect the efficiency of the reaction (entries 11 *vs.* 16). The presence of a methyl group in **2** (R_1 = Me) coupled with the disubstitution in cyclohexene oxide caused a drop in yield from 83 to 14%. In those cases where reaction went poorly or failed completely (entries 13–16) a number of conditions were evaluated to improve the process. Changing solvents (from THF to ether), changing temperatures (−78 to 20°), and addition of complexing agents (TMEDA, HMPA) failed to provide any significant improvements. Only in the case of styrene oxide (entry 4) was the yield of alkylation increased (from 60 to 100%) when **2** was complexed with TMEDA.

Of further interest was the fact that the substitution pattern in the lactones could be introduced sequentially in a single operation. For example, the lactone in entry 10 was prepared by initially treating the parent lithio oxazoline **2** (R_1 = H) with 1.0 equiv of benzyl chloride at −78° and allowed to warm to 25° to ensure complete reaction. The solution was then recooled to −78° and 1.1 equiv of *n*-butyllithium and the epoxide were added. Upon work-up, the α-benzyl lactone was obtained in 70% overall yield. The anticipated mixture of products from sequential alkylation was held to less than 10% and the desired lactone could readily be purified by distillation. When the sequential alkylation was attempted with methyl iodide (entry 5) followed by styrene oxide, a 60:40 isomeric mixture was formed. This is believed to be the result of the initially formed lithium iodide acting as a Lewis acid which lowers the regioselectivity of the ring opening in styrene oxide. Note the high degree of regioselectivity when the parent lithio oxazoline is treated with styrene oxide (entry 4), a system which is devoid of any soluble Lewis acid. It would be expected, therefore, that a higher yield of the γ-phenyl lactone would result if the reaction began with the 2-ethyloxazoline **1** (R_1 = Me), although this has not been performed. Currently, this study is being directed toward a convenient synthesis of α-methylene lactones and further work on the consecutive alkylations is a necessary prerequisite to this goal. In summary, this method should find considerable use in the preparation of a variety of substituted γ-lactones and compares favorably with other recent techniques.[5–8]

Experimental Section

n-Butyllithium was purchased from Ventron (Alfa Division), Beverly, Mass. Microanalyses were performed by Midwest Microlabs, Indianapolis, Ind. Spectra were taken on a Perkin-Elmer 257 grating infrared, Varian T-60, and JEOL MH-100 nmr instrument. Gas chromatography was performed on a Hewlett-Packard 5750 instrument using two different columns (FFAP and UC-W98) to check homogeneity. The epoxides utilized were commercially available except as indicated; exo-methylenecyclohexane oxide (entry 9) and 2-methyl-1-octene oxide (entry 17) were prepared from the corresponding ketones according to Corey;[9] *cis*-1-methyl-2-(*n*-amyl)oxirane (entry 15) was prepared by epoxidation of *cis*-2-octene.[10]

2-Oxazolines. 2,4,4-Trimethyl-2-oxazoline (**1**, R_1 = H) was prepared as previously described.[1] 2-(*n*-Hexyl)-4,4-dimethyl-2-oxazoline (**1**, R_1 = *n*-amyl) was prepared in the same manner using *n*-heptanoic acid: 40%; bp 96–98° (15 mm); ir (film) 1660 cm^{-1}; nmr (CCl_4) δ 3.80 (s, 2), 2.15 (m, 2), 1.8–1.3 (m, 8), 1.2 (s, 6), 0.9 (t, 3).

Alkylation of Epoxides with Lithio Oxazolines. General Procedure. A solution containing 2.50 g (22 mmol) of 2,4,4-trimethyl-2-oxazoline (1.7 *M*) in 13 ml of anhydrous THF was cooled to −78° under a nitrogen atmosphere. A solution of *n*-butyllithium (2.25 *M* in hexane, 23.1 ml, 1.05 equiv) was added dropwise and the lithio oxazoline precipitated from solution as a colorless light powder. The suspension was stirred for 30 min at −78° and 1.1 equiv of the epoxide (neat or diluted equally with THF) was added dropwise and stirred for 30 min. The cooling bath was removed and the solution was allowed to reach room temperature (4–5 hr). If the reaction temperature was to be maintained at −45° (see Table I), the Dry Ice–acetone bath was replaced with a −45° cryostat (Dry Ice–chlorobenzene) and stirred for 3–5 hr.

The reaction contents were poured into water (150 ml) and work-up proceeded in either of the following manners. (a) For low molecular weight (volatile) or water-soluble epoxides, the aqueous solution was merely poured into 100 ml of ether, and the organic layer was separated and washed with saturated brine. Drying of the ethereal solution ($MgSO_4$) and concentration left the hydroxypropyloxazoline **3**. (b) For higher molecular weight or water-insoluble epoxides, the quenched reaction mixture was cooled to 0° and acidified to pH 2 (9 *N* HCl). The solution was extracted with pentane or pentane–ether (1:1) to remove unreacted epoxide and then neutralized, while still cold, with 40% sodium hydroxide (pH 8–10). The oxazoline was removed by extraction with ether, and the extracts were dried ($MgSO_4$) and concentrated to give **3**. The purity of this material was usually quite high (vpc) and further purification was necessary only for analytical samples. Physical data for **3** are presented in Table II.

Hydrolysis of Oxazolines 3 to γ-Butyrolactones. General Procedure. A. Acidic Aqueous Method. The oxazoline (22 mmol) was stirred in 50 ml of 3 *N* HCl to effect solution and then heated at reflux for 15–20 min. After cooling, the acidic solution was extracted with ether (3 × 75 ml), dried ($MgSO_4$), and concentrated to give lactones of high purity (>90%, vpc). The pure lactones were obtained by bulb-to-bulb distillation. Physical properties are given in Table II.

B. Acidic Ethanol Method. This method was used primarily in those cases where the lactone was water soluble (Table I). A solution of the oxazoline (22 mmol) in 150 ml of 95% ethanol containing 6.0 ml of concentrated sulfuric acid was heated to reflux for 16–18 hr, cooled, and concentrated to 15 ml by fractional distillation. Addition of 100 ml of ether to the concentrate was followed by extraction with 15 ml of saturated brine. The ethereal solution was dried ($MgSO_4$) and concentrated (by fractional distillation for low-boiling lactones) to produce the γ-butyrolactone.

C. Toluenesulfonic Acid–Benzene Method. For lactones that formed slowly from their hydroxy acids (entry 16), the oxazoline **3** (5 mmol) was dissolved in benzene (20 ml), and water (2.5 ml) and toluenesulfonic acid (1.92 g) were then added. The solution was heated to reflux (18 hr) and the water was collected in an azeotrope (Dean-Stark) trap. Heating was continued until all the water had been collected. The solution was cooled, water was added so that two layers appeared, and the benzene layer was removed, dried, and concentrated to produce the lactone.

Reaction of Lithio Oxazoline (1, R_1 = H) with Ethyl *trans*-2,3-Epoxybutyrate (5). To 1.25 g (11 mmol) of **1** (R_1 = H) in 6 ml of THF at −78° was added 5 ml (11 mmol) of *n*-butyllithium and stirring was performed for 30 min. To the resulting suspension was added 1.35 ml (11 mmol) of epoxide **5** in a single portion at −78°, which caused the precipitate to disappear immediately. After 30 min, the solution was quenched (−78°) with saturated ammonium chloride and poured into 100 ml of ether. The ether layer was washed with saturated brine, dried ($MgSO_4$), and concentrated to give a pale yellow solid. Recrystallization from ether–hexane gave 1.8 g (87%) of a colorless solid: mp 96.5–97.5°; ir (KBr) 3270, 3110, 1635, 1560 cm^{-1}; nmr (CCl_4) δ 9.7 (br s, 1), 4.9 (s, 1), 2.9 (m, 2), 1.5 (s, 6), 1.35 (m, 3). The structure was consistent with **6** and the trans stereochemistry based upon comparison with the nmr spectrum of **5**.

Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.70; H, 7.81; N, 7.02.

Reaction of 1 (R_1 = H) with Bis Epoxide 7. The lithio oxazoline **1** (R_1 = H) was prepared as described in the General Procedure. The solution was then warmed to −64°, and 3.08 g of the bis epoxide 7[11] in 2 ml of THF was added, and the solution was stirred for 3.5 hr as the temperature rose slowly to −40°. The reaction solution was poured at this temperature into ice–water (50 ml), acidified with 9 *N* HCl (pH 2), and extracted with hexane (2 × 30 ml), and the hexane solution was discarded. The cold aqueous layer was neutralized with 40% alkali and extracted with ether, dried ($MgSO_4$), and concentrated to give 4.1 g (70–75%) of a clear, viscous oil. Distillation (bulb-to-bulb) at 0.02 mm gave pure **8**: ir (film) 3300, 1668 cm^{-1}; nmr (CCl_4) δ 4.4 (br s, OH), 3.85 (s, 2), 3.5–2.8 (m, 3), 2.3 (t, 2), 1.25 (s, 6), 2.2–0.9 (m, 9).

Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15. Found: C, 66.54; H, 9.02.

Consecutive Alkylation. α-Benzyl-γ,γ-dimethyl-γ-butyrolactone (Entry 10). The lithio oxazoline **1** (R_1 = H) was formed as described in the General Procedure. At −78°, benzyl chloride (2.53 ml, 1.0 equiv) was added neat in a dropwise manner. After stirring

Table II
Physical Data for Oxazolines and Lactones

Entry	Oxazolines 3		Lactones 4	
	Ir (film), cm^{-1}	Nmr (CCl_4), δ	Ir (film), cm^{-1}	Nmr (CCl_4), δ
1	1660, 3320	5.1 (1, OH), 3.9 (s, 2), 3.6 (t, 2), 2.4 (m, 2), 1.9 (m, 2), 1.3 (s, 6)	1770[a]	
2	1665, 3360	4.0–3.7 (m, 4), 2.4 (m, 2), 1.8 (m, 2), 1.2-1.1 (s, 6; d, 3)	1770[b]	
3	1670, 3380	4.35 (s, OH), 3.85 (s, 2), 3.45 (m, 1), 2.35 (t, 2), 1.9–1.3 (m, 4), 1.25 (s, 6), 0.9 (br t, 3)	1778	4.4 (m, 1), 2.7–1.3 (m, 6), 1.0 (t, 3)[c]
4	1665, 3380	7.3 (m, 5), 4.7 (t, 1), 4.5 (br s, 1), 3.9 (s, 2), 2.1 (m, 4), 1.2 (s, 6)	1780	7.4 (s, 5), 5.4 (m, 1) 2.4 (m, 4)[d]
5	1658, 3250, 3320	7.3 (m, 5), 4.6 (m, 2), 4.0–1.6 (m, 5), 1.4–0.8 (m, 9)	1770	7.26 (m, 5), 5.3 (m, 0.6), 4.2 (m, 0.4) 3.6–2.0 (m, 3), 2.0–0.6 (m, 3)[e]
6	1660, 3300	3.85 (s, 2), 3.55 (m, 3), 2.45 (m, 1), 2.0–0.8 (m, 19)	1780	4.2 (m, 2), 2.7–0.7 (m, 14)[f]
7	1660, 3360	3.85 (s, 2), 3.6 (m, 2), 2.5 (m, 1), 1.8–0.7 (m, 24)	1770	4.35 (m, 1), 2.4 (m, 1), 2.2–0.7 (m, 18)[g]
8	1665, 3370	3.83 (s, 2), 3.55 (s, OH), 2.3 (m, 2), 1.75 (m, 2), 1.22 (s, 6), 1.15 (s, 6)	1770	2.53 (AA'BB', 2), 2.0 (AA'BB', 2), 1.43 (s, 6)[h]
9	1660, 3250 (KBr)	3.9 (s, 2), 3.55 (s, OH), 2.3 (m, 2), 2.0–0.8 (m, 18)	1775	2.55 (AA'BB', 2), 2.0 (AA'BB', 2), 1.6 (br s, 10)[i]
10	1665, 3400	7.2 (s, 5), 3.8 (s, 2) 3.7–1.1 (m, 18)	1770	7.25 (s, 5), 2.9 (m, 3), 1.85 (m, 2), 1.3 (2 s, 6)[j]
11	1660, 3300	3.83 (s, 2), 3.8–1.1 (m, 19)	1775	3.7 (m, 1), 2.6–0.8 (m, 11)[k]
12	1665, 3320	4.8 (s, OH), 3.9 (s, 2), 3.8 (m, 1), 2.5–0.8 (m, 15)[o]		*p*
14	1665, 3340	3.9–3.2 (m, 4), 2.4–1.4 (m, 3), 1.3–0.6 (m, 12)	1780	4.6 (m, ~0.5), 4.1 (m, ~0.5), 2.7–1.8 (m, 3), 1.5–0.9 (m, 6)[l]
16	1660, 3300	3.9 (s, 2), 3.7–3.1 (m, 2), 2.5–0.9 (m, 19)[m]	1785	3.8 (m, 1), 2.8–1.1 (m, 13).
17	1670, 3360	3.85 (s, 2), 3.45 (br s, OH), 2.3 (m, 2), 1.75 (m, 2), 1.35 (br s, 10), 1.25 (s, 6), 1.1 (s, 3), 0.90 (br t, 3)	1778	2.5 (AA'BB', 2) 1.75–2.1 (AA'BB', 2), 1.2–1.65 (m, 10), 1.35(s, 3), 0.90(br t, 3)[n]

[a] Sadtler Prism ir no. 5330. [b] Sadtler Prism ir no. 3407. [c] O. Riobe, *C. R. Acad. Sci.*, **247**, 1016 (1958). [d] C. H. Depuy, F. H. Breitbeil, and K. L. Eilers, *J. Org. Chem.*, **29**, 2810 (1964). [e] C. H. Depuy, F. W. Breitbeil, and K. R. DeBruin, *J. Amer. Chem. Soc.*, **88**, 3347 (1966). *Anal.* Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.73; H, 6.74. [f] G. N. Nikishin, Yu. N. Ogibin, and A. D. Petrov, *Dokl. Akad. Nauk SSSR*, **38**, 498 (1961). [g] *Anal.* Calcd for $C_{11}H_{20}O_2$: C, 71.68; H, 10.95. Found: C, 71.93; H, 10.99. [h] T. Tsuji and S. Hosaka, *J. Amer. Chem. Soc.*, **87**, 4075 (1965). [i] B. M. Trost and M. J. Bogdanowicz, *ibid.*, **95**, 5321 (1973). [j] *Anal.* Calcd for $C_{13}H_{16}O_2$: C, 76.42; H, 7.90. Found: C, 76.18; H, 7.67. [k] W. Herz and L. A. Glick, *J. Org. Chem.*, **28**, 2970 (1963). *Anal.* Calcd for $C_8H_{12}O_2$: C, 68.53; H, 8.63. Found: C, 68.48; H, 8.57. [l] J. F. Laporte and R. Rambaud, *C. R. Acad. Sci., Ser. C*, **262**, 1095 (1966). [m] *Anal.* Calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29. Found: C, 69.17; H, 10.58. [n] Reference *i* above; P. E. Eaton, G. F. Cooper, R. C. Johnson, and R. H. Mueller, *J. Org. Chem.*, **37**, 1947 (1972). [o] *Anal.* Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.68; H, 9.65; N, 7.19. [p] Hydrolysis of the oxazoline adduct gave a mixture predominated by the hydroxy acid (ν_{max} 3400, 1720 cm^{-1}) (lactone, ν_{max} 1780 cm^{-1}) in low yield owing to the water solubility of the acid.

(30 min) the solution was allowed to warm to room temperature and again cooled to −78°. Addition of 11 ml (1.1 equiv) of 2.25 *M* *n*-butyllithium produced a red solution and after 30 min of stirring, 2.1 ml (24.2 mmol, 1.1 equiv) of isobutylene oxide was added neat in a dropwise manner. The red solution was immediately discolored and the reaction vessel was allowed to warm to ambient, with stirring overnight. Work-up followed the General Procedure given for water-insoluble epoxides and gave 6.78 g (~100%) of a clear oil. Vpc showed a major component (80–85%) along with some minor less volatile material (15–20%). The oily mixture (2.7 g) was heated in 50 ml of 3 *N* HCl for 15 min, cooled, saturated with salt, extracted with ether, dried (K_2CO_3), and concentrated. A clear oil, 1.6 g (80%), was obtained which was 88% pure (vpc). Distillation, bulb-to-bulb, gave pure (>95%) lactone. An analytical sample was collected from the vpc instrument. Physical and analytical data are given in Table II.

Acknowledgment. This work was supported by the National Institutes of Health, the National Science Foundation, and the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Registry No.—**5**, 36099-48-6; **6**, 51898-93-2; **7**, 106-87-6; **8**, 51849-75-3; heptanoic acid, 111-14-8.

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(4) Reaction of **5** and other glycidic esters with the lithium salt of methyl acetate and *N*-methylacetanilide at −78° also gave exclusive addition to the carbonyl group without effecting the epoxide function: A. I. Meyers and D. Horne, unpublished results.
(5) P. L. Creger, *J. Org. Chem.*, **37**, 1907 (1972).
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(7) A. Eschenmoser, T. K. Dasgupta, D. Felix, and U. M. Kempe, *Helv. Chim. Acta*, **55**, 2187 (1972).
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(11) Aldrich Chemical Co., Milwaukee, Wis.

Oxazolines. XI. Synthesis of Functionalized Aromatic and Aliphatic Acids. A Useful Protecting Group for Carboxylic Acids against Grignard and Hydride Reagents

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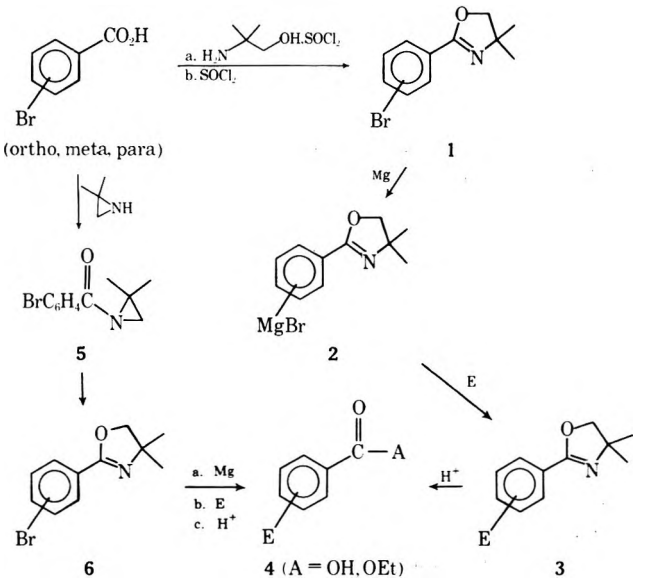
Received April 16, 1974

The use of an oxazoline to mask a carboxyl group is described. Since the oxazoline moiety is inert to Grignard reagents and lithium aluminum hydride, this technique serves as a novel means to elaborate or functionalize carboxylic acid derivatives. The carboxyl function may be masked either as its acid or ester derivative under generally mild conditions. A series of substituted benzoic acids, using the Grignard reagent of the *o*-, *m*-, or *p*-bromo derivatives was prepared while the carboxyl group was protected as the oxazoline. Furthermore, a series of keto-containing carboxylic acids was treated with Grignard or hydride reagents, producing hydroxy acids.

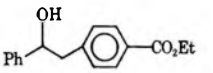
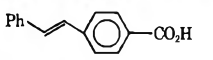
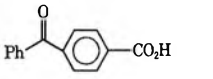
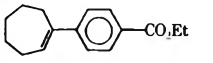
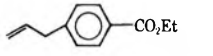
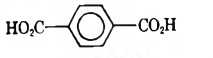
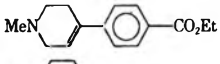
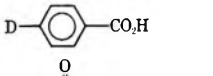
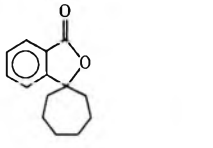
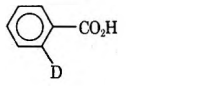
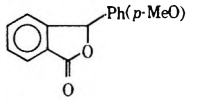
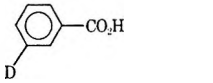
The synthetic utility of simple 2-oxazolines toward homologated acetic acids[3] and γ-butyrolactones[4] has been described in previous articles. Application of this heterocyclic system to the synthesis of functionalized aromatic and aliphatic acids is now reported. The technique is based on masking of the carboxylic group as its oxazoline derivative, which is inert to either the Grignard or lithium aluminum hydride reagent. Thus, bromo-substituted benzoic acids may be transformed into the corresponding bromophenyloxazoline **1** in high yield and then converted to its Grignard reagent **2**, with the carboxyl group safely masked as the oxazoline.[5] Addition of a wide variety of electrophiles (E) results in the substituted phenyloxazoline **3** which,



upon acidic hydrolysis or ethanolysis, releases the carboxyl group and provides the substituted benzoic acid or ester **4** (Table I). Alternatively, the isomeric oxazoline **6** may be readily prepared by treating the bromobenzoic acid with 1,1-dimethylaziridine, which furnishes the *N*-acylaziridine **5**. Rearrangement of the latter under very mild acidic conditions produces the requisite bromophenyloxazine **6**. Similar treatment of **6** with magnesium to form the Grignard followed by addition of an electrophile leads to the substituted benzoic acids or esters **4**. Since the bromobenzoic acids are very stable systems, the 4,4-dimethyloxazolines **1** were found to be more conveniently prepared and utilized. However, masking of more sensitive carboxylic acids (as described below) was performed using the dimethylaziridine method. As seen from Table I, yields and a variety of substitutions are quite satisfactory. In the case of *N*-methylpiperidone, reaction with **2** was poor (31%) under the usual conditions (15 hr, 25°, THF). This was rectified by introduction of 2.0 equiv of anhydrous magnesium bromide to the oxazoline Grignard prior to addition of the piperidone. The yield in this case rose to 82%, presumably by complexing the lone pair on the piperidone nitrogen, thus allowing the Grignard reaction to proceed normally. Of further interest is the accessibility of specifically deuterated benzoic acids *via* this technique. Simple quenching of the oxazoline Grignard in deuterium oxide leads, after hydrolysis, to benzoic acids of high deuterium content (>98%). This method should compare favorably with the recently reported technique[6] requiring sodium borodeuteride–palladium chloride reduction of bromobenzoic acids.

The purity of the magnesium employed was found to be rather critical. When "reagent" grade magnesium was used to prepare the Grignard reagent, the reactions were found to be slow and the yields were erratic. By using triply sublimed magnesium, the yields were consistently good and reproducible. Hydrolysis of the elaborated phenyloxazolines **3** was accomplished in a manner designed to produce the ethyl esters **4** (A = OEt) or the free acids **4** (A = H). By refluxing an ethanol solution of **3** containing 1.5 *N* sulfuric acid, the ethyl esters were smoothly formed, undoubtedly *via* transesterification of the initially formed open-chain amino esters. Presumably, other esters could be directly formed by utilizing the appropriate alcohol as a solvent.[3] The hydrolysis of **3** to the free carboxylic acids could be readily accomplished in either of two ways (Table I, method B or C). The choice of method usually was determined by the nature of the aryl substituent. Since it was difficult

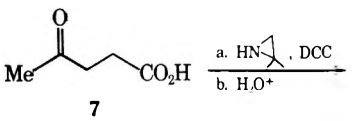
Table I
Substituted Benzoic Acids and Esters *via* Oxazoline Grignard Reagent (2)

2[a]	Electrophile	Registry no.	% 3	Hydrolysis[b] method	Acid or ester (4)[c]	Registry no.	%
p-MgBr	Styrene oxide	96-09-3	93	A		30058-62-9	81
				B		7329-77-3	94
p-MgBr	Benzonitrile	100-47-0	90	B		611-95-0	90
p-MgBr	Cycloheptanone	502-42-1	86	A		30058-58-3	92
p-MgBr	Allyl bromide	106-95-6	88[d]	A		19819-94-4	77
p-MgBr	Ethyl chloroformate	541-41-3	90	B		100-21-0	85
p-MgBr	*N*-Methylpiperidone	1445-73-4	82[d]	A		51849-82-2	27
p-MgBr	D_2O		97	C		4551-62-6	87
o-MgBr	Cycloheptanone		92	A		30058-63-0	85
o-MgBr	D_2O		97	C		51898-94-3	88
o-MgBr	*p*-Methoxybenzaldehyde	123-11-5	90	A		21615-74-7	87
m-MgBr	D_2O	7789-20-0	95	C		4551-61-5	90

[a] Triply sublimed magnesium (Dow) used for preparing Grignard reagents. [b] Method A, heated to reflux in 1.5 *N* ethanolic sulfuric acid; method B, heated to reflux in 3 *N* hydrochloric acid (15–20 min), followed by heating in 20% methanolic sodium hydroxide; method C, heated for 1 hr in 3 *N* hydrochloric acid. See Experimental Section for complete details. [c] Comparable yields were obtained in selected cases starting from **6**. [d] One equivalent of magnesium bromide used.

to predict which would be the most efficient, a small pilot experiment was performed using both techniques.

The oxazoline system was also found to be an excellent masking group for carboxylic acids if Grignard reagents are to be added to a functional group already present. For example, levulinic acid (**7**) was transformed into the oxazoline **8** (*via* rearrangement of the *N*-acylaziridine) and treated with the phenyl Grignard reagent. The carbinol **9** was produced smoothly and hydrolysis then gave γ-methyl-γ-phenylbutyrolactone (**10**). In this instance, the carboxyl



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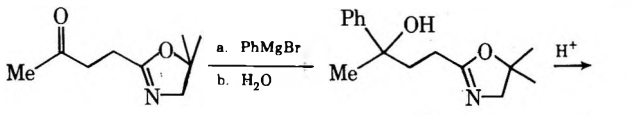
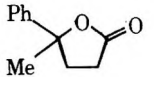
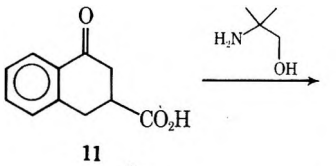


8 9



10



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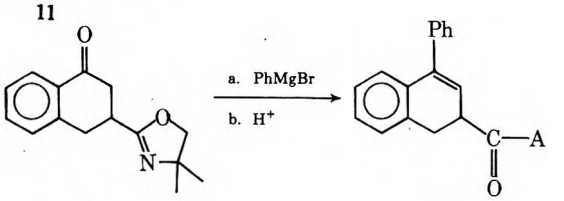
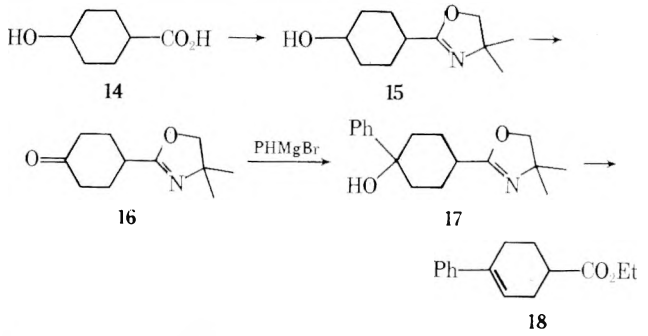


12 13

(A = OH, OEt)

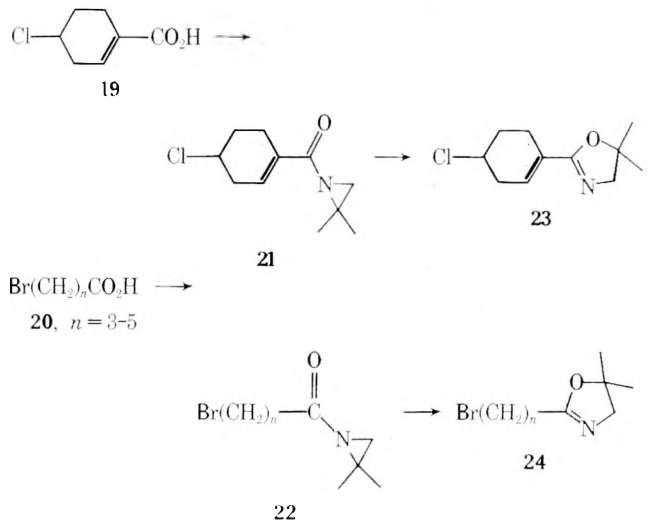
group of levulinic acid was masked using the acylaziridine method, since direct formation of the oxazoline using 2-methyl-2-aminopropanol gave only tarry products. However, the direct oxazoline formation was successfully employed for 3-carboxytetralone (**11**). The resulting oxazoline **12** could be readily converted into the carbinol using phenylmagnesium bromide. Hydrolysis gave the unsaturated acid **13** or its corresponding ester. Still a further example of this technique was demonstrated by transformation of 4-hydroxycyclohexanecarboxylic acid (**14**) to 1-phenyl-4-car-

boethoxycyclohexene (18). Direct transformation of 14 to the oxazoline 15 using 2-methyl-2-aminopropanol followed by chromic acid oxidation to the keto oxazoline 16 proceeded smoothly without detrimental effect to the masking group. Grignard reaction gave the carbinol 17 which, upon ethanolysis, led to the ester 18. It therefore appears that



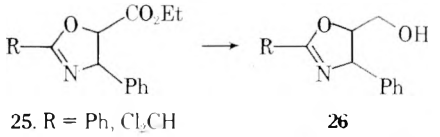
this carboxyl protecting group possesses significant synthetic value for elaborating both aliphatic and aromatic carboxylic acids.

A limitation to this method appears when Grignard reagents of bromoalkyloxazolines are to be employed. Carboxylic acids containing a halogen substituent (19, 20) could not be transformed into the haloalkyloxazolines (23, 24) owing to their instability under reaction conditions. Although the *N*-acylaziridines (21, 22) were readily prepared,

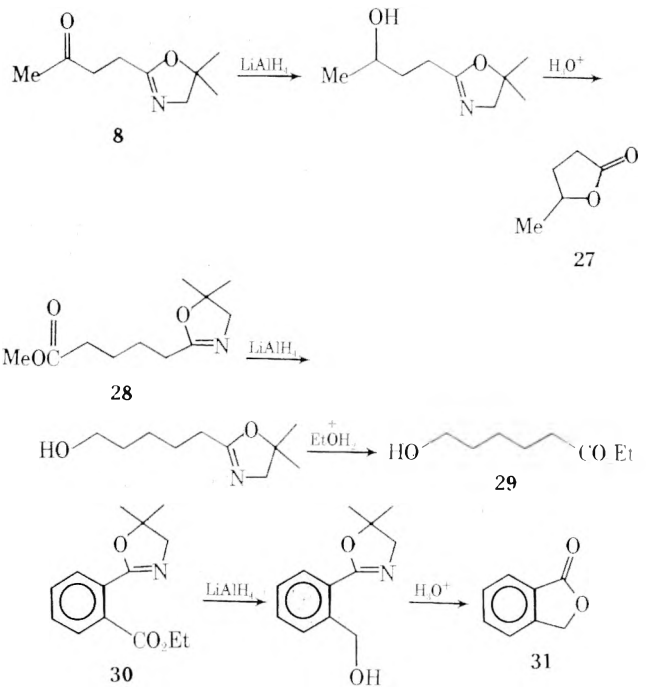


rearrangement to 23 and 24 was accompanied by elimination and polymerization reactions and the oxazolines proved to be highly sensitive materials that could not be manipulated further. This is in contrast to the haloalkyldihydro-1,3-oxazines,[7] which did respond well to Grignard formation and subsequent addition reactions.

The use of the oxazoline moiety as a protecting group for carboxylic acids against lithium aluminum hydride was also evaluated. This was based upon earlier observations[8] that ester-containing oxazolines 25 could be reduced to the carbinols 26. However, the synthetic potential of this trans-

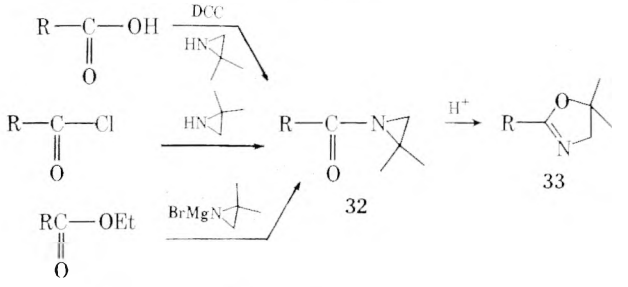


formation does not appear to have been further explored. Several examples depicting the protecting group ability of oxazolines were examined and the results are given below. Thus, levulinic acid was transformed into lactone 27, ester oxazoline 28 from the half-ester of adipic acid was transformed into hydroxy ester 29, and phthalide 31 was pre-

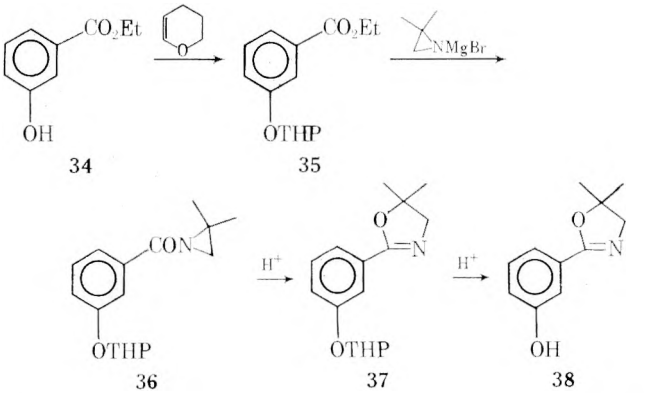


pared from oxazoline 30. All of the above proceeded without event and the carboxyl group was deblocked in the manner already described.

Masking of the carboxyl group initially required the preparation of the *N*-acylaziridine 32. This was performed using the acid, acid chloride, or ester. The latter was ac-



complished using the magnesium halide salt of 2,2-dimethylaziridine. In order to demonstrate that carboxyl masking could be carried out on polyfunctional compounds, ethyl *m*-hydroxybenzoate (34) was successfully transformed into 2-(*m*-hydroxyphenyl)oxazoline (38) *via* the sequence depicted. Two significant points are evident



from this sequence. First, oxazolines may be introduced into a molecule containing a hydroxyl group, since the tetrahydropyranyl masking group is stable to the acylaziridine–oxazoline rearrangement (36 to 37). Second, the tetrahydropyranyl ether may be cleaved under conditions which do not effect the oxazoline (37 to 38).

In general, rearrangement of acylaziridines 32 was found

to proceed smoothly in ether or dichloromethane (depending upon solubility) with 0.2–0.5 mol % of sulfuric acid, toluenesulfonic acid, pyridinium tosylate, triethylammonium tosylate, or potassium bisulfate for 12–15 hr at room temperature. This is considerably milder than the previous conditions reported for acylaziridine–oxazoline rearrangements.[9]

It is obvious that the rearrangement occurs under essentially neutral conditions, since the acid catalyst is neutralized by the basic oxazoline after only a few per cent of the reaction has taken place. In fact, the protonated oxazoline is probably the source of the required proton necessary for rearrangement. This was substantiated by successfully employing a small quantity of the oxazoline sulfate or tosylate as the catalyst.

It is of interest that the rearrangement was not general acid catalyzed, since hydrogen chloride, pyridinium chloride, or triethylamine hydrochloride failed to bring about reaction. Thus, the acid counterion was critical to the rearrangement, perhaps by virtue of its solvation properties. It was also found that the *N*-acylaziridine **32** need not be isolated en route to the oxazoline **33**. For example, *p*-bromobenzoyl chloride was treated with 2,2-dimethylaziridine in ether containing 1.0 equiv of triethylamine. After formation of the *N*-acylaziridine **5**, the triethylamine hydrochloride was removed by filtration and a drop of concentrated sulfuric acid was added. Continued stirring of the ethereal solution gave the bromophenyloxazoline in 85% yield.

Experimental Section[10]

2,2-Dimethylaziridine. A modification of the reported procedure was used[11] which did not involve destruction of the reaction vessel and gave product that was found to be stable for 10 months at ambient temperature. The reported preparation claims that the aziridine polymerizes within 10 hr at room temperature.

To a mixture of 100 g (1.12 mol) of 2-amino-2-methylpropanol and 200 ml of water was added a cold (0–5°) mixture of 110 g of concentrated sulfuric acid and 200 ml of water. The mixture was heated so that water distilled off and until the temperature of the pot residue reached 115°. The water was then completely removed under aspirator pressure (10–15 mm) while heating continued and this resulted in the solidification of the pot residue. After cooling, a solution of 100 g (2.5 mol) of sodium hydroxide in 200 ml of water was slowly added and then allowed to stand overnight to allow trituration of the solid mass. Distillation of the alkaline slurry was performed at atmospheric pressure until the distillation temperature reached 101°. The distillate was repeatedly saturated with potassium hydroxide pellets until two layers appeared. The aziridine (top layer) was removed, dried in potassium hydroxide, and distilled from potassium hydroxide to give 35 g (44%), bp 72°.

2-(4-Bromophenyl)-4,4-dimethyl-2-oxazoline 1 (*p*-Br). 4-Bromobenzoic acid (50 g, 0.25 mol) was added to 90.0 g (0.75 mol) of thionyl chloride and the mixture was stirred at 25° for 24 hr. The excess thionyl chloride was distilled and the remaining dark oil was distilled (123°, 20 mm) to yield 48.8 g (90%) of the acid chloride. The 48.8 g (0.22 mol) of acid chloride was dissolved in 100 ml of methylene chloride and added in a dropwise manner to a magnetically stirred solution of 39.2 g (0.44 mol) of 2-amino-2-methyl-1-propanol in 100 ml of methylene chloride at 0°. The mixture was stirred at 25° for 2 hr. The white precipitate was filtered and washed with water and the solid remaining combined with that obtained by concentrating, cooling, and filtering the methylene chloride solution to give a total yield of 62.0 g (100%) of *N*-(2,2-dimethyl-3-hydroxypropyl)-*p*-bromobenzamide.

To cyclize the amide, thionyl chloride (35.8 g, 0.30 mol) was added dropwise with stirring to 25.0 g (0.092 mol) of the benzamide. When the vigorous reaction had subsided, the yellow solution was poured into 150 ml of dry ether and 26.8 g (100%) of white crystals separated out with swirling and were filtered. The hydrochloride salt was neutralized with cold 20% sodium hydroxide and extracted with ether. The ether was dried (K_2CO_3) and evaporated to yield a pale yellow oil which solidified on cooling, giving 18.0 g (77%) of oxazoline. A portion was recrystallized from hexane to give white spires: mp 37–38°; ir (film) 1650 cm^{-1}; nmr ($CDCl_3$) δ 7.60 (d, 2), 7.70 (d, 2), 4.01 (s, 2), 1.32 (s, 6).

Anal. Calcd for $C_{11}H_{12}NOBr$: C, 51.98; H, 4.77; N, 5.51. Found: C, 52.01; H, 4.68; N, 5.47.

2-(2-Bromophenyl)-4,4-dimethyl-2-oxazoline 1 (*o*-Br) was prepared in the same manner using o-bromobenzoic acid: mp 33–35.5°; 90%; bp 63° (0.2 mm); colorless oil (hydrochloride mp 108–110°); ir (film) 1650 cm^{-1}; nmr ($CDCl_3$) δ 7.66 (m, 2), 7.27 (m, 2), 4.05 (s, 2), 1.37 (s, 6).

Anal. Calcd for $C_{11}H_{12}NOBr$: C, 51.98; H, 4.77; N, 5.51. Found: C, 51.87; H, 4.74; N, 5.59.

2-(3-Bromophenyl)-4,4-dimethyl-2-oxazoline 1 (*m*-Br) was prepared in the same manner using *m*-bromobenzoic acid: 84%; bp 105–108° (0.05 mm); ir (film) 1653 cm^{-1}; nmr (CCl_4) δ 8.2–7.1 (m, 4), 4.05 (s, 2), 1.33 (s, 6).

Anal. Found: C, 51.88; H, 4.68; N, 5.63.

2-(4-Bromophenyl)-5,5-dimethyl-2-oxazoline 6 (*p*-Br). To a solution of 7.1 g (10 mmol) of 2,2-dimethylaziridine and 12.1 g (12 mmol) of dry triethylamine in 100 ml of benzene, cooled to 10° was added dropwise 21.9 g (10 mmol) of *p*-bromobenzoyl chloride in 100 ml of benzene. The reaction mixture was stirred at room temperature (15 hr) and the salts were removed by filtration. Evaporation of the solvent gave 23.0 g (91%) of the *N*-acylaziridine which was sufficiently pure for subsequent use. Pure material (mp 35–37°) was obtained by chromatography on Woelm Grade I neutral alumina: ir (film) 1660 cm^{-1}; nmr (neat, 38–40°) δ 7.30–7.80 (m, 4), 2.10 (s, 2), 1.00 (s, 6).

A solution of the above in dichloromethane (16.0 g in 350 ml) was treated with 0.1 ml of concentrated sulfuric acid and stirred at room temperature for 15 hr. After addition of 1.0 g of sodium bicarbonate, the solution was filtered and concentrated to give an oil which was distilled, bp 103° (0.3 mm), and crystallized on cooling: mp 59–61°; yield 11.0 g (70%); ir (KBr) 1630 cm^{-1}; nmr ($CDCl_3$) δ 7.40–7.90 (m, 4), 3.80 (s, 2), 1.50 (s, 6).

Anal. Calcd for $C_{11}H_{12}NOBr$: C, 51.98; H, 4.77; N, 5.51. Found: C, 52.16; H, 4.92; N, 5.62.

Formation of Grignard Reagent from 2-(Bromophenyl)-4,4-dimethyl-2-oxazoline 2 (*o*-, *m*-, or *p*-Br). A solution of 5.0 g (20 mmol) of the bromophenyloxazolines 1 in 60 ml of dry tetrahydrofuran was added dropwise to 0.61 g (25 mg-atoms) of triply sublimed magnesium. The reaction became immediately exothermic and the rate of addition was adjusted to maintain gentle reflux. (A crystal of iodine may be introduced to initiate reaction.) After stirring for 2 hr to ensure complete reaction, the Grignard reagent was used for the following reactions.

General Procedure for Products in Table I. All reactions were carried out under a nitrogen atmosphere.

Reaction of 2 (*p*-Br) with Styrene Oxide. 1-Phenyl-2-(4-carboethoxyphenyl)ethanol. To the Grignard reagent, formed above, was added 1.25 equiv of styrene oxide diluted with 10 volumes of tetrahydrofuran and the solution was heated to reflux for 4 hr. Aqueous quenching of the 7 solution resulted in a two-phase system. The organic layer was removed and the aqueous layer was extracted several times with ether, combined with the organic layer, dried (K_2CO_3), and concentrated to give crystalline material. Recrystallization from ether–petroleum ether gave 7.5 g (90%): mp 105–107°; *m/e* 295; ir (Nujol) 1640, 3300 cm^{-1}; nmr (CCl_4) δ 7.70 (d, 2), 7.05 (m, 7), 4.70 (t, 1), 4.00 (s, 2), 2.85 (d, 2), 1.22 (s, 6). The oxazoline carbinol (295 mg) was heated to reflux in 40 ml of ethanol containing 3.6 ml of concentrated sulfuric acid for 8 hr and the ethanol was removed (~60–70%) by evaporation. The residue 7 was poured into saturated salt solution and the mixture was extracted with ether. The ethereal solution was washed with 10% bicarbonate solution, dried (K_2CO_3), and concentrated. Purification was accomplished by elution through alumina using chloroform–ethanol (10:1). Recrystallization from ether–hexane also gave crystalline material; mp 53–55°; 81%; ir (Nujol) 1710, 3460 cm^{-1}; nmr ($CDCl_3$) δ 8.00 (d, 2), 7.30 (m, 7), 4.91 (t, 1), 4.35 (q, 2), 3.00 (m, 3), 1.35 (t, 3); *m/e* 270.

4-Carboxystyrene. The oxazoline carbinol (2.0 g) was heated in 3 *N* hydrochloric acid for 20 min and the solid amino ester hydrochloride was removed and added to 50 ml of 20% methanolic sodium hydroxide (using 50% aqueous sodium hydroxide). The solution was heated to reflux for 30 min and concentrated to 20–25 ml, cooled in an ice bath, and acidified with 9 *N* hydrochloric acid. The product was collected and recrystallized from chloroform: mp 260–262° (90%); *m/e* 224; λ_{max} (EtOH) 320 nm.[12]

Reaction of 1 (*p*-Br) with Benzonitrile. 4-Benzoylbenzoic acid. The Grignard reagent 2 (*p*-MgBr, 39 mmol) in 60 ml of tetrahydrofuran at reflux was treated with 4.12 g (40 mmol) of benzonitrile and heating was continued for 8 hr. After cooling, the mixture was quenched with 150 ml of 10% ammonia and extracted

with 150 ml of ether and then 150 ml of chloroform. Drying (K_2CO_3) and concentration gave 11.3 g of a viscous red oil which was passed through alumina (ether–chloroform, 1:1): ir (film) 1650 cm^{-1} (broad); nmr ($CDCl_3$) δ 7.05–8.00 (m, 9), 4.10 (d, 2), 1.40 (s, 6). The *p*-benzoylphenyloxazoline (3.4 g) was hydrolyzed in 3 *N* hydrochloric acid followed by sodium hydroxide as above, to give 2.7 g (92%) of carboxylic acid, mp 196–198°, *m/e* 226.[13]

Reaction of 1 (*p*-Br) with Cycloheptanone. Ethyl 4-Cycloheptenylbenzoate. A solution of cycloheptanone (2.36 g, 21 mmol) in 20 ml of tetrahydrofuran was added to the Grignard reagent 2 (*p*-MgBr, 19.5 mmol) in 30 ml of tetrahydrofuran at room temperature. After stirring at room temperature for 8 hr, and heating to reflux for 2 hr, the solution was quenched with 20 ml of 20% ammonia. Work-up in the usual manner and passage through alumina (petroleum ether) gave the carbinol (86%), mp 106–108° (petroleum ether), *m/e* 289. Cleavage of the oxazoline carbinol (141 mg) in 10 ml of ethanol containing 0.75 ml of concentrated sulfuric acid was accomplished by heating for 16 hr. The ester was isolated as described earlier. Chromatography of the crude ester (alumina using ether) gave pure material: ir (film) 1710 cm^{-1}; nmr ($CDCl_3$) δ 8.16 (d, 2), 7.52 (d, 2), 6.33 (t, 1).

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.68; H, 8.29.

Reaction of 1 (*p*-Br) with Allyl Bromide. Ethyl 4-Allylbenzoate. A solution of *p*-bromophenyloxazoline (11.20 g, 44 mmol) in 50 ml of tetrahydrofuran was treated with 4.15 g of ethylene dibromide. This solution was added to 2.34 g of magnesium in 40 ml of tetrahydrofuran. After addition was complete, another 4.15 g of ethylene dibromide was added and the reaction mixture was stirred at room temperature for 2 hr. Allyl bromide (21.4 g) was introduced neat and the mixture was heated at reflux overnight. Work-up in the general manner gave 8.4 g (88%) of a viscous yellow oil which was solvolyzed in acidic ethanol to the ester: 4.0 g (77%); bp 80–85° (0.075 mm); ir (film) 1720 cm^{-1}; nmr ($CDCl_3$) δ 8.22 (d, 2), 7.39 (d, 2), 6.50–5.78 (m, 1), 5.40–4.85 (m, 2), 4.49 (q, 2), 3.46 (d, 2), 1.37 (t, 3).

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.60; H, 7.38.

Reaction of 1 (*p*-Br) with Ethyl Chloroformate. Terephthalic Acid. The Grignard reagent 2 (*p*-MgBr) prepared in the General Procedure was treated all at once with 6.6 g (60 mmol) of ethyl chloroformate at 0°. The reaction mixture was then heated to reflux for 12 hr and quenched with 10% ammonia. Work-up gave 7.6 g of a viscous oil which was purified by alumina chromatography (neutral) using ether-petroleum ether (1:1): oil; ir (film) 1740, 1650 cm^{-1}; nmr ($CDCl_3$) δ 7.97 (d, 2), 7.34 (d, 2), 4.20 (q, 2), 4.10 (s, 2), 1.40 (s, 6), 1.25 (t, 3). Hydrolysis was performed on 3.8 g using 20 ml of 3 *N* hydrochloric acid. The gummy material was removed, placed in 20 ml of methanolic sodium hydroxide, and refluxed for 3 hr. Evaporation of the solvent and acidification with 3 *N* hydrochloric acid gave 2.8 g (85%) of colorless crystals: mp 300° (sublimes); ir (Nujol) 1685 cm^{-1}; nmr (D_2SO_4) δ 8.28 (s, 4).

Reaction of 1 (*p*-Br) with *N*-Methyl-4-piperidone. 4-(Carboethoxyphenyl)-1-methyl-1,2,5,6-tetrahydropyridine. A solution of 5.00 g (20 mmol) of 1 (*p*-Br) and 7.52 g (40 mmol) of ethylene dibromide in 40 ml of tetrahydrofuran was added dropwise to 1.44 g (60 mg-atoms) of magnesium in 60 ml of tetrahydrofuran. The reaction was moderated with an ice bath. To the resulting Grignard reagent–magnesium bromide was added 2.50 g (22 mmol) of *N*-methyl-4-piperidone in 20 ml of tetrahydrofuran and the mixture was heated to reflux for 16 hr. The reaction mixture was quenched with 10% ammonia solution (150 ml) and 100 ml of ether. The layers were separated and the aqueous layer was extracted with ether, combined, dried ($MgSO_4$), and concentrated to yield 5.80 g of an oil. The oil was repeatedly washed with cold petroleum ether and dried to give 4.7 g (82%) of oxazoline adduct: ir (film) 1650, 3350 cm^{-1}; nmr ($CDCl_3$) δ 7.88 (d, 2), 7.35 (d, 2), 4.12 (s, 2), 2.00–3.00 (m, 8), 2.16 (s, 3), 1.40 (s, 6). This product was heated for 16 hr in 50 ml of ethanol containing 4 ml of concentrated sulfuric acid and after usual work-up gave 3.3 g of viscous dark oil. Purification was performed by passage through alumina (neutral) using ether and then chloroform. The product was an unstable oil (27%): ir (film) 1710 cm^{-1}; nmr ($CDCl_3$) δ 8.00 (d, 2), 7.32 (d, 2), 5.00 (t, 1), 4.25 (q, 2), 2.18 (br s, 3), 1.0–2.5 (m, 6), 1.35 (t, 3); *m/e* 231.

Reaction of 1 (*o*-Br) with Cycloheptanone. Benzospirolactone. The Grignard reagent 1 (o-Br) as prepared in the General Procedure was treated with 2.35 g (21 mmol) of cycloheptanone and the reaction mixture was stirred for 16 hr at room temperature and heated to reflux for 1 hr. After cooling, the mixture was quenched with 100 ml of 20% aqueous ammonia. Work-up gave 5.40 (98%) of a pale yellow solid which was recrystallized from petroleum ether to give 5.23 g (95%) of colorless crystals: mp 95–97°; ir (Nujol) 1670, 3100 cm^{-1}; nmr ($CDCl_3$) δ 7.20–7.90 (m, 4), 3.50 (s, 2), 3.20 (s, 1, OH), 1.55–2.20 (m, 12), 1.40 (s, 6); *m/e* 275. Cleavage to the lactone was accomplished using 2.0 g of the oxazoline in 50 ml of ethanol containing 4.0 ml of concentrated sulfuric acid and heating to reflux for 16 hr. Evaporation of the solvent followed by addition of 200 ml of ether gave a solution which was washed twice with 100-ml portions of saturated salt solution. Drying ($MgSO_4$) and concentration of the ethereal solution gave 1.5 g (95%) of the spiro lactone as a viscous oil which solidified in storage. Recrystallization from ether–petroleum ether gave pure material: mp 85–87; ir (Nujol) 1755 cm^{-1}; nmr (CCl_4) δ 7.30–7.89 (m, 4), 1.60–2.20 (m, 12); *m/e* 216.

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.40; H, 7.70.

Reaction of 1 (*o*-Br) with *p*-Methoxybenzaldehyde. Grignard reagent 2 (o-MgBr) was treated with an equimolar amount (21 mmol) of *p*-methoxybenzaldehyde as described in the previous experiment. Work-up gave 6.0 g (95%) of the oxazoline as an oil: ir (film) 1645, 3250 cm^{-1}; nmr (CCl_4) δ 6.60–8.00 (m, 8), 3.95 (s, 2), 3.86 (s, 1, OH), 3.65 (s, 3), 1.40 (s, 6). Conversion to the lactone (2.0 g) was accomplished by heating (16 hr) in ethanolic sulfuric acid as previously described: yield 1.6 g (98%); mp 110–112° (petroleum ether); ir (Nujol) 1750 cm^{-1}; nmr (CCl_4) δ 6.70–8.10 (m, 8), 6.40 (s, 1), 3.29 (s, 3); *m/e* 240.

Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 74.99; H, 5.16.

Reaction of 1 (*o*-, *m*-, *p*-Br) with Deuterium Oxide. *o*-, *m*-, and *p*-Deuteriobenzoic Acid. The Grignard reagents 2 from *o*-, *m*-, and *p*-bromophenyloxazoline were each treated with deuterium oxide and worked up using aqueous ammonia (10%) as above. The corresponding deuteriophenyloxazolines were each hydrolyzed in 3 *N* hydrochloric acid (reflux, 1 hr), cooled, extracted with ether, concentrated, and recrystallized.

***o*-Deuteriobenzoic acid:** 88% yield; mp 121°; nmr (CCl_4) δ 13.0 (s, 1), 8.15 (m, 1), 7.55 (m, 3); % D >98% (mass spectrum and nmr).

***m*-Deuteriobenzoic acid:** 90% yield; mp 121°; nmr (CCl_4) δ 12.9 (s, 1), 8.2 (m, 2), 7.5 (m, 2); % D >98% (mass spectrum and nmr).

***p*-Deuteriobenzoic acid:** 87% yield; mp 121°; nmr (CCl_4) δ 11.6 (s, 1), 8.2 (d, 2), 7.5 (d, 2); % D >98% (mass spectrum and nmr).

γ-Methyl-γ-phenylbutyrolactone (10). To a solution of 11.6 g (0.10 mol) of distilled levulinic acid (7) in 100 ml of dichloromethane cooled to 5° was added portionwise 20.0 g (97 mmol) of dicyclohexylcarbodiimide (DCC). A white slurry was formed before all of the DCC was added (10 min).To this was added 8.0 g (11 mmol) of 2,2-dimethylaziridine (exothermic). The mixture was stirred at room temperature for 16 hr and filtered and evaporation of volatiles gave 18.0 g of crude *N*-acylaziridine. The latter was triturated with 150 ml of hexane and filtered and the filtrate was evaporated to dryness to give 16.0 g (95%) of 1-(γ-ketopentoyl)-2,2-dimethylaziridine.

The analytical sample was prepared by molecular distillation: ir (film) 1720, 1680 cm^{-1}; nmr ($CDCl_3$) δ 2.40–2.90 (m, 4), 2.20 (s, 5), 1.30 (s, 6).

Anal. Calcd for $C_9H_{15}NO_2$: C, 63.86; H, 8.95; N, 8.28. Found: C, 63.58; H, 8.79; N, 8.13.

To a solution of 10.0 g of the above *N*-acylaziridine in 100 ml of ether was added 2 drops of concentrated sulfuric acid and stirring was performed at room temperature for 16 hr. The reddish reaction mixture was washed with 5% sodium bicarbonate (K_2CO_3). Filtration and evaporation of solvent gave 8.0 g (80%) of 2-(γ-ketobutyl)-5,5-dimethyl-Δ^2-oxazoline (8) as an oil: ir (film) 1720, 1665 cm^{-1}; nmr ($CDCl_3$) δ 3.50 (t, 2), 2.40–2.90 (m, 4), 2.20 (s, 3), 1.40 (s, 6).

To 0.73 g (0.03 g-atom) of magnesium in 10 ml of ether was added dropwise 4.7 g (30 mmol) of bromobenzene in 50 ml of ether. After completion of the exotherm, the reaction mixture was stirred at room temperature for an additional 30 min. To the resulting phenylmagnesium bromide was added dropwise 5.0 g (30 mmol) of 8 in 20 ml of ether. The resulting slurry was stirred at room temperature for 30 min and then poured into ice–water. The ethereal extracts were dried (K_2CO_3), filtered, and evaporated to give 4.0 g (55%) of 2-(γ-hydroxy-γ-phenylbutyl)-5,5-dimethyl-Δ^2-oxazoline (9), mp 84–88°. The analytical sample was prepared by two recrystallizations from hexane: mp 92–93°; ir (KBr) 3225, 1655 cm^{-1}; nmr ($CDCl_3$) δ 7.20–7.60 (m, 5), 4.70–5.20 (br s, 2, OH), 3.50 (s, 2), 2.20 (s, 4), 1.60 (s, 3), 1.40 (s, 6).

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.98; H, 8.57; N, 5.66. Found: C, 73.07; H, 8.41; N, 5.73.

To 0.342 g of **9** was added 15 ml of 3 *N* HCl. After 30 min at reflux, the reaction mixture was cooled and extracted with ether and the ethereal extracts were dried ($MgSO_4$). Evaporation of solvent gave 0.211 g (87%) of γ-methyl-γ-phenylbutyrolactone (**10**):[14] ir (film) 1770–1780 cm^{-1}; nmr ($CDCl_3$) δ 7.35 (m, 5), 2.45 (m, 4), 1.70 (s, 3).

3-Carboxy-1-phenyl-3,4-dihydronaphthalene (13, A = OH). 3-Carboxy-1-tetralone (**11**, 20.0 g, 10.6 mmol) was mixed with 2-amino-2-methyl-1-propanol (9.40 g, 10.6 mmol), and the mixture was heated (Nujol bath) with stirring at 190–200° until 2 equiv of water had been distilled into hexane. The dark residue was distilled (170°, 0.10 mm) to yield 14.6 g (57%) of a viscous oil **12**, which solidified upon standing (mp 95–96°): ir (Nujol) 1655, 1680 cm^{-1}; nmr (CCl_4) δ 7.95 (d, 1), 7.30 (q, 3), 3.90 (s, 2), 2.70–3.20 (m, 5), 1.20 (d, 6). A phenylmagnesium bromide–magnesium bromide mixture in 100 ml of tetrahydrofuran was prepared from bromobenzene (6.29 g, 40 mmol), ethylene bromide (4.22 g, 20 mmol), and magnesium turnings (1.45 g). To the stirred solution of Grignard reagent was added 4.70 g (19.3 mmol) of **12** in 40 ml of tetrahydrofuran over a 30-min period. The mixture was stirred for 12 hr, refluxed for 1 hr, and then cooled in an ice bath and decomposed with 50 ml of cold, dilute ammonia solution. The organic layer was decanted and the aqueous layer was extracted with ether. The combined extracts were dried ($MgSO_4$) and evaporated to yield a viscous oil [3-(4,4-dimethyl-Δ^2-oxazolino)-1-hydroxy-1-phenyltetralin] which solidified upon standing. The material was recrystallized from ether–petroleum ether to yield 6.00 g (96%) of white crystals: mp 148–149°, ir (Nujol) 3200, 1655, 715, 770 cm^{-1}; nmr ($CDCl_3$) δ 7.26 (d, 9), 3.90 (s, 2), 2.45–3.20 (m, 5), 1.24 (s, 3), 0.90 (s, 3).

The oxazoline carbinol from above (1.00 g, 3.1 mmol) was dissolved in 40 ml of 3 *N* hydrochloric acid and refluxed for 15 min. The solution was cooled and the resulting solid precipitate was dissolved in chloroform, dried ($MgSO_4$), and evaporated to yield 0.70 g (91%) of a viscous oil **13** which solidified upon standing. The solid was recrystallized from ether: mp 158–161°; ir (Nujol) 1690 cm^{-1}; nmr ($CDCl_3$) δ 7.00–7.50 (m, 9), 6.16 (d, 1), 2.90–3.67 (m, 3).

Anal. Calcd for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C, 81.39; H, 5.59.

Ethyl 1-Phenyl-3,4-dihydronaphthalene-1-carboxylate (13, A = OEt). 3-(4,4-Dimethyl-Δ^2-oxazolino)-1-hydroxy-1-phenyltetralin (1.00 g, 3.1 mmol) obtained in the previous experiment was dissolved in 50 ml of ethanolic sulfuric acid (prepared from 95% ethanol and 3.9 ml of acid) and refluxed for 12 hr. The solution was cooled and poured into 200 ml of ether. The ether solution was washed with 50 ml of saturated sodium carbonate solution, dried ($MgSO_4$), and evaporated to yield **13** (A = OEt) as an oil. The oil eluted from a Woelm Grade I neutral alumina column with chloroform to yield 0.72 g (8) of a viscous oil: ir (film) 1730 cm^{-1}; nmr ($CDCl_3$) δ 6.90–7.50 (m, 9), 6.12 (d, 1), 4.11 (q, 2), 2.89–3.50 (m, 3), 1.20 (t, 3).

Anal. Calcd for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52. Found: C, 81.85; H, 6.73.

4-Carboethoxy-1-phenylcyclohexene (18). A mixture of 4-hydroxycyclohexanecarboxylic acid (**14** 5.0 g, 35 mmol) and 2-amino-2-methyl-1-propanol (3.12 g, 35 mmol) was heated with stirring in an oil bath and the volatiles distilling between 112 and 275° were collected into a receiver containing 50 ml of ether. The water was separated from the ethereal solution in the distillate, and after drying (K_2CO_3) and concentration gave 4.4 g (64%) of a pale yellow oil. The latter was dissolved in cold 3 *N* hydrochloric acid and extracted with ether, and evaporation produced 0.3 g of the lactone derived from the starting acid. The aqueous solution was neutralized with cold 4 sodium hydroxide and extracted twice with ether. After drying (K_2CO_3) and concentration, there remained 4.3 g (63%) of oxazoline **15**: ir (film) 1660, 3320 cm^{-1}; nmr ($CDCl_3$) δ 3.90 (s, 2), 3.45 (m, 2), 1.4–2.3 (m, 9) , 1.2 (s, 6). The product **15** was oxidized to **16** without further purification as follows. A mixture containing 2.2 g (10.5 mmol) of **15** and 5.0 g of chromic anhydride in 50 ml of pyridine was stirred at room temperature for 18 hr, poured into 100 ml of water, and extracted with ether. The extracts were dried ($MgSO_4$) and concentrated to give 1.5 g (72%) of **16**: ir (film) 1660, 1710 cm^{-1}; nmr (CCl_4) δ 3.90 (s, 2), 1.90–2.90 (m, 9), 1.20 (s, 6).

Reaction of **16** with phenylmagnesium bromide was performed in exactly the same manner as described for **13**. Yield of **17** was 77%: mp 146–148°; the product showed a single spot on tlc (ether), R_f 0.40; ir (Nujol) 1650, 770, 710 cm^{-1}; nmr ($CDCl_3$) δ 7.25–7.70 (m, 5), 4.00 (s, 2), 2.14–2.50 (m, 2), 1.80–2.14 (m, 8); *m/e* 285.

A solution of **17** (612 mg) in 50 ml of ethanol containing 7.5 g of concentrated sulfuric acid was heated to reflux for 16 hr. The mixture was cooled and poured into 200 ml of ether. The ethereal solution was shaken with saturated salt solution and dried ($MgSO_4$). Concentration left 0.43 g (78%) of **18** as an oil. Purification was accomplished by passage through neutral alumina (ether): *m/e* 230; ir (film) 1730 cm^{-1}; nmr ($CDCl_3$) δ 7.33 (m, 5); 6.12 (br s, 1), 4.15 (q, 2), 2.05–2.85 (m, 7), 1.22 (t, 3).

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.09; H, 7.99.

Ethyl 6-Hydroxyhexanoate (29). To 16.0 g (10 mmol) of adipic acid monoethyl ester in 100 ml of dichloromethane cooled to 5° was added 20.0 g (97 mmol) of DCC followed by 8.0 g (11 mmol) of 2,2-dimethylaziridine. The resulting slurry was stirred at 5° for 15 min and then at ambient temperature for 16 hr. Filtration of urea and evaporation of volatiles gave 23 g of residue. This residue was triturated with 300 ml of hexane and filtered and the filtrate was evaporated to dryness to give 18.0 g (84%) of ester acylaziridine. The analytical sample was prepared by molecular distillation at 50° (0.3 mm): ir (film) 1740, 1685 cm^{-1}; nmr ($CDCl_3$) δ 3.75 (s, 3), 2.30–2.60 (m, 4), 2.20 (s, 2), 1.60–1.90 (m, 4), 1.40 (s, 6).

Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.93; H, 9.00; N, 6.57. Found: C, 61.68; H, 9.07; N, 6.31.

Ester oxazoline **28** was prepared in 80% yield by stirring 10.7 g of the acylaziridine at ambient temperature (16 hr) in 75 ml of ether containing 2 drops of concentrated sulfuric acid. The analytical sample was prepared by molecular distillation at 50° (0.3 mm): ir (film) 1740, 1665 cm^{-1}; nmr ($CDCl_3$) δ 3.75 (s, 3), 3.60 (t, 2), 2.30–2.60 (m, 4), 1.60–1.90 (m, 4), 1.35 (s, 6).

Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.93; H, 9.00; N, 6.57. Found: C, 62.22; H,9.26; N, 6.47.

The hydroxypentyloxazoline was prepared in 75% yield by slow addition (25°) of 10.7 g (50 mmol) of **28** to 2.1 g of lithium aluminum hydride in 100 ml of ether. The mixture was stirred at room temperature for 2 hr and hydrolyzed with ice–water and the ethereal extracts were dried ($MgSO_4$). Filtration and evaporation *in vacuo* gave hydroxypentyloxazoline, which was purified by distillation: bp 60° (0.3 mm); ir (film) 3300–3400, 1660 cm^{-1}; nmr δ 4.40–4.80 (br s, 2), 3.50–3.80 (m, 4), 2.10–2.40 (m, 2), 1.42–1.80 (m, 6), 1.40 (s, 6).

Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.81; H, 10.36; N, 7.56. Found: C, 65.06; H, 10.64; N, 7.28.

Hydrolysis of the above oxazoline (7.0 g, 38 mmol) was performed by refluxing in 210 ml of 8% ethanolic sulfuric acid for 16 hr. After evaporation to 40 ml of residue, 200 ml of ether was added and neutralized with 10% sodium bicarbonate solution. The ethereal extracts were washed twice with water and the organic layer was dried ($MgSO_4$). Filtration and evaporation gave 4.0 g (82%) of ethyl 6-hydroxyhexanoate (**29**).[15]

Distillation at 60° (0.3 mm) gave pure samples (vpc), ir (film) 3300–3400, 1735 cm^{-1}.

Phthalide 31. A mixture of 10.1 g (10 mmol) of triethylamine, 7.1 g (10 mmol) of 2,2-dimethylaziridine, and 19.8 g (10 mmol) of 2-carboethoxybenzoyl chloride[16] in 200 ml of benzene was stirred for 1.0 hr at 5°. After work-up, there was obtained 21.0 g (90%) of the ester aroylaziridine, mp 52–54°. The analytical sample was prepared by recrystallization from petroleum ether: mp 53–54°; ir (KBr) 1730, 1660 cm^{-1}; nmr ($CDCl_3$) δ 7.35–7.85 (m, 4), 3.90 (s, 3), 2.30 (s, 2), 1.35 (s, 6).

Anal. Calcd for $C_{14}H_{17}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.66; H, 6.54; N, 5.90.

Rearrangement to **30** was performed from 4.0 g of the aziridine in 75 ml of dichloromethane (in ether no rearrangement takes place) and 2 drops of concentrated sulfuric acid after stirring at ambient temperature for 16 hr. There was obtained, after distillation, 2.88 g (72%) of ester oxazoline **30**: bp 128° (1.3 mm); ir (film) 1730, 1650 cm^{-1}; nmr ($CDCl_3$) δ 7.40–7.80 (m, 4), 3.90 (s, 3), 3.80 (s, 2), 1.40 (s, 6).

To 1.0 g of lithium aluminum hydride in 50 ml of ether was added 2.88 g (12 mmol) of ester oxazoline **30**. After stirring for 4 hr at room temperature and hydrolysis with ice–water, 2.38 g (95%) of crude hydroxymethyloxazoline was obtained, ir (film) 3300, 1640 cm^{-1}. This was used in the next step without further purification.

Hydrolysis to phthalide **31** was effected by refluxing 2.05 g of the hydroxymethyloxazoline in 150 ml of 3 *N* hydrochloric acid for 16 hr. Extraction with chloroform and evaporation gave 0.65 g

(50%) of phthalide: mp 71–72° (after recrystallization from water) (lit.[17] mp 73°); ir (KBr) 1750 cm^{-1}; nmr ($CDCl_3$) δ 7.20–8.00 (m, 4), 5.40 (s, 2).

γ-Methylbutyrolactone (27). The keto oxazoline **8** (0.85 g, 5.0 mmol) in 10 ml of ether was added to lithium aluminum hydride (95 mg, 2.5 mmol) in 30 ml of ether (foaming results) and the mixture was stirred at room temperature for 1.5 hr. Ice–water was added dropwise and the mixture was filtered and evaporated to give 0.63 g of the oxazoline carbinol (80%), ir (film) 3350, 1660 cm^{-1}. Hydrolysis to the lactone was performed using 30 ml of 5% ethanolic sulfuric acid and heating to reflux for 15 hr. The ethanol was removed by fractional distillation and the residue was taken up in ether, washed with saturated brine, and dried ($MgSO_4$) to give 0.51 g of lactone **27**. This material was identical with that prepared using propylene oxide and the lithio oxazoline.[4]

Formation of Oxazolines 33 (R = Ph) without Isolation of Intermediate Acylaziridine 32. To 5.1 g (50 mmol) of triethylamine and 3.6 g (50 mmol) of 2,2-dimethylaziridine in 300 ml of anhydrous ether at 0° was added 7.0 g of benzoyl chloride. The resulting white slurry was stirred for 30 min and the triethylamine hydrochloride was removed by filtration. The filtrate was cooled to 0°, 0.2 ml of concentrated sulfuric acid was added, and the solution was stirred overnight at room temperature. The ethereal solution was extracted with cold (0–10°) 10% hydrochloric acid and the aqueous layer was neutralized with bicarbonate. The aqueous solution was extracted with ether, dried, and concentrated to give 7.3 g (85%) of 2-phenyl-5,5-dimethyl-2-oxazoline (**33**, R = Ph): mp 36–37°; ir (film) 1645 cm^{-1}; nmr ($CDCl_3$) δ 7.90–8.10 (m, 2), 7.30–7.60 (m, 3), 3.80 (s, 2), 1.45 (s, 6).

Anal. Calcd for $C_{11}H_{13}NO$: C, 75.38; H, 7.49; N, 8.00. Found: C, 75.48; H, 7.48; N, 8.04.

Conversion of Ethyl *m*-Hydroxybenzoate (34) to Oxazoline 38. A mixture of **34** (8.3 g, 50 mmol) and dihydropyran (5.0 g, 60 mmol) was stirred for 15 min at room temperature and the excess dihydropyran was removed *in vacuo*. The residue was distilled (from three or four sodium hydroxide pellets) to give 11.3 g (90%) of **35**, bp 133° (0.8 mm), ir (film) 1720 cm^{-1}.

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.17; H, 7.26. Found: C, 66.89; H, 7.25.

A solution of **35** (4.7 g, 19 mmol) in 20 ml of ether was treated with the magnesium bromide salt of 2,2-dimethylaziridine (prepared from 25 mmol of ethylmagnesium bromide and 25 mmol of 2,2-dimethylaziridine in 70 ml of ether) and stirred at room temperature for 5 hr. The mixture was quenched in cold water, and the ethereal layer was dried and concentrated to give the crude acylaziridine **36**. This was dissolved in 100 ml of dichloromethane containing 0.6 g of triethylammonium tosylate and the solution was stirred overnight. After addition of 1.0 g of sodium carbonate, the solvent was removed and the residue was taken up in ether, washed with water, dried, and concentrated to give 4.0 g of **36**. If the ethereal solution was shaken with cold 1 hydrochloric acid, and the aqueous solution neutralized, there was obtained 2.0 g of **38**: mp 132–133° (hexane–benzene); ir (KBr) 3200–3400, 1650 cm^{-1}; nmr ($CDCl_3$) δ 7.10–7.60 (m, 5), 3.95 (s, 2), 1.50 (s, 6).

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.08; H, 6.86; N, 7.33. Found: C, 69.36; H, 6.77; N, 7.42.

Acknowledgment. This work was supported by the National Institutes of Health, the National Science Foundation, and the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Registry No.—**1** (*p*-Br), 32664-14-5; **1** (*o*-Br), 32664-13-4; **1** (*o*-Br) HCl, 51849-83-3; **1** (*m*-Br), 51849-84-4; **6** (*p*-Br), 51849-85-5; **7**, 123-76-2; **8**, 38285-58-4; **9**, 51849-86-6; **10**, 21303-80-0; **11**, 6566-40-1; **12**, 29947-04-4; **13** (A = OH), 17560-23-5; **13** (A = OEt), 51849-87-7; **14**, 17419-81-7; **15**, 51849-88-8; **16**, 51849-89-9; **17**, 51849-90-2; **18**, 29947-07-7; **28**, 38285-59-5; **29**, 5299-60-5; **30**, 51849-91-3; **31**, 87-41-2; **33** (R = Ph), 33561-48-7; **34**, 7781-98-8; **35**, 51849-92-4; **36**, 51849-93-5; **38**, 51849-94-6; 2,2-dimethylaziridine, 2658-24-4; 2-amino-2-methylpropanol, 124-68-5; 4-bromobenzoic acid, 586-76-5; *N*-(2,2-dimethyl-3-hydroxypropyl)-*p*-bromobenzamide, 52306-15-7; *o*-bromobenzoic acid, 88-65-3; *m*-bromobenzoic acid, 585-76-2; *p*-bromobenzoyl chloride, 586-75-4; *N*-(*p*-bromobenzoyl)-2,2-dimethylaziridine, 32158-85-3; 2-[γ-hydroxy-γ-(*p*-bromophenyl)butyl]-5,5-dimethyl-Δ-oxazoline, 51849-96-8; 2-(*p*-benzoylphenyl)-4,4-dimethyl-Δ^2-oxazoline, 51849-97-9; oxazoline carbinol (mp 106–108°), 51849-98-0; oxazoline adduct (ir 1650, 3350 cm^{-1}), 51849-99-1; oxazoline carbinol (mp 95–97°), 51850-00-1; oxazoline adduct (ir 1645, 3250 cm^{-1}), 51933-46-1; 1-(γ-ketopentoyl)-2,2-dimethylaziridine, 38278-95-4; 3-(4,4-dimethyl-Δ^2-oxazolino)-1-hydroxy-1-phenyltetralin, 29947-05-5; adipic acid monomethyl ester, 627-91-8; 1-(5-carbomethoxypentoyl)-2,2-dimethylaziridine, 38285-55-1; 2-(5-hydroxypentyl)-5,5-dimethyl-Δ^2-oxazoline, 51850-02-3; 2-carboethoxybenzoyl chloride, 22103-82-8; 1-(2-carboethoxybenzoyl)-2,2-dimethylaziridine, 51850-03-4; benzoyl chloride, 98-88-4.

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Notes

Synthesis of 7α-Methoxycephalosporins

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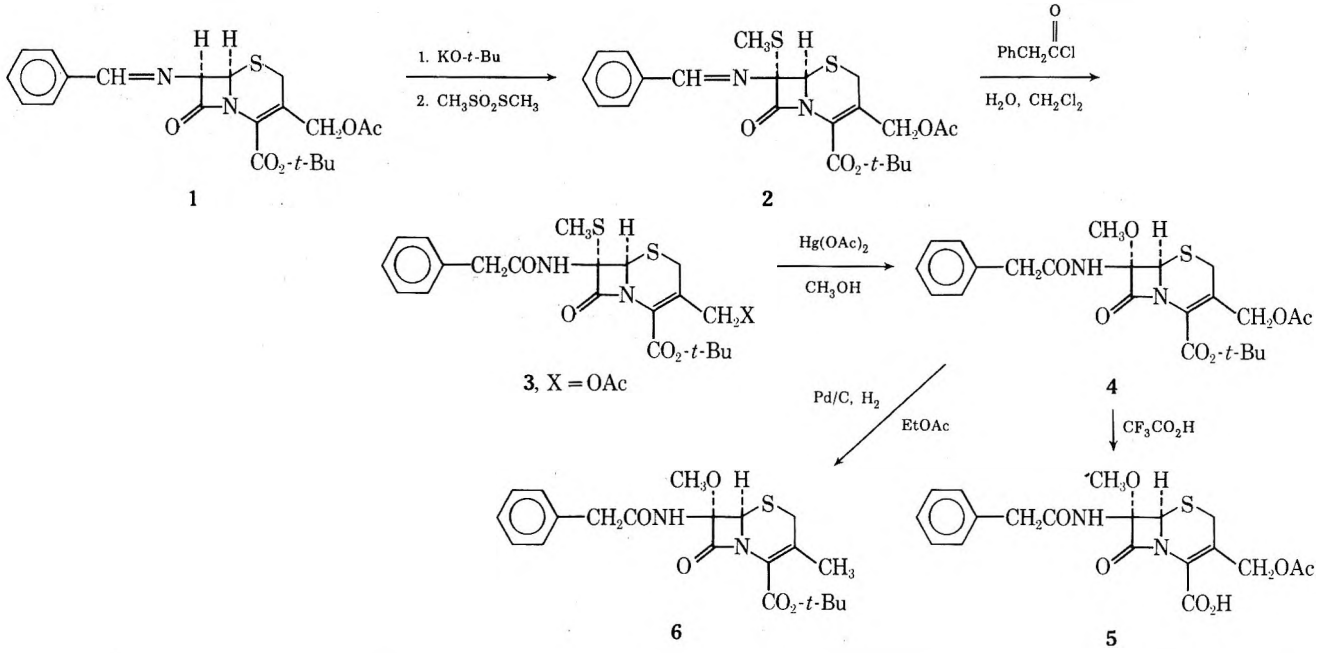
Received June 6, 1974

We have previously published a novel synthetic route to 7α-substituted cephalosporins and 6α-substituted penicillins,[1] and the volume of literature in this biologically important area is growing rapidly as a result of the work of numerous groups.[2] Our earlier publication reported that a Schiff base (*e.g.*, 1) could be readily converted to an anion, then alkylated stereoselectively to give a predominance of the α-oriented substituent adjacent to the β-lactam carbonyl.[1a] X-Ray studies corroborated the assignments of structures, and confirmed the usefulness of studies of nuclear Overhauser effects (NOE) to facilitate stereochemical assignment.[1b] We have extended the earlier synthesis[3] of 7-methoxy-7-aminodeacetoxycephalosporins to compounds derived from a 7-aminocephalosporanic acid nucleus itself. The synthesis described here provides an extremely convenient method for synthesizing 7α-methoxycephalosporins.

7α-Methoxy-7-phenylacetamidocephalosporanic acid (**5**) was readily synthesized according to modifications of our previous published procedure, as shown in the sequence below.



The product **5** was found to be highly active against both gram-positive and gram-negative bacteria. Minimum inhibitory concentrations against several susceptible gram-positive and gram-negative organisms ranged from 0.1 to 10 μg/ml. Nuclear Overhauser effects were observed for various adjacent groups, but the close proximity of the absorption peaks prevented quantitation. Hydrogenolysis of the ester **4**, however, provided a corresponding deacetoxy analog (**6**) that was identical with the major 7-methoxy epimer (75% yield), which we had obtained by mercuric acetate–methanol solvolysis of the deacetoxy analog of **3** (X = H), but was assigned the *7β-methoxy orientation* on the basis of NOE studies.[3] To resolve this ambiguity, we resorted to an X-ray crystallographic determination of the major 7-methoxy epimer resulting from treatment of the deacetoxy analog of **3** with mercuric acetate–methanol.

The molecular geometry indicated clearly that the methoxy group is α, or cis, to the hydrogen at the 6 position.

The 7α-methoxy free acid derived from **6** was inactive at 100 μg/ml against the gram-negative and gram-positive microorganisms tested. The NOE values previously reported for compound **6** were OCH_3-6-H, 5%, and NH-6-H, 10%. These values have been confirmed by a repeat study on the original sample. A solution of a freshly prepared and purified sample, however, gave opposite values: OCH_3-6-H, 16%, and NH-6-H, 5%. The reason for the anomalous results observed with the original sample is not yet known.

Although there has been no question of the correctness of assignments of other 7α-methoxy structures previously reported,[2b,c] this study represents the first confirmation of the absolute configuration of a 7-methoxycephalosporin with marked microbiological activity.

Experimental Section

The pmr spectra were obtained on Varian nuclear magnetic resonance spectrometers (Models T-60 and XL-100-15), and chemical shifts are reported on the τ scale, with tetramethylsilane used as an internal standard. Perkin-Elmer spectrometers (Models 257 and 621) were used to measure infrared spectra, and mass spectra were obtained from an AEI-MS-902 mass spectrometer. Melting points are uncorrected.

7α-Methylthio-7-benzaliminocephalosporanic Acid *tert*-Butyl Ester (2). The 7α-methylthio Schiff base **2** was prepared in a facile manner by modification of the previously reported procedure, which provided **2** in 21% yield and required extensive chromatography. The improved procedure affords **2** as a crystalline

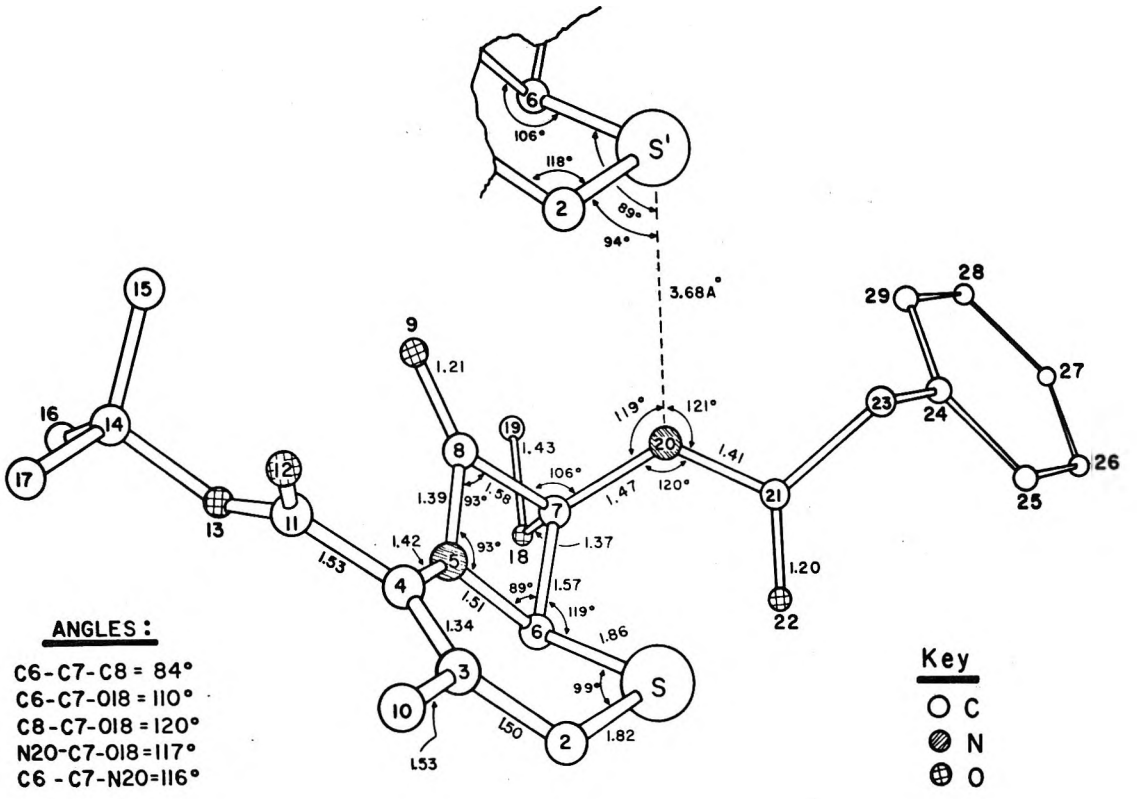


Figure 1.

product in 50% yield (85% yield as determined from pmr integrations of crude material).

To a stirred solution of Schiff base 1 (23.8 g, 57 mmol) in dimethoxyethane (530 ml, freshly distilled from $LiAlH_4$) at −50 to −60° under N_2 was added sublimed potassium *tert*-butoxide (6.13 g, 57 mmol). The dark-red solution was stirred for 3 min. Methyl methanethiolsulfonate (7.03 g, 57 mmol) in dimethoxyethane (10 ml) was added, and the mixture was stirred for 50 min at −50°. The dark mixture was poured into ice-cold 0.2 *M* pH 6.6 phosphate buffer (1500 ml) and extracted with $CHCl_3$ (3 × 700 ml). The $CHCl_3$ extract was washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated *in vacuo* to a residue, which crystallized readily from CH_3OH to give 13.2 g (50% yield) of 7α-methylthio Schiff base 2 having mp 125–126° and spectral properties as previously described. Further quantities of 2 could be obtained by chromatography of the mother liquor on silica gel, using $CHCl_3$–hexane (9:1) as solvent.

7α-Methylthio-7-phenylacetamidocephalosporanic Acid *tert*-Butyl Ester (3, X = OAc). 3 (X = OAc) was prepared in gram quantities, as previously described.

7α-Methoxy-7-phenylacetamidocephalosporanic Acid *tert*-Butyl Ester (4). To 7α-methylthio *tert*-butyl ester 3 (449 mg, 0.91 mmol) in dry CH_3OH (4 ml) under N_2 was added mercuric acetate (291 mg, 0.91 mmol). The mixture was stirred at room temperature for 40 min and evacuated *in vacuo* to a residue. The residue was washed repeatedly with $CHCl_3$, and the $CHCl_3$ extract was washed with water (4 × 50 ml), dried (Na_2SO_4), and evaporated to a residue (410 mg). Further purification was effected by tlc chromatography on silica gel (three PQIF plates, 20 cm × 40 cm × 1 mm) in the system $CHCl_3$–hexane (9:1), which provided 4 as a colorless residue (202 mg, 47% yield): pmr ($DCCl_3$) τ 8.48 (9 H, s, *tert*-butyl) 7.93 (3 H, s, *O*-acetyl), 6.83, 6.43 (2 H, AB q, *J* = 19 Hz, C-2), 6.55 (3 H, s, OCH_3), 6.30 [2 H, s, $PhCH_2(C{=}O)N$], 5.22, 4.92 (2 H, AB q, *J* = 14 Hz, C-3 methylene), 4.93 (1 H, s, C-6), 3.27 (1 H, broad s, NH), and 2.6 (5 H, s, aromatics); ir ($CHCl_3$) 1782 (β-lactam C=O), 1730 (broad, ester C=O's), and 1695 cm^{-1} (amide C=O); mass spectrum, weak molecular ion at *m/e* 476.

7α-Methoxy-7-phenylacetamidocephalosporanic Acid (5). To 7α-methoxy *tert*-butyl ester 4 (128 mg, 0.27 mmol) in a stoppered flask at 0° was added trifluoroacetic acid (5 ml). The flask was removed from the ice bath and allowed to warm to room temperature over the course of 15 min, during which time the stopper was loosened to release pressure. The trifluoroacetic acid was removed *in vacuo*, and the residue was taken up in $CHCl_3$–H_2O. The pH was adjusted to 7.5 with aqueous $NaHCO_3$ and, after shaking, the $CHCl_3$ layer was removed. Fresh $CHCl_3$ was added to the aqueous layer, and the pH was adjusted to 2.0 with 1 *N* HCl. Solid NaCl was added, and the acid layer was extracted repeatedly with $CHCl_3$. The combined $CHCl_3$ extracts were dried (Na_2SO_4) and evaporated to give 72 mg (63% yield) of crude acid 5: pmr ($DCCl_3$–CD_3OD) τ 7.92 (3 H, s, *O*-acetyl), 6.80, 6.43 (2 H, AB q, *J* = 19 Hz, C-2), 6.53 (3 H, s, OCH_3), 6.30 [2 H, s, $PhCH_2(C{=}O)N$], 5.12, 4.82 (2 H, AB q, *J* = 14 Hz, C-3 methylene), 4.92 (1 H, s, C-6), and 2.6 (5 H, s, aromatics); ir ($CHCl_3$) 1780 (β-lactam C=O), 1735 (broad, acid and ester C=O's), and 1690 cm^{-1} (amide C=O); mass spectrum, no molecular ion but peaks at *m/e* 360 (M − CH_3COOH) and 205 [$C_6H_5CH_2C(=O)NHC(OCH_3)=C=O$]; mass spectrum molecular ion of trimethylsilyl ester at *m/e* 492.

Recrystallization from acetone–hexane provided crystals, mp 161–162°.

Anal. Calcd for $C_{19}H_{20}N_2O_7S$: C, 54.28; H, 4.80; N, 6.66; S, 7.62. Found: C, 53.74; H, 5.13; N, 6.29; S, 7.85.

Hydrogenolysis of 7α-Methoxy-7-phenylacetamidocephalosporanic Acid *tert*-Butyl Ester (4) to 7α-Methoxy-7-phenylacetamidodeacetoxycephalosporanic Acid *tert*-Butyl Ester (6). Prior to hydrogenolysis, 7α-methoxy *tert*-butyl ester 4 was dissolved in EtOAc and filtered through charcoal. The ester 4 (132 mg) and 10% palladium on charcoal (530 mg) in 10 ml of EtOAc was shaken with hydrogen at 35 psi for 3 days at room temperature. The catalyst was removed by filtration, and the EtOAc was evaporated to a residue. Silica gel tlc in the system hexane–$CHCl_3$ (1:1), followed by pmr analysis, indicated a mixture of esters 4 and 6. Preparative silica gel tlc in the system hexane–$CHCl_3$ (1:1) provided two major components, the less polar of which yielded 22 mg of 6, mp 168–170°, on crystallization from CH_3OH. This sample and the major epimer from the mercuric acetate methanolysis of the deacetoxy analog of 3 were found to be identical in comparisons of pmr, ir (KBr), mixture melting point, and silica gel tlc [EtOAc–hexane (1:1)].

X-Ray Determination of the Structure of 6. Crystals of 6 from methanol were found to be monoclinic with *a* = 23.14, *b* = 5.796, c = 17.69 Å, β = 116.0°, d_{meas} = 1.33 g/cm^3, and space group *C*2 with *Z* = 4. All of the nonhydrogen atoms were located by Patterson and Fourier methods based on 1070 symmetry-independent intensities measured on a Syntex $P2_1$ automatic diffractometer (Cu Kα, λ = 1.542 Å). Least-squares refinements of all coordinates (except *y* for S) and individual isotropic temperature parameters reduced the conventional *R* factor to its present value of 0.09 for

the 865 observed intensities.[4] The fractional atomic coordinates relative to a twofold axis through the origin are given in Table I;[4] Figure 1 presents bond distances and agles in the solid-state molecular conformation.

Although no attempt was made to locate the hydrogen atoms, the positions of all but the methyl hydrogens may be defined within small limits. The molecular geometry clearly indicates that the methoxy group is α, or cis, to the hydrogen attached to C-6. The sulfur atom is displaced by 0.76 Å from the least-squares plane (P1) of the five other atoms of the dihydrothiazine ring (rms displacement of these five atoms 0.06 Å). The dihedral angle between P1 and the least-squares plane (P2) through the four atoms of the β-lactam ring (rms displacement 0.00 Å) is 30°. The least-squares plane (P3) of the exocyclic amide and benzylic carbon atoms, N-20, O-22, C-21, C-23, defines dihedral angles of 53 and 108° with P2 and the plane of the phenyl ring, respectively. The peptide-like hydrogen bonding between the exocyclic amide groups of neighboring molecules commonly found in crystal structures of cephalosporin derivatives[5] is not present in this crystal structure, nor is any other type of (N-20)–H···O hydrogen bonding evident. Instead, the (N-20)–H bond points directly toward the sulfur atom, S^1, of a (*b*) translationally related molecule (see Figure 1 for the intermolecular geometry of this approach), with S^1 displaced by only 0.67 Å from the exocyclic amide plane, P3.

Acknowledgment. We thank Dr. P. Funke for obtaining mass spectra, Mr. J. Alicino for combustion analyses, and Mr. H. Basch for microbiological data.

Registry No.—**1**, 36954-82-2; **2**, 37787-02-3; **3** (X = OAc), 37787-03-4; **4**, 51932-72-0; **5**, 51932-73-1; **6**, 37786-97-3.

Supplementary Material Available. Tables of fractional coordinates and isotropic temperature factors will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-2794.

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Oxidation–Reduction of 9-(*p*-Methoxyphenyl)-9-fluorenylacetaldehyde on Activated Alumina

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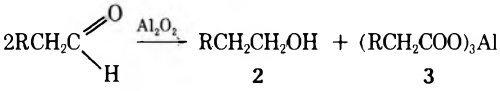
Received July 17, 1973

During a study of the alumina-catalyzed condensation reactions of aldehydes, we found that when 9-(*p*-methoxyphenyl)-9-fluorenylacetaldehyde (**1**) is chromatogrammed in the usual manner through a column prepared with activated alumina (Woelm neutral, activity grade I, pH 7.5), it undergoes an oxidation and a reduction reaction, reminiscent of the Cannizzaro reaction, yielding, in approximately equal amounts, the alcohol **2**, mp 107.5–109°, and a salt tentatively assigned the aluminum salt **3**.[2] The overall yield for the reaction was 90% based on converted aldehyde.



1 **2** **3**

R = [9-(*p*-methoxyphenyl)-9-fluorenyl]

Structure **2** was readily assigned on the basis of infrared and nmr analysis. The infrared spectrum of **3** is typical of a carboxylate salt. For identification purposes **3** was converted to the parent acid (**4**), mp 193–195°, by treatment with 5% sulfuric acid and extraction with ether. The parent acid was then identified by the usual spectral methods. Final confirmation of structure was obtained by synthesis. Reduction of **1** with sodium borohydride yields **2** (94%) while oxidation with silver oxide yields **4** (89%). The identity of these compounds with those obtained from the column was established by comparison of ir and nmr spectra and by mixture melting point determination.

The results were found to be reproducible. The length of the column and the amount of alumina used did not affect the course of the reaction.[3] Elution was carried out with mixtures of hexane, benzene, chloroform, ether, and methanol in increasing polarity and finally with 5% acetic acid–methanol solution. Unreacted aldehyde was eluted in early chloroform fractions followed by **2**. The compound **3** was isolated from the column with 5% acetic acid–methanol elution. Apparently the alumina surface serves a unique role in this conversion, since the base-catalyzed reaction of **1** under the usual Cannizzaro reaction conditions gave no reaction.[4]

The alumina oxidation of alcohols to carboxylic acids at elevated temperatures[5,6] and the reduction of benzaldehydes to benzyl alcohols[7] have previously been reported in the literature. Very recently, Kuiper, *et al.*,[8] reported a spectral study of benzaldehyde adsorbed on alumina. They observed bands in the infrared and Raman spectra which they attributed to benzoate and benzyl alcoholate bonds formed on the alumina surface. Products were not isolated, though benzyl alcohol was detected by gas chromatography.

The present study reports the first instance in which both oxidation and reduction products have been isolated from a column reaction.

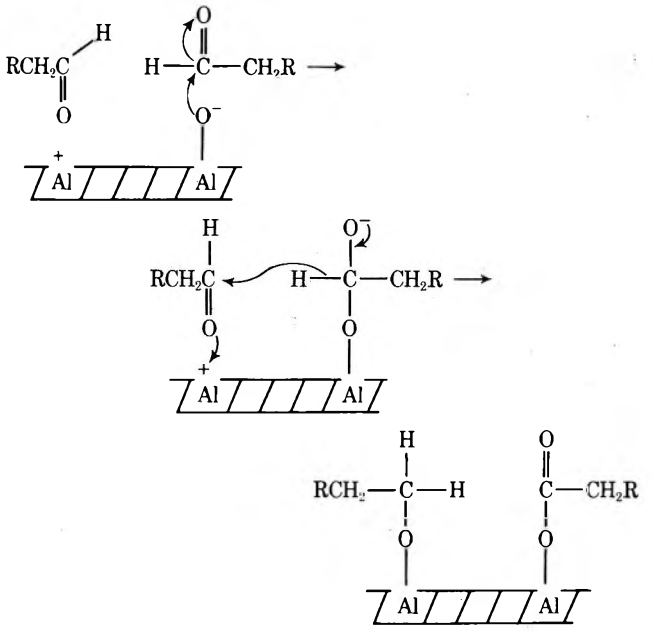
It would be rather premature to attempt to describe a precise mechanism at this time without additional information. However, a general mechanism can be postulated using Peri's description of the γ-alumina catalyst.[9] According to this description, the alumina surface is composed of exposed aluminum ions, oxide groups, and hydroxide groups of various basicity.

If one aldehyde group reacts with an oxide group while a second molecule reacts at a neighboring exposed aluminum ion site, hydride transfer would occur as shown in Scheme I.[10,11] Upon elution, the catalyst surface undergoes an exchange reaction, releasing **2** and **3**.

It is interesting to note that 9-carbazolylacetaldehyde, which is substituted with a less bulky group at the α carbon, undergoes an alumina-catalyzed condensation reaction instead.[12] The condensation may require enol formation, which is more favorable in the carbazole compound than in **1**.[13]

The mechanism of this reaction is under investigation and results will be reported at a later time.

Scheme I



Experimental Section[14]

Melting points are uncorrected and were determined on a Mel-Temp melting point apparatus. The nuclear magnetic resonance (nmr) spectra were recorded on a Jeolco C-60HL spectrometer at 60 MHz using tetramethylsilane as an internal standard. Infrared spectra were determined in potassium bromide on a Perkin-Elmer Model 700 spectrophotometer.

Reaction of 1 with Alumina. 9-(*p*-Methoxyphenyl)-9-fluorenylacetaldehyde (**1**, 1.00 g) was dissolved in benzene–hexane (1:1) and placed on a column prepared with 100 g of activated alumina (Woelm neutral, activity grade I, pH 7.5). The column was eluted with benzene–hexane (1:1), benzene, benzene–chloroform (1:1), chloroform, chloroform–ether (9:1), chloroform–ether (3:1), ether, methanol, and 5% acetic acid in methanol. Unreacted aldehyde (0.474 g) was eluted in early chloroform fractions as determined by mixture melting point determination and infrared analysis. This was followed by elution of the alcohol **2** (0.254 g, 48%): mp 107.5–109° (tlc); ir 3330 cm^{-1} (OH); nmr ($CDCl_3$) δ 7.3 (m, 12, Ar), 3.7 (s, 3, CH_3O), 2.97 (t, 2, J = 6.0 Hz, $-CH_2-$), 2.87 (t, 2, J = 6.0 Hz, $-CH_2O$), and 1.27 (s, 1, OH). The band at δ 1.27 disappeared when the nmr spectrum was run in D_2O. The compound **3** was isolated from the column with 5% acetic acid–methanol elution.

Acknowledgment. We are grateful to the Research Committee of the University of Rhode Island for the financial support of this research.

Registry No.—**1**, 31462-49-4; **2**, 50515-86-1; **3**, 50515-87-2; **4**, 50515-88-3.

Supplementary Material Available. A supplementary experimental section will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-2796.

References and Notes

(1) To whom correspondence should be addressed.
(2) An acid-treated sample of the salt gave a positive aluminum lake test. No test was obtained prior to acid treatment.
(3) We have evidence, however, which suggests that there is a direct relationship between the amount of alumina used and the amount of reaction.
(4) Under more severe conditions (50% aqueous sodium hydroxide, 130°, 2.5 hr) a small amount of acid and alcohol formed, though the principal reaction was decarbonylation.
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(10) At this point the mechanism would be similar to that proposed for the base-catalyzed Cannizzaro reaction. See J. Hine, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1962, p 267, and references cited therein.
(11) A similar mechanism has recently been proposed by Kuiper, *et al.* (ref 8).
(12) B. M. Vittimberga and M. L. Herz, *J. Org. Chem.*, **35**, 3674 (1970).
(13) Preliminary studies indicate that aldehydes that are not substituted with large groups on the α carbon, such as hexanal or heptanal, undergo the aldol condensation on activated alumina.
(14) See paragraph at end of paper regarding supplementary material.

Calculation of Resonance Effect Reaction Parameters. I. Arylene, Vinylene, and Ethynylene Skeletal Groups

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Received February 27, 1974

Consider a set of compounds, XGY, in which X represents a substituent, Y a reaction site, and G the skeletal group to which X and Y are bonded. We have previously shown that the Hammett ρ values for various groups G may be calculated in the case of the ionization constants of carboxylic acids[1,2] and rates of alkaline hydrolysis of ethyl carboxylates.[2,3]

Taft[4] has proposed an expanded form of the Hammett equation. The ρ values calculated for groups G may be

$$Q_X = \alpha\sigma_{IX} + \beta\sigma_{RX} + h \qquad (1)$$

identified with the α values of eq 1, as α represents the magnitude of the localized electrical effect, and these ρ values were calculated from an equation derived by combining the Hammett and Kirkwood–Westheimer equations. It seemed of interest to develop a method for calculating the β parameters of eq 1 as a function of G.

Dewar and Grisdale,[5] in calculating new σ constants for substituted naphthalene and biphenyl sets, have proposed that the delocalized effect is proportional to the formal negative charge q (at the carbon atom of G which bears the reaction site) in the ion $^-CH_2GH$. When G is derived from an alternant hydrocarbon, q may be simply and easily calculated[6] by the method developed by Dewar. We have examined the relation

$$\beta_G = mq_G + c \qquad (2)$$

Equation 2 has been studied for the ionization of carboxylic acids in water at 25°, in 50% v/v EtOH–H_2O at 25°, and in 80% v/v methyl cellosolve–H_2O at 25°. Also studied were the rates of alkaline hydrolysis of ethyl carboxylates in 85–88.7% EtOH–H_2O at 30° and the rates of reaction of carboxylic acids with diphenyldiazomethane at 30° in EtOH.

We have also examined the applicability of eq 2 to the ionization of azaarenes. The q values for the corresponding arene, G, have been used in the correlation on the assumption that q_N, the charge on the nitrogen, will be directly

proportional to the charge q on the corresponding carbon atom of G.

$$q_N = nq \quad (3)$$

To determine the validity of eq 2, β values were correlated with q values by linear regression analysis. Many β values were determined for this purpose by correlation of the appropriate data with eq 1 by means of multiple linear regression analysis. The σ_I constants required were taken from our compilation.[7] The σ_R constants were obtained from eq 4. The σ_p constants were generally taken from the

$$\sigma_R = \sigma_p - \sigma_I \quad (4)$$

collection of McDaniel and Brown.[8] For the data used and the results of the correlations with eq 1, see paragraph at end of paper regarding supplementary material. Values of β and of q are given in Tables I and II, respectively.

Results of the correlations with eq 2 are set forth in Table III. The results show that of the six sets studied, two gave excellent, three gave fair, and one gave poor correlation as determined by the F test. The "student t" test for the significance of m resulted in one excellent, one very good, three fair, and one poor result. The correlation for set 2 (2A in Table III) was improved by dropping the values for the *trans,trans-* and *cis,trans*-phenylbutadienylene groups (set 2B). The "student t" tests on sets 1, 2A, and 3–6 all show that the intercept c in eq 2 is not significant. In set 2B, however, c is significant at the 99.0% CL. It would seem that in most cases eq 5 would be sufficient.

$$\beta_G = mq_G \quad (5)$$

The results obtained above indicate that eq 2 is generally obeyed at least approximately, and that eq 3 would be satisfactory in most cases. It seems likely that had more data been available, better correlations would have been obtained. It is interesting to note that excellent results were obtained in the case of the azaarenes (set 6), thus justifying eq 3.

We may therefore conclude that estimation of β is possible when m and c are known for the reaction being studied and q can be calculated. If eq 5 is really satisfactory, then it should be possible to combine data in a number of solvents at various temperatures by correlating γ_R values where

Table I
Values of β

1. Ionization Constants of Carboxylic Acids in H_2O at 25°

trans-CH=CH–, −2.09; [a] 4-$C_{10}H_6$-1-, −1.54; 4-C_6H_4-1-, −0.985; [b] *trans*-4-C_6H_4CH=CH–, −0.477; *cis*-4-C_6H_4-CH=CH–, −0.643 [b]

2. Ionization Constants of Carboxylic Acids in 50% v/v EtOH–H_2O at 25°

trans-CH=CH–, −4.27; [a] 4-$C_{10}H_6$-1-, −1.85; 4-C_6H_4-1-, −1.38; 5-$C_{10}H_6$-1-, −0.569; 8-$C_{10}H_6$-2-, −0.548; 6-$C_{10}H_6$-2-, −0.633; 7-$C_{10}H_6$-1-, −0.568; *trans,trans*-4-C_6H_4CH=CHCH=CH–, −0.351; *cis,trans*-4-C_6H_4CH=CHCH=CH–, −0.337

3. Ionization Constants of Carboxylic Acids in 80% MCS–H_2O at 25°

trans-CH=CH–, −3.34; [a] 4-C_6H_4-1-, −1.68; *trans*-4-C_6H_4CH=CPh–, −0.838; *cis*-4-C_6H_4CH=CPh–, −0.517

4. Rate Constants for the Alkaline Hydrolysis of Ethyl Carboxylates in 85–88.7% w/w EtOH–H_2O

4-$C_{10}H_6$-1-, 2.23; 4-C_6H_4-1-, 2.34; *cis*-4-C_6H_4CH=CH–, 1.12; *trans*-4-C_6H_4CH=CH–, 1.15; 4-$C_6H_4C_6H_4$-4-, 0.633

5. Rate Constants for the Reaction of Carboxylic Acids with Diazodiphenylmethane in EtOH at 30°

trans-CH=CH–, 1.60; [a] 4-C_6H_4-1-, 0.861; *trans*-4-C_6H_4-CHCH–, 0.357; 4-$C_6H_4C_6H_4$-4-, 0.224 [b]

6. Ionization Constants of Azaarenes in H_2O at 20°

4-C_9H_6N-1-, −6.29; 4-C_6H_4N, −5.11; 5-C_9H_6N-1-, −1.49; [c] 7-C_9H_6N-1-, −2.73; [c] 4-C_6H_4CH=CHC_5H_4N-4-, −0.768

[a] From M. Charton, *Progr. Phys. Org. Chem.*, **10**, 81 (1973). [b] Calculated from the ρ value obtained from correlation with the Hammett equation. [c] From M. Charton, *J. Org. Chem.*, **30**, 3341 (1965).

Table II
Values of q Calculated by the Method of Dewar

G	q	G	q
trans-CH=CH–	0.500	6-$C_{10}H_6$-2-	0.0588
4-$C_{10}H_6$-1-	0.200	7-$C_{10}H_6$-1-	0.0588
4-C_6H_4-1-	0.143	5-$C_{10}H_6$-1-	0.050
trans-4-C_6H_4CH=CH–	0.125	8-$C_{10}H_6$-2-	0.050
cis-4-C_6H_4CH=CH–	0.125	4-$C_6H_4C_6H_4$-4-	0.0323
trans-4-C_6H_4CH=CPh–	0.0909	4-C_6H_4CH=CHC_6H_4-4-	0.0286
cis-4-C_6H_4CH=CPh–	0.0909	*trans,trans*-4-C_6H_4CH=CHCH=CH–	0.111
		cis,trans-4-C_6H_4CH=CHCH=CH–	0.111

Table III
Results of Correlations with Equation 2

Set	m	c	r [a]	F [b]	s_{est} [c]	s_m	s_c [c]	n [d]
1	−3.70	−0.338	0.891	11.52 [j]	0.349	1.09 [j]	0.285 [n]	5
2A	−8.57	0.0544	0.968	104.6 [e]	0.340	0.838 [e]	0.165 [o]	9
2B	−8.30	−0.146	0.9996	5908 [o]	0.0434	0.108 [e]	0.0232 [g]	7
3	−6.15	−0.326	0.961	24.12 [j]	0.428	1.25 [j]	0.335 [n]	4
4	10.3	0.203	0.829	6.608 [k]	0.485	4.02 [k]	0.547 [o]	5
5	2.88	0.183	0.952	19.45 [j]	0.233	0.654 [j]	0.175 [m]	4
6	−31.9	−0.217	0.981	75.98 [f]	0.530	3.65 [g]	0.434 [o]	5

[a] Confidence levels of F and of "Student t" tests of s_m and s_c are indicated by superscripts.[e–p] r = correlation coefficient. [b] F tests for significance of regression. [c] Standard errors of estimate, m, and c. [d] Number of points in the set. [e] 99.9% confidence level (CL). [f] 99.5% CL. [g] 99.9% CL. [h] 98.0% CL. [i] 97.5% CL. [j] 95.0% CL. [k] 90.0% CL. [l] <90.0% CL. [m] 80.0% CL. [n] 50.0% CL. [o] 20.0% CL. [p] 20.0% CL.

$$\gamma_{R,G} = \frac{\beta_G}{\beta_G^\circ} = \frac{mq_G}{mq_G^\circ} \quad (6)$$

The β values were obtained under the same reaction conditions. Choosing the *p*-phenylene group as G°

$$\gamma_{R,G} = q_G/0.143 = 7q_G \quad (7)$$

For a comparison of values of γ_R calculated from eq 7 with observed values of γ_R see paragraph at end of paper. The results obtained show that eq 7 is only a crude approximation; calculation of β values is best accomplished by eq 2.

In the calculation of q by the method of Dewar, the carbon atoms in the species $-GCH_2-$ are divided into two sets of $n + 1$ and n atoms. The value of q at the atoms of the n set is zero. Examples are *m*-phenylene, and 6-substituted 1-naphthylene groups. Sets such as these do show significant values of q, however. We have previously attempted[9] to predict β values for such sets from the equation

$$\beta = m'\sum q_{adj} + c \quad (8)$$

where $\sum q_{adj}$ is the sum of the q's on the carbon atoms adjacent to that carbon atom which bears the reaction site. To determine the validity of eq 8, values of β_G for the ionization of carboxylic acids in 50% v/v EtOH–H_2O and the ionization of azaarenes in H_2O at 20° were correlated with it. The correlations obtained were not significant. We may reject eq 8 as a means of predicting β values.

We propose that q values for groups such as *m*-phenylene and 6-substituted 1-naphthylene may be calculated from some reference series for which good values of m and c are available. Values of q for other types of groups for which calculation by the method of Dewar is not possible may also be obtained from eq 2 when β, m, and c are known. Such groups are those which contain triple bonds, and those in which a saturated side chain intervenes between reaction site and ring. For values of q calculated in this manner, see paragraph at end of paper.

It is interesting to note that for the $-C\equiv C-$, 4-$C_6H_4C\equiv C-$, and 4-$C_6H_4C\equiv CC_6H_4$-4- groups a linear relationship exists between their q values and the q values of the corresponding groups with double bonds in place of the triple bonds. Thus

$$q_{C\equiv C-} = nq_{C=C} + d \quad (9)$$

For a comparison of β values calculated from the q values obtained from eq 2 with observed β values see paragraph at end of paper.

Supplementary Material Available. Data used in correlations with eq 1, results of these correlations, values of γ_R, q values calculated from eq 2, and values calculated from these q values will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $4.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74 -2797.

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Oxidative Decyanation of Arylacetonitriles. A Synthesis of Ligusticumic Acid

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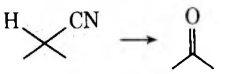
Received April 11, 1974

Little methodology exists for effecting the oxidative decyanation of secondary nitriles 1 to ketones 2.[1] As primary



1 2

nitriles can be monoalkylated to afford secondary nitriles,[2] a procedure capable of effecting this transformation (1 → 2) would render nitriles a member of the class of synthetic intermediates called acyl carbanion equivalents.[3] We now wish to report a convenient synthesis of aryl alkyl ketones and diaryl ketones from substituted arylacetonitriles.

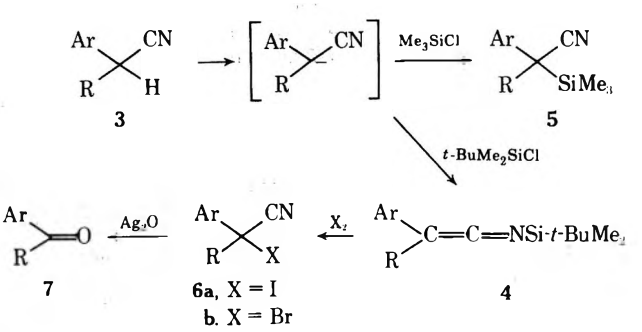
Anions derived from the reaction of secondary arylacetonitriles 3 underwent regioselective N-silylation with *tert*-butyldimethylchlorosilane[4] to provide *N-tert*-butyldimethylsilyl ketenimines 4 in good yield (see Table I) and

Table I
Silylation and Oxidative Decyanation of Arylacetonitriles ArCHRCN

ArCHRCN registry no.	Ar	R	Yield[a] of ketenimine 4, %	Yield of ketone 7, %
1823-91-2	Ph	Me	89	71[b]
51965-61-8	*p*-FPh	Me	72	79[b]
2184-88-5	*p*-ClPh	Me	71	61[b]
769-68-6	Ph	Et	73	81[b]
5558-29-2	Ph	*i*-Pr	78	82[c]
15601-30-6	Ph	*n*-Oc	76	77[c]
86-29-3	Ph	Ph	90	63[c]
24168-42-1	α-Np	Me	71	63[b]

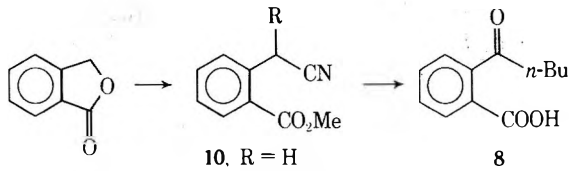
[a] Isolated by distillation at reduced pressure. [b] Isolated using Girard T reagent. [c] Isolated by thick layer chromatography on Merck silica gel F254.

C-silylation with trimethylchlorosilane to provide α-trimethylsilyl nitriles 5.[5] On bromination or iodination of 4,



α-halonitriles **6** are obtained.[6] The treatment of α-iodonitriles **6a** but not the inert α-bromonitriles **6b** with silver oxide in tetrahydrofuran afforded aryl alkyl ketones **7** or diaryl ketones **7** (R = Ar) in good yield (see Table I). Unfortunately, dialkyl ketones could not be made by this procedure.

The use of nitriles as acyl carbanion equivalents was illustrated in a synthesis of the acetogenin,[7] ligusticumic acid (**8**).[8] Phthalide (**9**) was converted to the nitrile ester **10** *via* sequential treatment with sodium cyanide and diazomethane. Alkylation of **10** with *n*-butyl bromide afforded the nitrile **11** in 79% yield. Application of the oxidative decyanation procedure described above and subsequent saponification of the carboxylic ester provided ligusticumic acid (**8**).



9 **10**, R = H; **11**, R = *n*-Bu; **8**

Experimental Section

Infrared spectra were determined on a Perkin-Elmer Infracord spectrophotometer. Nmr spectra were determined on a Varian A-60A spectrophotometer. Mass spectra were determined on a Varian MAT CH5 mass spectrometer. Melting points were determined using a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlabs, Atlanta, Ga.

The following is a representative example of the oxidative decyanation procedure.

***N*-(*tert*-Butyldimethylsilyl)ethylphenylketenimine (4).** To 111 mg (1.1 mmol, 1.1 equiv) of diisopropylamine in 2.5 ml of anhydrous tetrahydrofuran at −78° under a nitrogen atmosphere was added 0.48 ml (1.1 mmol) of 2.29 *M* *n*-butyllithium in hexane. The solution was stirred for 10 min. To the lithium diisopropylamide solution was added 145 mg (1.0 mmol) of 2-phenylbutyronitrile in 1.0 ml of anhydrous tetrahydrofuran. The solution was stirred for 10 min. To the lithionitrile solution was added 316 mg (2.1 mmol, 2.1 equiv) of *tert*-butyldimethylchlorosilane in 1.0 ml of anhydrous tetrahydrofuran. The solution was stirred for 30 min at −78° and 60 min at 25°. The solvents were evaporated at reduced pressure, and the product was evaporatively distilled at 135–140° (oven temperature) (0.25 mm) to afford 244 mg (94%) of yellow ketenimine **4** (R = Et; Ar = Ph). Repetition of this experiment using 3.32 g of 2-phenylbutyronitrile afforded 4.13 g (73%) of **4**: bp 95–99° (0.15 mm); ir (TF) 4.98 (C=C=N) and 6.31 μ (Ar); nmr (CCl_4) δ 0.25 [s, 6, $Si(CH_3)_2$], 1.00 [s, 9, $SiC(CH_3)_3$], 1.17 (t, *J* = 7 Hz, 3, CH_2CH_3), 2.31 (q, *J* = 7 Hz, 2, CH_2CH_3) and 6.8–7.4 (m, 5, ArH).

Propiophenone. To 259 mg (1.0 mmol) of ketenimine **4** (R = Et; Ar = Ph) in 1.0 ml of tetrahydrofuran at 0° was added 280 mg (1.1 mmol, 1.1 equiv) of iodine in tetrahydrofuran. The dark brown solution was stirred for 15 min at 0°. To this solution was added 1160 mg (5.0 mmol, 2.5 equiv) of freshly prepared,[9] moist silver oxide. The mixture was refluxed for 30 min, cooled, and filtered through a pad of Celite 545. The Celite pad was thoroughly washed with three 20-ml portions of ether. The ethereal solutions were combined, washed with 20 ml of brine, and dried over anhydrous magnesium sulfate. The solvents were evaporated to afford 590 mg of yellow oil. Girard "T" reagent[10] was utilized to effect the isolation of 108.2 mg (81%) of propiophenone which was identical with an authentic sample.

Methyl 2-Cyanomethylbenzoate (10). To 174 mg (1.0 mmol) of *o*-carboxyphenylacetonitrile[11] (Aldrich) in 10 ml of anhydrous ether at 0° was distilled diazomethane[12] in ether until nitrogen evolution ceased. The solution was stirred for 2 hr at 25°. The excess diazomethane was destroyed by the dropwise addition of acetic acid. The ethereal solution was washed with 20 ml of water, 20 ml of saturated sodium bicarbonate solution, and 20 ml of brine and dried over anhydrous magnesium sulfate. The solvent was evaporated to afford 185 mg (98%) of **10** as a tan solid: mp 48.5–49.5° (lit.[13] mp 48°); ir ($CHCl_3$) 4.44 (C≡N), 5.79 (C=O), 6.26, and 6.34 μ (Ar); nmr ($CDCl_3$) δ 3.92 (s, 3, OCH_3), 4.19 (s, 2, CH_2CN), and 7.2–8.2 (m, 4, ArH).

Anal. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18. Found: C, 68.60; H, 5.27.

Methyl 2-(1-Cyanopentyl)benzoate (11). The alkylation[2e] of **10** afforded 256.5 mg of oil which was chromatographed on two 20 × 20 cm thick layer Merck silica gel F254 plates in 1:3 ether–hexane to afford 181 mg (79%) of **11**: ir (TF) 4.47 (C≡N) and 5.81 μ (C=O); nmr (CCl_4) δ 0.93 (t, 3, CH_2CH_3), 1.1–2.0 (m, 6, CH_2), 3.90 (s, 3, OCH_3), 5.05 (d of d, *J* = 6 and 8 Hz, 1, CHCN), and 7.1–8.1 (m, 4, ArH); mass spectrum (70 ev) *m/e* (rel intensity) 231 (27) and 188 (100).

An analytical sample was prepared by evaporative distillation at 140–145° (oven temperature) (0.2 mm).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41. Found: C, 72.85; H, 7.42.

Ligusticumic Acid (8). Repetition of the silylation procedure described above using 231 mg (1.0 mmol) of **11** afforded 284 mg (82%) of ketenimine **4** (R = *n*-Bu; Ar = *o*-CO_2MePh), ir (TF) 4.87 (C=C=N) and 5.79 μ (C=O). Repetition of the iodine–silver oxide procedure described above using 282 mg of this ketenimine afforded 428 mg of crude yellow oil. The crude keto ester was refluxed in 1 ml of methanol and 3 ml of 2 *M* aqueous potassium hydroxide for 1 hr. The product was diluted with 50 ml of water and extracted with two 20-ml portions of ether. The ethereal solutions were washed with 10 ml of water. The combined aqueous solutions were acidified with 10 ml of 3 *M* hydrochloric acid and extracted with two 20-ml portions of ether. The ethereal solutions were washed and dried as described previously. The solvent was evaporated to afford 128.7 mg (77%) of ligusticumic acid (**8**) a a viscous oil. The purity of this material was estimated to exceed 90% according to tlc (silica gel, 1:3:3 methanol–ether–hexane). The propensity of **8** to suffer lactonization–dehydration[14]precluded crystallization and required characterization of **8** as the phthalazone,[15] mp 150–153° (lit.[16] mp 153–154°).

Acknowledgment. The financial support of the Research Corporation is gratefully acknowledged. I would also like to thank Mr. Richard E. Morehouse for invaluable library assistance.

Registry No.—**3** (R = H; Ar = *o*-CO_2HPh), 6627-91-4; **4** (R = Et; Ar = Ph), 51965-62-9; **4** (R = *n*-Bu; Ar = *o*-CO_2MePh), 28060-41-5; **8**, 550-37-8; **10**, 5597-04-6; **11**, 28060-41-5; *tert*-butyldimethylchlorosilane, 18162-48-6.

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Thermal Decomposition of 2-(Cyanoethylthio)benzenediazonium Tetrafluoroborate in Acetonitrile Solution[1]

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Received May 3, 1974

The thermal decomposition of ortho-substituted arenediazonium tetrafluoroborate salts[3] in the presence of aliphatic or aromatic nitriles has been shown to result in the formation of the corresponding nitrilium tetrafluoroborate salts,[4] some of which have been isolated.[4a] If these nitrilium salts, formed *in situ*, are allowed to react with a substituent, either an aromatic ring[1c,5a] or a heteroatom,[5a-d] positioned ortho to it, a facile entry into a number of novel heterocyclic ring systems results. For example, the syntheses of substituted phenanthridines,[1b,5a] morphananthridines,[5a] dibenzo[*b,f*][1,4]oxazepines,[5a] dibenzo[*b,f*][1,4]thiazepines,[5a] 4*H*-[3,1]benzoxazines,[5a,b,d] and benzoxazoles[5c] have been described.

In a few examples cited where the nitrilium ion attacks a heteroatom,[5a-e] the heteroatom is usually unsubstituted.[6] It was of interest to us to investigate the decomposition of a diazonium salt in which the heteroatom is blocked by an alkyl group. We describe here a study of the decomposition of diazonium salt **2** in acetonitrile solution in which a cyclization reaction is observed, albeit accompanied by fragmentation.

The diazonium tetrafluoroborate salt **2**, readily obtained from the amine **1**,[7] was decomposed in refluxing acetonitrile solution. After aqueous bicarbonate work-up three products were obtained and identified as 3-(2-acetamidophenylthio)propionitrile (**3**), 2-methylbenzothiazole (**4**), and 3-(2-fluorophenylthio)propionitrile (**5**) (Scheme I).

Table I
Results of the Thermal Decomposition of 2 in Refluxing Acetonitrile[a]

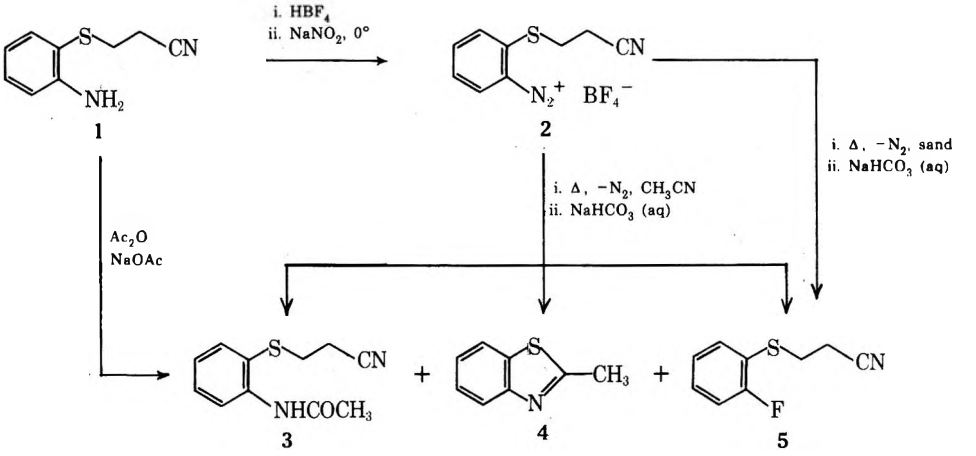
Concn of 2, mol/l.	% yield[b] 3	4	5
1.17	13	39	48
0.19	29	41	29
0.05	100		
0.02	100[c]		

[a] In each case, the reaction time was 20 hr. [b] Determined by nmr. [c] Analysis (tlc) of the crude reaction mixture, after hydrolysis and work-up, indicates the presence of a single component; recrystallization from toluene affords the amide **3**, mp 89–90°.

counts for the formation of the products **3–5**. In the first step the diazonium salt **2** undergoes decomposition in the acetonitrile solution with the evolution of nitrogen gas to form the nitrilium tetrafluoroborate salt **6**. This salt may cyclize in a reaction which is probably reversible to give **7**, and then fragment, with the loss of the cyanoethyl moiety, to give 2-methylbenzothiazole (**4**). The formation of the amide **3** undoubtedly arises from hydrolysis, during the work-up, of uncyclized nitrilium salt **6**, a reaction for which there is ample precedent.[4b] The fluoronitrile **5** most probably arises from the reaction of tetrafluoroborate ion with **2** (Baltz–Schiemann reaction),[11] although the formation of **5** from **6** cannot be ruled out.

As noted earlier, the product composition in the decomposition of **2** in acetonitrile solution varies with concentration (Table I). The variation of the amount of **3** and **5** appears to be consistent with two competitive divergent reaction pathways (Scheme II). In concentrated solution tetrafluoroborate ion competes favorably with acetonitrile in the reaction with **2**, and, as a result, the amount of fluoronitrile **5** which is formed, relative to the total amount of products (**3** + **4**) derived from the nitrilium ion **6**, is appre-

Scheme I

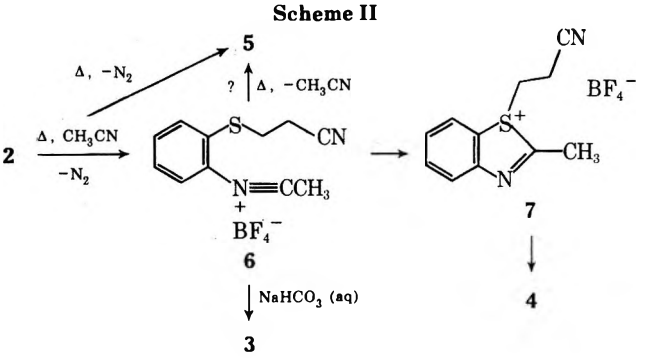


The ratio of these products was found to vary dramatically with concentration as may be seen by the product ratios summarized in Table I.

The structure of amide **3** was confirmed by independent synthesis from the amine **1**. The benzothiazole **4** was identified by comparison of its infrared and pmr[8] spectra and glc retention times with those of **4** obtained commercially. The structure of the fluoronitrile **5** follows from its elemental analysis, infrared and pmr[9] spectra, mass spectral fragmentation pattern,[10] and independent synthesis from **2**.[11,12]

In Scheme II we outline a possible mechanism which ac-

Scheme II



ciable. In contrast, in dilute solution the reaction of acetonitrile with **2** is dominant and in very dilute solution no product derived from reaction of tetrafluoroborate ion with **2** could be detected and only the amide **3** was obtained.

One puzzling aspect of the decomposition of **2** in acetonitrile is the way in which the yield of benzothiazole **4** varies with concentration. The fact that **4** is only obtained from the decompositions of **2** in relatively concentrated solutions and that **4** is totally absent from the products of decomposition of **2** in dilute solutions argues against a unimolecular decomposition of the presumed intermediate cyclic sulfonium salt **7**. It would appear that one or more of the starting materials or products is involved in the decyanoethylation of **7** to give **4**.[13] Solvation effects on intermediates **6** or **7** might also play a role in the variation in the amounts of **4** as well as **3** and **5** which are formed. The reaction sequence to give **4**, as we have formulated it, is undoubtedly an incomplete oversimplification of the actual events and, in reality, may be considerably more complicated. Further studies, involving the synthesis of heterocyclic ring systems using diazonium salts, are continuing.

Experimental Section

General Procedures. Spectra were determined as follows: ir, Vaseline mull, Perkin-Elmer 337; nmr, $CDCl_3$ solution, Varian A-60A; mass spectra, Hitashi Perkin-Elmer RMU-6A operating at 70 eV. Elemental analyses were performed by Chemalytics, Inc., Tempe, Ariz. Melting points were measured in a Thomas-Hoover apparatus and are uncorrected. Analysis by thin layer chromatography (tlc) involved the use of Eastman Kodak precoated silica gel sheets, with fluorescent indicator, as the adsorbent, elution with chloroform, and visualization with iodine vapor and/or with ultraviolet light. Analysis by glc was performed using a 210 × 0.6 cm i.d. Pyrex column packed with 25% DC Hyvac silicone grease on 60–80 mesh Chromosorb P at 190°. Preparative separations were performed using an annular column 160 cm long made of a 3.2-cm o.d. Pyrex tube surrounding an inner 1-cm o.d. sealed Pyrex tube the annular space of which was packed with 20% silicone grease on 60–80 mesh Chromosorb P at 140°.

Preparation of 3-(2-Aminophenylthio)propionitrile (1). A solution of freshly distilled o-aminothiophenol (50.1 g, 0.40 mol) in acrylonitrile (42.6 g, 0.77 mol) was stirred for 0.5 hr at room temperature and then allowed to stand overnight. The crude product was distilled at 1 atm and two fractions, bp 62 (*ca.* 5 ml) and 76° (*ca.* 35 ml), were discarded. The remainder was distilled at reduced pressure, providing the aminonitrile **1**, 53.5 g (74%), bp 128–134° (0.12 Torr), which solidified, giving almost colorless crystals, mp 44–46°. Recrystallization from benzene raised the melting point to 45.5°.

Anal. Calcd for $C_9H_{10}N_2S$: C, 60.64; H, 5.61. Found: C, 60.43; H, 5.61.

Ir (Vaseline) 3490 m, 3390 (NH_2), 2260 w–m (CN), 750 cm^{-1} s (aromatic ring, 1,2 disubstituted[14]); nmr ($CDCl_3$) δ 2.47 (2 H, m, $-CH_2CN$), 2.98 (2 H, m, $-CH_2S-$), 4.21 (2 H, br s, $-NH_2$), 7.37–6.40 (4 H, m, aromatic).

An alternate method of preparing **1** was also evaluated. A solution of 2-aminothiophenol (125 g, *ca.* 1.0 mol) in acrylonitrile (200 ml) was stirred for a total of 48 hr. The excess acrylonitrile was removed by distillation at 1 atm and the residual material was recrystallized three times from toluene to give 49.8 g (28%) of **1**, mp 41–42.5°. The yield of **1**, prepared in this way, was not optimized, and a work-up of the mother liquors would probably have raised the yield significantly.

Synthesis of 2-(Cyanoethylthio)benzenediazonium Tetrafluoroborate (2). To a cooled (−5°), vigorously stirred solution of **1** (10.1 g, 0.057 mol) in 48–50% fluoroboric acid (50 ml) was added dropwise during 25 min a solution of sodium nitrite (12.0 g, 0.174 mol) in 10 ml of water. The temperature was maintained between −5 and 0°. After addition was complete, the green slurry was stirred for an additional 10 min and then filtered. The crystals were washed with cold ether and dried at 25° under vacuum, affording 14.3 g (90.5%) of **2**, mp 82–83° dec, which was stored at 0° in an aluminum foil-wrapped bottle. Recrystallization of **2** from methanol–ether raised the melting point to 86.5° dec.

Anal. Calcd for $C_9H_8BF_4N_3S$: C, 39.01; H, 2.89. Found: C, 39.28; H, 2.71.

Ir (Vaseline) 2230–2250 m (CN, N_2^+), 1460 s, 1370 m, 1040 m, v broad, 760 cm^{-1} s (aromatic ring, 1,2-disubstituted[14]).

The tetrafluoroborate salt **2** is a yellow, crystalline solid which is stable indefinitely when kept at 0° and protected from moisture and light. The salt **2** appears to decompose slowly if kept at room temperature. The decomposition is indicated by a darkening of the yellow color of the crystals.

Thermal Decomposition of 2 in Acetonitrile Solution. General Procedure. An acetonitrile solution of **2** in a round-bottomed flask equipped with a reflux condenser, magnetic stirrer, and gas bubbler was plunged into a preheated (95–100°) oil bath. After a few minutes gas evolution began and the solution started to reflux. Gas evolution ceased after 20–30 min and boiling was continued for a total of 20 hr. The reaction mixture was cooled, the acetonitrile was removed under vacuum, and the residue was dissolved in $CHCl_3$ (50–100 ml). The $CHCl_3$ solution was then washed with saturated aqueous $NaHCO_3$ solution (3 × 75 ml) and dried (anhydrous Na_2SO_4) and the $CHCl_3$ was evaporated. Table I summarizes the detailed results of these decompositions.

Thermal Decomposition of 2 in Sand. The diazonium fluoroborate **2** (5.0 g, 0.18 mol) was combined with 50 g of sand and placed in a flask that was heated to 80–85°. Gas evolution had ceased and the color of the diazonium salt had disappeared after 15–20 min, but heating was continued for a total of 1 hr. After cooling the sand was leached overnight with methylene chloride, which was washed with saturated sodium bicarbonate solution, dried (anhydrous sodium sulfate), and evaporated, giving 2.6 g (80%) of an oil which was shown to be **3-(2-fluorophenylthio)propionitrile (5)**. An analytically pure sample of **5** was obtained by preparative glc.

Anal. Calcd for C_9H_8FNS: C, 59.64; H, 4.45. Found: C, 59.81; H, 4.54.

Ir (film) 3050 w, 2925 w, 2240 m (CN), 1260 m, 1220 m, 1120 m, 1070 m, 955 w, 815 m, 750 cm^{-1} s (aromatic ring, 1,2-disubstituted[14]); nmr ($CDCl_3$) δ 2.50 (2 H, m, $-CH_2CN$), 3.08 (2 H, m, $-CH_2S-$), 7.55–6.66 (4 H, m, aromatic); mass spectrum *m/e* (rel intensity) 181, M^+ (53), 141 (100), 127 (13), 83 (33).

Acetylation of 3-(2-Aminophenylthio)propionitrile (1). A solution of **1** (1.07 g, 0.59 mol) in acetic anhydride (25 ml) with a catalytic amount of sodium acetate was heated at 90° for 3 hr. The solution was cooled and poured over ice with stirring. The resulting solid was collected, washed with water, and dried, providing 1.24 g (95%) of crude product. Recrystallization from toluene gave analytically pure **3-(2-acetamidophenylthio)propionitrile (3)**, mp 89.5–90°.

Anal. Calcd for $C_{11}H_{12}N_2OS$: C, 59.97; H, 5.49. Found: C, 59.82; H, 5.55.

Ir (Vaseline) 3040 m (NH), 2230 m (CN), 1660 (amide I, C=O), 1525 m, 1565 m (amide II), 1010 m, 750–760 cm^{-1} s (aromatic ring, 1,2-disubstituted[14]); nmr (DMSO-d_6) δ 2.68 (2 H, m, $-CH_2CN$), 3.09 (2 H, m, $-CH_2S-$), 2.08 (3 H, s, $COCH_3$), 7.66–7.00 (4 H, m, aromatic), 9.11 (1 H, br s, NH).

Acknowledgments. We are grateful to the Edward G. Schlieder Educational Foundation and to the National Science Foundation (GP-11004) for support of this study. We thank Professor Gary W. Griffin and the University of New Orleans for making available to us the nmr spectrometer which was employed in this work. R. A. V. wishes to thank the Office of Education for a NDEA Fellowship.

Registry No.—**1**, 4327-52-0; **2**, 51932-75-3; **3**, 37587-95-4; **4**, 120-75-2; **5**, 51932-76-4; o-aminothiophenol, 137-07-5; acrylonitrile, 107-13-1.

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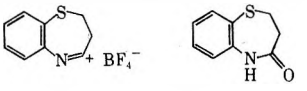

i ii

reaction mixture and of a pure sample of ii[12b] proved that none of ii was present among the reaction products.[12c] (b) W. H. Mills and J. B. Whitworth, *J. Chem. Soc.*, 2738 (1927). (c) We have decomposed **2** in a variety of other organic solvents, in hopes that the intramolecular cyclization might be observed. Thus far, only complex mixtures of products, largely derived from reactions of the solvents with **2**, have been obtained.
(13) The fate of the cyanoethyl moiety in the conversion **7** → **4** is not known with certainty. Decyanoethylation of **7**, for example, may conceivably occur by (a) elimination as acrylonitrile, (b) elimination as β-fluoropropionitrile from attack of BF_4^- at the carbon which is β to the cyano group in **7**, or (c) β-hydroxypropionitrile formed during the hydrolytic work-up. In a single experiment, we have identified (glc) acrylonitrile (route a) in the reaction mixture, prior to hydrolysis. However, it is not known whether pathways b or c are also involved or at what stage (before hydrolysis or during hydrolysis) decyanoethylation actually occurs.
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Preparation of Some Bicyclo[3.3.1]nonane Derivatives from Adamantanone

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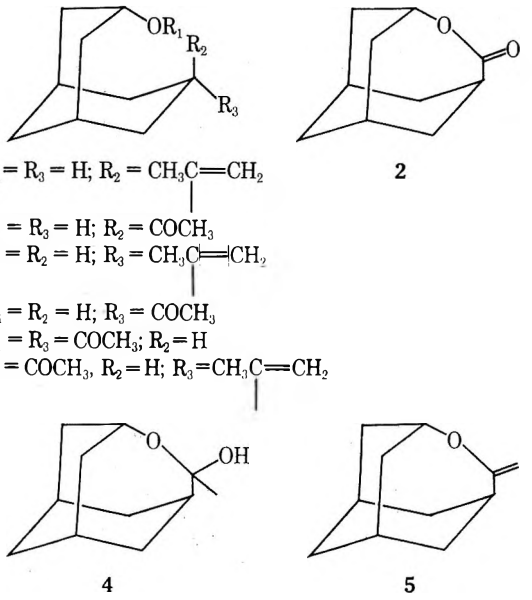
Received March 12, 1974

In connection with syntheses in these laboratories, the compound **1** was desired. In an attempt to prepare it the following approach was adopted; however, this gave the epimeric compound **6.**

Addition of slightly more than 1 equiv of methylmagnesium iodide to the lactone **2**,[1] obtained by Baeyer–Villiger oxidation of adamantanone, gave a monoadduct in 80% yield. The infrared spectrum showed absorptions at 3370 and 1720 cm^{-1} consistent with the structural formula **3.** The nmr spectrum was more consistent with a mixture of **3** and the cyclic hemiacetal **4** (in the ratio 1:4). Attempts to



1, $R_1 = R_3 = H$; $R_2 = CH_3C{=}CH_2$
2
3, $R_1 = R_3 = H$; $R_2 = COCH_3$
6, $R_1 = R_2 = H$; $R_3 = CH_3C{=}CH_2$
7, $R_1 = R_2 = H$; $R_3 = COCH_3$
8, $R_1 = R_3 = COCH_3$; $R_2 = H$
9, $R_1 = COCH_3$, $R_2 = H$; $R_3 = CH_3C{=}CH_2$

4 **5**

acetylate or benzoylate this product in pyridine gave a mixture of unchanged starting material and a liquid product in both cases. The spectral properties of the new product were consistent with the structure **5:** ν_{max} 1650 cm^{-1} (enol ether); nmr (CCl_4) δ 4.62 (methylene group).

A Wittig reaction[2] on the ketol **3** using methylenetriphenylphosphorane in ether was incomplete even after 48 hr. However, a compound having spectral properties consistent with the structure **1** could be isolated in 60% yield: ν_{max} 3350, 3080, 1640, and 885 cm^{-1}; nmr (CCl_4) δ 4.66 (methylene protons), 3.95 (proton next to oxygen), 3.14 (hydroxylic proton), and 1.68 (vinylic methyl group).

Because of the sluggishness of the Wittig reaction, epimerization at the center C_7 in the ketol **3** may have occurred prior to reaction. Therefore doubt existed as to whether the compound formed had structure **1** or structure **6.** The configuration of the isopropenyl side chain was established in the following manner.

Equilibration[3] of the ketol **3** with sodium methoxide in methanol gave a mixture of epimers in approximately a 1:1 ratio which could be separated by preparative tlc. The compound of lower R_f was the new epimer **7** which was readily converted to the acetate **8.** Moreover, the Wittig reaction on the ketol **7** was complete in less than 15 hr and gave a compound identical in all respects with that prepared from the ketol **3.** Furthermore, this compound from the Wittig reactions was converted to its acetate **9** and the double bond in the molecule was cleaved by ozonolysis to give a compound which was identical by melting point and mixture melting point to the compound **8** prepared above. This establishes that the product of each Wittig reaction is the compound **6,** the C_7 epimer of compound **1.**

Experimental Section

General Melting points were recorded on a Kofler hot stage and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 337 spectrophotometer. Nmr spectra were recorded on a Varian T-60 spectrometer using TMS as an internal standard. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6D spectrometer. Elemental analyses were performed by the Australian Microanalytical Service, Melbourne. All preparative tlc plates were prepared from 50% Kieselgel G and 50% HF 254 applied to the glass plates as a suspension in water, and activated at 120°.

endo-**7-Acetyl-***endo*-**3-hydroxybicyclo[3.3.1]nonane (3).** Methylmagnesium iodide (6 ml, 2.33 *M*, 0.013 mol) was added slowly under nitrogen to a stirred solution of the lactone **2** (1.8 g, 0.01 mol) in ether (20 ml) and after the addition stirring was continued for a further 2 hr at 20°. The mixture was cooled, treated with saturated ammonium chloride solution (10 ml), and extracted

with ether (3 × 15 ml). The combined ethereal extracts were washed with water (2 × 20 ml), dried (Na_2SO_4), and evaporated to dryness to afford a white, crystalline solid. Purification by preparative tlc gave the compound **3** (1.8 g, 85%): mp 100–101°; ν_{max} (Nujol) (3370, 1720 cm^{-1}; nmr (CCl_4) δ 4.36 (br), 4.06 (br) (total 1 H) in ratio 1:4, 3.18 (br, exchangeable, 1 H, OH), 1.45 [s, *ca.* 2.5 H, $OC(CH_3)OH$] superimposed on 2.8–1.0 (complex, methylene envelope) (ratio of 4.06 to 1.45, 1:3); *m/e* 164 ($M^+ - H_2O$). *Anal.* Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.94. Found: C, 72.32; H, 9.68.

The ketol **3** (70 mg, 0.39 mmol) was stirred with acetic anhydride (0.5 ml) and pyridine (1 ml) for 15 hr under nitrogen. Water (5 ml) was added to the reaction mixture and the resulting solution was extracted with ether (3 × 8 ml). The combined ethereal extracts were washed with HCl (10%, 4 × 5 ml), water (5 ml), and saturated sodium bicarbonate (2 × 5 ml), dried (Na_2SO_4), and evaporated to give a colorless liquid (40 mg, 57%) with the probable structure **5**: ν_{max} (film) 1650 cm^{-1}; nmr δ 4.62 (2 H, s, $C{=}CH_2$), 4.28 (1 H, s, HCOC), and 1.0–2.3 (13 H, complex, methylene envelope).

***endo*-3-Hydroxy-*exo*-7-isopropenylbicyclo[3.3.1]nonane (6) and Its Acetate (9). A.** A suspension of methyltriphenylphosphoniumiodide (1.3 g, 3.3 mmol) and potassium *tert*-butoxide (0.34 g, 3.0 mmol) in anhydrous ether (10 ml) was stirred at 18° under nitrogen for 1 hr. A solution of the ketol **3** (0.18 g, 1 mmol) in dry ether (10 ml) was added and the ethereal layer was separated. The aqueous layer was extracted with ether (2 × 15 ml) and the combined ethereal extracts were dried (Na_2SO_4) and evaporated to leave a pale yellow oil. The crude product was purified by preparative tlc (70% ether–petroleum ether). The band of lower R_f afforded a white, crystalline solid (0.11 g, 58%): mp 34–35°; ν_{max} (Nujol) 3350, 3080, 1640, and 885 cm^{-1}; nmr (CCl_4) δ 4.66 (2 H, s, $C{=}CH_2$), 3.95 (1 H, m, HCOH), 3.14 (1 H, br, exchangeable, OH), 1.68 (3 H, s, $CH_3C{=}C$) superimposed on 1.0–2.2 (13 H, complex, methylene envelope); *m/e* 180 (M^+). *Anal.* Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.83; H, 11.16. The material of higher R_f showed identical R_f and spectral data with the starting material.

B. A solution of the Ketol **7** (0.18 g, 1 mmol) in dry ether (10 ml) was added to the Wittig reagent prepared as in part A and the mixture was stirred for 15 hr, at which time tlc showed that no starting material was present. Water (50 ml) was added and the ethereal layer was separated. The aqueous layer was extracted with ether and the combined ethereal extracts were dried (Na_2SO_4) and evaporated to leave a pale yellow oil. Purification by preparative tlc (70% ether–petroleum ether) afforded a white, crystalline solid (0.15 g, 84%), mp 35–37°. This compound had identical spectral properties with those of that prepared in part A. The mixture melting point with the compound from part A was 35–37°. Acetylation of compound **6** with acetic anhydride in pyridine for 15 hr at 20° gave the compound **9** (74%): mp 58–59°; ν_{max} (Nujol) 3080, 1730, 1640, 1235, 1020 cm^{-1}; nmr (CCl_4) δ 4.89 (1 H, m, HCOCO), 4.68 (2 H, s, $C{=}CH_2$), 1.92 (3 H, s, CH_3COO), and 1.71 (3 H, s, $CH_3C{=}C$) superimposed on 1.0–2.3 (13 H, complex, methylene envelope); *m/e* 162 ($M^+ - AcOH$).

***exo*-7-Acetyl-*endo*-3-hydroxybicyclo[3.3.1]nonane (7) and Its Acetate** (8). The ketol **3** (100 mg, 0.55 mmol) was added under nitrogen to a stirred solution of sodium methoxide in dry methanol (15 ml) (from 2 g of sodium) and stirring was continued for 16 hr at 18°. The reaction mixture was poured into water (40 ml) and extracted with ether (3 × 15 ml). The combined ethereal extracts were dried (Na_2SO_4) and evaporated to give a colorless oil. The crude material was purified by preparative tlc plate (20% ether–chloroform). Starting material (49 mg, 55%) was recovered and the ketol **7** (lower R_f) was isolated (40 mg, 45%): mp 69–71°; ν_{max} (Nujol) 3420, 1690, 1060, 1020 cm^{-1}; nmr (CCl_4) δ 4.05 (1 H, m, HCOH), 3.28 (1 H, br, exchangeable, OH), 2.14 (3 H, s, CH_3CO) superimposed on 1.0–2.5 (13 H, complex, methylene envelope); *m/e* 164 ($M^+ - H_2O$). *Anal.* Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.94. Found: C, 72.29; H, 9.90.

Acetylation of the product with acetic anhydride in pyridine for 15 hr at 20° gave compound **8** (82%): mp 36–37°; ν_{max} (Nujol) 1730, 1700, 1230, 1010 cm^{-1}; nmr (CCl_4) δ 5.05 (1 H, m, CHOCO), 2.12 (3 H, s, CH_3COO), and 2.04 (3 H, s, CH_3CO) superimposed on 1.1–2.2 (13 H, complex, methylene envelope); *m/e* 164 ($M^+ - AcOH$). *Anal.* Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 70.03; H, 9.22.

Ozonolysis of the Olefin 9. The vinyl acetate **9** (40 mg, 0.18 mmol) in methanol (2 ml) was cooled to −78° (Dry Ice–acetone bath) and treated with ozone (*ca.* 3%, 600 ml/min) for 30 min. The reaction mixture was then poured with stirring into a solution (cooled in a Dry Ice–acetone bath) of methanol (10 ml), acetic acid (3 ml), and sodium iodide (4.8 g). The solution was extracted with ether (2 × 10 ml) and the combined ethereal extracts were washed with 10% sodium thiosulfate solution (2 × 10 ml), saturated sodium bicarbonate (2 × 10 ml), and water (2 × 10 ml). The ether extract was dried (Na_2SO_4) and evaporated to give a colorless oil which crystallized on trituration with ether. Recrystallization from ether–petroleum ether gave a white, crystalline product (33 mg, 82%), mp 37–39°. The mixture melting point with compound **8** was 36–37°.

Registry No.—**2**, 21898-84-0; **3**, 51911-60-5; **5**, 51911-61-6; **6**, 51911-62-7; **7**, 51922-41-9; **8**, 51911-63-8; **9**, 51911-64-9.

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(3) Compound **7** on treatment with sodium methoxide in methanol gave the same approximate ratio of products. This product ratio thus represents the end point of a complex series of equilibria in which presumably the hemiacetal **4** plays an important role. It should be noted that, in the diagrams of the bicyclic structures above, no conformational preference is implied.

Condensation of Cyclic Nitrones with 3,5-Dicarbomethoxypyridinium Tosylate

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Received April 5, 1974

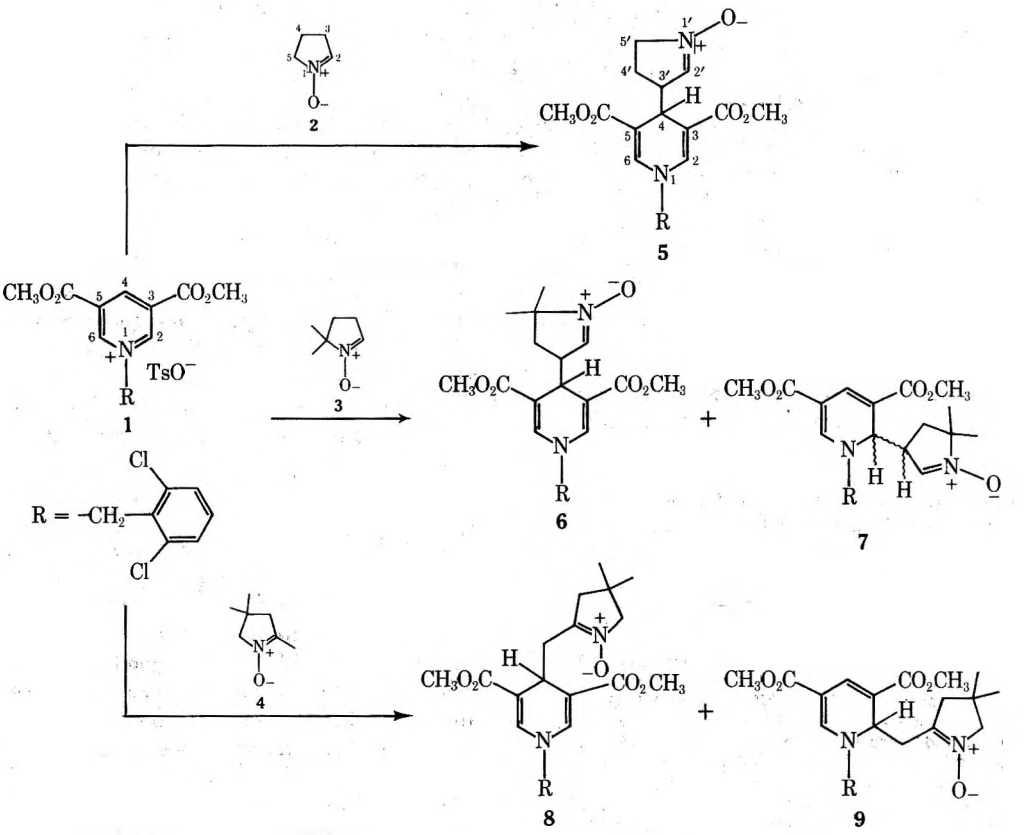
While a wide variety of nucleophiles will condense with pyridinium salts,[1] there are relatively few reported examples of condensations involving carbon nucleophiles which form stable dihydropyridines.[1,2] Since nucleophilic attack by carbon nucleophiles leads to the formation of new carbon–carbon bonds, these reactions are of potential synthetic utility. We would like to report an unusually facile condensation between the pyridinium nucleus and cyclic nitrones.

A single product **5** was formed when the pyridinium salt **1** was allowed to stand for 2 days at room temperature in an excess of the nitrone **2** (Scheme I). Spectroscopic data indicated that **5** was a 1,4-dihydropyridine formed through the condensation between **1** and **2** with the loss of toluenesulfonic acid: mass spectrum *m/e* 438 (M^+); nmr δ 4.20 ppm (1 H, doublet, J = 3 Hz, proton at C_4 in the dihydropyridine nucleus); λ_{max} (MeOH) 220 nm (ϵ 30,900), 265 (15,100), and 353 (8750).[1,3] These data, when interpreted within the framework of known nitrone chemistry,[4] suggest that the position of attachment to the nitrone ring is at the 3′-carbon atom rather than the 5′-carbon atom, which cannot be excluded on the basis of the spectroscopic data alone.

Support for this structure assignment was provided by the condensation between 5,5-dimethyl-Δ^1-pyrroline 1-oxide (**3**) and **1**. This reaction afforded a mixture of dihydropyridine isomers. The major isomer was the crystalline 1,4-dihydropyridine **6** which was analogous to **5**. **6** had mass spectrum *m/e* 466 (M^+); nmr δ 4.20 ppm (1 H, doublet, J = 3 Hz); λ_{max} (MeOH) 223 nm (ϵ 32,300), 250 sh (14,300), and 358 (7430). The minor component was an oil that appeared to be a mixture of the 1,2-dihydropyridine diastereomers **7** which could not be resolved even after extensive chromatography.

The condensation of **1** with nitrone **4** also yielded both the 1,4- (**8**) and the 1,2-dihydropyridines (**9**). In this case

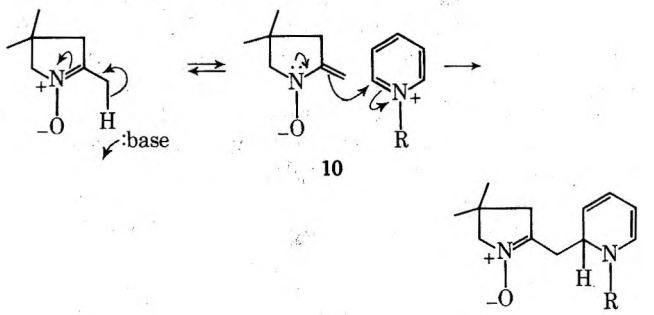
Scheme I



reaction took place at the 2-methyl group rather than the 3 position of the pyrroline ring of **4**. Thus, only a single 1,2-dihydropyridine was formed, since only one asymmetric center is generated in the condensation.

These condensations most probably proceed through the nitrone anion **10** (Scheme II).[4] Since no external base is required, the nitrone itself must serve in this capacity.

Scheme II



Experimental Section

Melting points were determined with a Mettler FP2 melting point apparatus. Spectroscopic studies were conducted with the following instruments: mass spectra, Hitachi Perkin-Elmer RMU-7; uv-visible, Cary 14; ir, Perkin-Elmer 337; nmr spectra, a Brüker HFX-90 and a Varian T-60. Proton assignments were made on the basis of decoupling experiments. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Preparation of the Dihydropyridines. General Procedure. The pyridinium salt **1**[5] was dissolved in an excess of the neat nitrone (1:3 molar ratio) and the homogeneous mixture was allowed to stand at room temperature for 2 days. The resulting homogeneous, viscous, yellow-brown oil was dissolved in chloroform and resolved by chromatography on thick layer plates (Brinkmann $PF_{254+366}$ silica gel) developed with chloroform–methanol.

The dihydropyridines were recrystallized from chloroform–ether to afford pale yellow crystals in the case of the 1,4 isomers and bright yellow crystals in the case of the 1,2 isomer.

1-(2,6-Dichlorobenzyl)-3,5-dicarbomethoxy-4-[3′-(Δ¹′-pyrrolinyl 1′-oxide)]-1,4-dihydropyridine (5). Condensation of **1** and **2**[6] afforded **5** in 53% yield (149 mg): mp 176.3–176.4°; ir ($CHCl_3$) 2920, 1700, 1570, 1420, 1400, 1225, 1200, 1160, 1085 cm^{-1}; λ_{max} (MeOH) 220 nm (ϵ 30,900), 265 (15,100), and 353 (8570); nmr ($CDCl_3$) δ 1.94 (m, 2 H), 3.16 (br, 1 H), 3.73 (m, 2 H), 3.73 (s, 6 H), 4.20 (d, J = 3 Hz, 1 H), 4.90 (s, 2 H), 6.73 (m, 1 H), 7.48 ppm (m, 5 H); mass spectrum m/e M^+ 438, base 354.

Anal. Calcd for $C_{20}H_{20}N_2O_5Cl_2$: C, 54.68; H, 4.59; N, 6.38; Cl, 16.14. Found: C, 54.44; H, 4.86; N, 6.29; Cl, 16.25.

1-(2,6-Dichlorobenzyl)-3,5-dicarbomethoxy-4-[3′-(5′,5′-dimethyl-Δ¹′-pyrrolinyl 1′-oxide)]-1,4-dihydropyridine (6). Condensation of **1** and **3**[7] afforded a mixture of dihydropyridine isomers which could be partially resolved in one elution with chloroform–methanol (90:10). The material derived from the more polar colorless band was **6**: 15% yield (32 mg); mp 162.5–162.8°; ir ($CHCl_3$) 2930, 1700, 1570, 1430, 1400, 1230, 1197, 1163, 1085 cm^{-1}; λ_{max} (MeOH) 223 nm (ϵ 32,300), 250 sh (14,300), and 358 (7430); nmr ($CDCl_3$) δ 1.17 (s, 3 H), 1.23 (s, 3 H), 1.57 (d, J = 3 Hz, 1 H), 1.83 (d, J = 6 Hz, 1 H), 3.03 (b, 1 H), 3.73 (s, 6 H), 4.20 (d, J = 3 Hz, 1 H), 4.83 (s, 2 H), 6.60 (d, J = 3 Hz, 1 H), 7.33 (s, 2 H), 7.40 ppm (m, 3 H); mass spectrum, m/e M^+ 466, base 354.

Anal. Calcd for $C_{22}H_{24}N_2O_5Cl_2$: C, 56.54; H, 5.18; N, 5.99. Found: C, 56.80; H, 5.32; N, 5.92.

An oily mixture of diastereomers **7** was obtained from the less polar yellow band immediately above the band due to **6**. That the material isolated from this band was probably a mixture of the 1,2-dihydropyridine diastereomers **7** was indicated by the chromatographic behavior (*vide infra*) and the nmr spectrum, which exhibited four methyl singlets centered at δ 1.30 ppm and two overlapping benzyl AB patterns centered at δ 4.90 ppm. Both of these nmr features must arise from the proximity of chiral centers such as those present in **7**. Unfortunately, extensive thick layer chromatography failed to separate this oil into its constituents.

4-[1-(2,6-Dichlorobenzyl)-3,5-dicarbomethoxy-1,4-dihydropyridyl]-2′-[4′,4′-dimethyl-Δ¹′-pyrrolinyl 1′-oxide]methane (8) and 2-[1-(2,6-Dichlorobenzyl-3,5-dicarbomethoxy-1,2-dihydropyridyl]-2′-[4′,4′-dimethyl-Δ¹′-pyrrolinyl 1′-oxide] methane (9). Condensation of **1** and **4**[7] afforded a mixture of dihydropyridine isomers which could be resolved in two elutions with chloroform–methanol (93:7). The material derived from the more polar, colorless band was **8**: 16% yield (100 mg); mp 135.5–136.0°; ir ($CHCl_3$) 2930, 1700, 1575, 1430, 1400, 1230, 1160, 1079 cm^{-1}; λ_{max}

(MeOH) 221 nm (ε 27,700), 260 (9530), and 361 (9190); nmr ($CDCl_3$) δ 1.17 (s, 6 H), 2.60 (d, J = 5 Hz, 2 H), 2.65 (s, 2 H), 3.63 (s, 2 H), 3.73 (s, 6 H), 4.03 (t, J = 5 Hz, 1 H), 4.83 (s, 2 H), 7.33 ppm (m, 5 H); mass spectrum m/e M^+ 480, base 354.

Anal. Calcd for $C_{23}H_{26}N_2O_5Cl_2$: C, 57.39; H, 5.44; N, 5.82; Cl, 14.73. Found: C, 57.44; H, 5.16; N, 5.78; Cl, 14.84.

The less polar, yellow band immediately above the band due to 8 provided **9**: 37% yield (202 mg); mp 175.5–175.6°; ir ($CHCl_3$) 2935, 1675, 1620, 1535, 1425, 1228, 1143 cm^{-1}; λ_{max} (MeOH) 223 nm (ε 32,400), 274 (13,800), and 380 (8420); nmr ($CDCl_3$) δ 1.10 (s, 3 H), 1.17 (s, 3 H), 2.50 (m, 2 H), 3.27 (br d, J = 5 Hz, 1 H), 3.50 (br d, J = 5 Hz, 1 H), 3.67 (s, 2 H), 3.73 (s, 6 H), 4.97 (m, 1 H), 5.09 (d, J = 7.5 Hz, 1 H), 5.45 (d, J = 7.5 Hz, 1 H), 7.37 (m, 3 H), 7.67 ppm (m, 2 H); mass spectrum m/e M^+ 480, base 354.

Anal. Calcd for $C_{23}H_{26}N_2O_5Cl_2$: C, 57.39; H, 5.44; N, 5.82; Cl, 14.73. Found: C, 57.48; H, 5.11; N, 5.79; Cl, 14.86.

Acknowledgment. This research was supported by a Grant (GM 17267) from the National Institutes of Health, U. S. Public Health Service.

Registry No.—**1**, 51898-97-6; **2**, 24423-88-9; **3**, 3317-61-1; **4**, 6931-11-9; **5**, 51849-12-8; **6**, 51849-13-9; **8**, 51849-14-0; **9**, 51849-15-1.

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Structural Analysis by Lanthanide-Induced Shifts. V.[1] Influence of Steric and Conjugative Effects on the Barriers to Rotation in *N,N*-Dimethylamides

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Received January 23, 1974

Dynamic nuclear magnetic resonance (dnmr) is one of the most powerful tools for the evaluation of rate constants and of the free-energy barriers to rotation (ΔG^*),[2] and the relative simplicity of this technique encourages a systematic search in order to assess the relative merits of steric and conjugative effects on the barriers to internal rotation in *N,N*-dimethylamides.[3-7]

However, this task is somewhat hampered by the necessity of using different solvents in dnmr work, in order to overcome solubility problems and the accidental isochrony of signals in a given solvent. Solvent effects on the barrier height are in fact of an order of magnitude comparable to steric or conjugative effects.[7]

The latter difficulty represented a serious problem also in our case since, in our hands, several of the amides studied by us yielded $CDCl_3$ spectra unsuitable for the measurement of ΔG^* at the coalescence point.

The use of lanthanide shift reagents (LSR) to simplify the amide spectra[8,9] offers a convenient way to avoid uncertainties caused by comparing data obtained in different solvents. Our results, in agreement with those of other authors,[10,11] show that the use of $Eu(fod)_3$ at low shift reagent/substrate molar ratios does not affect sensibly the ΔG^*. This fact allowed us to measure the ΔG^* of a series of structurally related *N,N*-dimethylamides in the same solvent ($CDCl_3$), even if some of the compounds studied exhibited accidental isochronous methyl signals in the undoped spectra.

The resulting set of immediately comparable data has provided detailed information on the relative strength of conjugative effects of some unsaturated amides. For instance, it can be inferred that the conjugative power of the phenyl group is intermediate between that of furan and thiophene, and that the vinyl and cyclopropyl groups are about as "strong" as furan. Furthermore, in some cases, differences in ΔG^* could be attributed to finer conformational effects.

Results

In Tables I and II are reported the results of our measurements, performed on two series of structurally related amides and diamides.

For some compounds in Table I, our ΔG^* estimates in the absence of LSR are in good agreement with data already available in the literature (references in the last column in Table I). The addition of $Eu(fod)_3$ at low shift reagent/substrate molar ratios does not affect sensibly the ΔG^*, but it does increase the separation of the diastereotopic *N*-methyl signals.

The advantage of performing coalescence measurements on peaks well resolved at low temperature is obvious. However, although the peak separation may be varied at will by increasing the amount of LSR, in our experience the optimal separation ranges between 15 and 60 Hz, corresponding to a molar ratio $Eu(fod)_3$/amide of *ca.* 0.1–0.2. Higher separations cause expand of uncertainties in the T_c estimates.

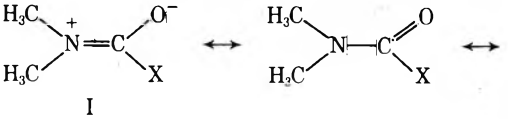
Despite the experimental evidence produced here that, in several cases, measurements of barriers with and without the LSR produces sensibly the same result, *it cannot be inferred that the LSR does not affect the barrier to rotation in the complexed substrate.* In fact, quite recently, in the case of trimethyl carbamate,[11] experiments performed at increasing shift reagent/substrate molar ratios have shown that the observed rate constant is the weighted average for isomerization of free and complexed substrate and, by extrapolation, it was possible to estimate the ΔG^* for both processes (the free-energy difference is about 2.5 kcal/mol.[11]

Of course, using *low* shift reagent/substrate molar ratios, only a small amount of complex is formed (most of the amide being present in the free state), so that our findings seem quite reasonable.

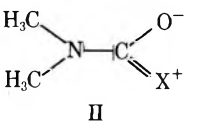
Discussion

Structural effects on the barrier to internal rotation in amides have been acknowledged in the recent literature.[3-7]

Considering the resonance structures I and II as possible contributors to the planar ground state of *N,N*-dimethyl-

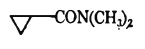
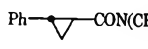
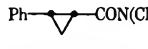
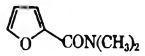
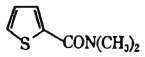
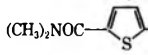


I



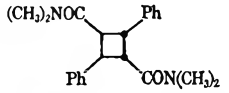
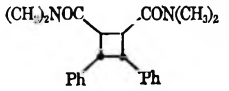
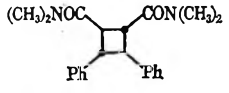
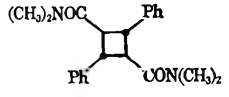
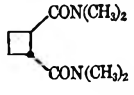
II

Table I
Barrier Heights to Site Exchange in Various *N,N*-Dimethylamides Measured in the Presence or Absence of Eu(fod)$_3$

	Compd	Registry no.	Molar ratio of Eu(fod)$_3$ to amide	$\Delta\nu$, Hz	ΔG^{*},[a] kcal mol^{-1}	T_c, °C	Ref[b]
1	$CH_3CON(CH_3)_2$	127-19-5	0	6.0	18.4	71	3, 7, 8
			0.08	18.5	18.3	83	
2	$CH_2{=}CHCON(CH_3)_2$	2680-03-7	0	[c]			
			0.10	40.0	16.9	65.5	
3	$PhCH{=}CHCON(CH_3)_2$	13156-74-6	0	[c]			5b, 5c, 6
			0.16	56.8	16.5	63	
4	$CH_2{=}C(CH_3)CON(CH_3)_2$	6976-91-6	0	4.5	15.6	16.5	
			0.09	31.0	15.8	41	
5		17696-23-0	0	[c]			5d
			0.10	27.0	16.6	54.5	
6		35682-53-2	0	6.0			5d
			0.21	61.5	17.0	73	
7		5279-83-4	0	13.0	16.6	47	5d
			0.12	16.0	17.1	58	
8	$PhCON(CH_3)_2$	611-74-5	0	7.8	15.8	26	4, 5a, 5b,
			0.13	59.5	15.9	51	5c
9	$(o\text{-}CH_3)PhCON(CH_3)_2$	6639-19-6	0	18.0	18.0	76	
			0.12	55.0	17.8	87.5	
10		13156-75-7	0	[c]			
			0.13	42.5	16.8	26	
11		30717-57-8	0	[c]			
			0.15	41.5	14.1	12	
12		51869-10-4	0	[c]			
			0.18	45.5	14.3	17.5	
13	$(CH_3)_2NOCCH{=}CHCON(CH_3)_2$ trans	17878-64-7	0	6.0	17.8	63	
			0.12	13.8	17.7	68.5	
14	$(CH_3)_2NOCCH{=}CH$ trans $(CH_3)_2NOC{-}CH{=}CH$ trans	51869-47-7	0	[c]			
			0.14	30.5	16.8	60	

[a] ΔG^{*} measured at T_c. [b] References leading to ΔG^{*} data from other authors (determined in absence of LSR). [c] Accidental isochronous signals, in the experimental conditions (see Experimental Section).

Table II
Barrier Heights for Some Cyclobutanedicarboxamides Measured in the Presence or Absence of Eu(fod)$_3$

	Compd	Registry no.	Molar ratio of Eu(fod)$_3$ to amide	$\Delta\nu$, Hz	ΔG^{*},[a] kcal mol^{-1}	T_c, °C
1		51869-48-8	0	2.0		
			0.20	12.0	19.2	93
2		51869-49-9	0	7.5	17.5	57
			0.25	17.7	17.6	69
3		51898-47-6	0	9.5	18.7	82
			0.23	30.5	18.5	94
4		51898-48-7	0	21.0	17.4	68
			0.18	51.0	17.5	81
5		51936-10-8	0	4.5	18.5	68
			0.12	20.5	18.2	82

[a] ΔG^{*} measured at T_c.

amides and assuming the transition state to be one in which the –COX moiety has been twisted out of planarity by 90°, the magnitude of the torsional barrier will depend on the relative weight of structures I and II, respectively.

In fact, when X is an aliphatic group, structure I contributes to a high degree to the above resonating systems and the partial double-bond character of the ground state will therefore result increased. On the other side, when X is a strong electron-donating group, structure II becomes more important and the partial double-bond character of the ground state will be reduced.

The measured torsional barrier will therefore reflect the

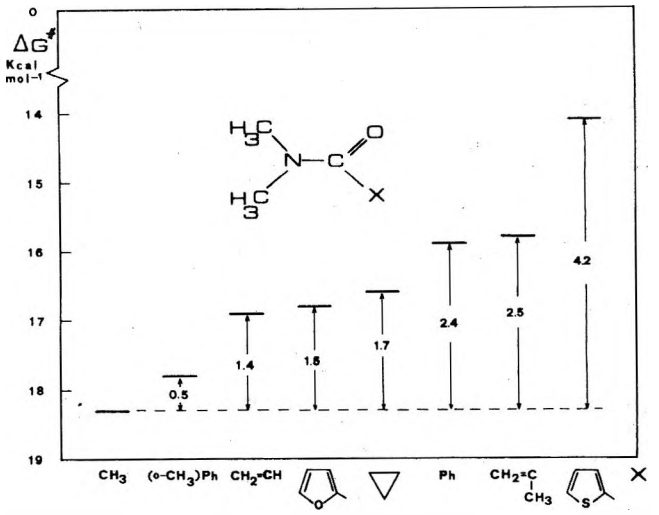


Figure 1. Energy barriers to internal rotation for some *N,N*-dimethylamides (see text for discussion).

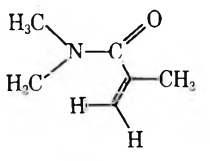
relative contributions of structures I and II in the resonating system.

Within this theoretical framework, the diagram in Figure 1 serves well to illustrate some of the salient features coming from the analysis of the ΔG^* data in Table I. Since the highest torsional barrier is that of DMA (X = CH_3), one can assume that the energy barrier lowering in the remaining compounds is a measure of the ability of a specific substituent to interact with the amide carbonyl group (conjugative power).

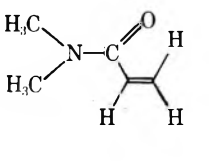
In fact, the energy differences observed (Figure 1) for the various substituents are in close correspondence with their relative *conjugative power*, as it can be deduced from the general qualitative picture coming from studies with different techniques.

Furthermore, an interesting effect is observed in aromatic amides (compounds 8–12, Table I). The conjugative power of the phenyl group is found to be intermediate between that of furan and thiophene, while in compound 9 (where the ortho methyl group hinders the molecular planarity) the ΔG^* rises almost to the level of DMA. It has to be noted that these observations could not be done working in absence of LSR, since both furan and thiophene amides yield accidental isochronous methyl signals in $CDCl_3$ (Table I).

Finally, data in Table I and Figure 1 indicate that α-methyl substitution lowers the ΔG^* in compound 4 with respect to compound 2. This effect may be ascribed to the different conformational preference adopted by these two molecules. Compound 4 was reported to adopt predominantly the s-trans form[12,13] (III); in contradistinction compound 2 exists predominantly in the s-cis conformation[12,13] (IV).



III



IV

Therefore, the ΔG^* difference observed should reflect the relative conjugative power of the two forms, and the s-trans conformation is known[14] to be favored in this respect.

Data in Table II further illustrate the reliability of the ΔG^* estimates in the presence of LSR, and also disclose a small but definite ΔG^* difference between cyclobutane cis diamides (compounds 2 and 4, Table II) and the corresponding trans diamides (compounds 1, 3, and 5, Table II).

This difference is possibly due to some steric hindrance and/or induced local field effects of the two amide groups in the cis position.

Experimental Section

Spectra. The ^1H nmr spectra were recorded on a Varian A-60D spectrometer equipped with variable-temperature accessories. Temperature measurements were based on the chemical shift separation of the protons of an ethylene glycol or methanol sample, and utilized the temperature-shift correlation of Van Geet.[15] T_c values in Tables I and II represent the average of several measurements.[16] The Gutowsky–Holm[16] approximation was used in order to calculate the rate constants for the site exchange; these rates were employed to derive the free energies of activation (ΔG^*) from the Eyring equation, at the coalescence temperature. The estimated error in the ΔG^* values reported is ±0.2 kcal/mol based almost exclusively on uncertainties in T_c.

$Eu(fod)_3$ was added from a stock solution (0.32 *M*) with the help of a 50-μl microsyringe to a ~5% $CDCl_3$ solutions of amide (TMS as internal reference).

Synthetic. *N,N*-Dimethylacetamide (compound 1, Table I) was a commercial product (Aldrich) and was distilled under reduced pressure before use. The following amides were prepared according to the interfacial condensation procedure described below and characterized according to the literature: amides 2,[17] 3,[18] 4,[19] 5,[20] 6,[21] 7,[5d] 8,[18] 9,[22] 10,[23] 11,[24] and 13[25] in Table I and amide 3 in Table II.[26] The amides 12 and 14 in Table I and 1, 2, 4, and 5 in Table II were hitherto unreported and in Table III are summarized their physical and chemical characteristics.

Table III
Physical and Chemical Characteristics of Some Diamides[a]

Compd	Mp, °C	Recrystn solvent	Formula
12[b]	125–126	Acetone	$C_{10}H_{14}N_2O_2S$
14[b]	224–225	Ethanol–water	$C_{10}H_{16}N_2O_2$
1	204–205	Benzene	$C_{22}H_{26}N_2O_2$
2[c]	158–159	Benzene	$C_{22}H_{26}N_2O_2$
4[c]	109–110	Hexane–benzene	$C_{22}H_{26}N_2O_2$
5[c]	85–86	Petroleum ether	$C_{10}H_{18}N_2O_2$

[a] Satisfactory analytical values (±0.3% for C, H, N) were reported for all compounds in table: Ed. [b] See Table I. [c] See Table II.

A 0.01-mol portion of acid chloride[27] dissolved in dry ether or benzene and 0.01 mol of dimethylamine hydrochloride (Aldrich) dissolved in water were mixed under stirring in a blender jar. While the mixture was rapidly stirred, a solution of 0.02 mol of sodium hydroxide in water was added dropwise. The temperature was then raised for 30 min. The reaction mixture was poured onto crushed ice, and the organic layer was extracted with chloroform. The solvent was removed under reduced pressure and the crude product was distilled under vacuum or recrystallized from opportune solvent and vacuum dried (see Table III).

Registry No.—$Eu(fod)_3$, 17631-68-4.

References and Notes

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(27) All the acid chlorides were prepared from the corresponding acids by treatment with thionyl chloride and their characteristics were coincident with those reported in the literature.

Hydrogen Bonding. III. Tetrapropylammonium Hydrogen Difluoride and the Thermal Elimination Reaction of Tetrapropylammonium Fluoride Hydrates[1]

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Received February 5, 1974

Results

In the course of studies of strongly hydrogen bonded water–anion species in tetraalkylammonium ion salt hydrates[2] we have prepared the lower hydrates of tetrapropylammonium fluoride. Removal of water from an aqueous solution of the fluoride at minimum temperatures with prolonged drying *in vacuo* gives successively the hexa-, tri-, and dihydrates; these substances are low-melting white solids which exist as crystalline slushes at room temperature. Additional water cannot be removed from the dihydrate without a concurrent Hofmann-type elimination reaction occurring.

Miller, Fried, and Goldwhite[3] have suggested that fluoride ion may function as a base in the Hofmann elimination from the observation that some ethylene, triethylamine, and residual acid are formed on extended drying of tetraethylammonium fluoride; this appears to be the only report[4] of fluoride ion functioning in this manner. We find that rapid heating of the tetrapropylammonium fluoride tri- or dihydrates to 140° *in vacuo* results in a smooth and quantitative conversion to propene, tripropylamine, and tetrapropylammonium hydrogen difluoride.

$$2(C_3H_7)_4N^+F^-\cdot 2H_2O \rightleftharpoons (C_3H_7)_3N + C_3H_6 + (C_3H_7)_4N^+HF_2^- + 4H_2O \quad (1)$$

The apparently anomalous generation of a strong acid and a fairly strong base from a neutral substance, that is, the formation of the hydrogen difluoride and tripropylamine instead of tripropylammonium fluoride, is not unexpected in light of our observations[5] on *p*-toluidinium fluoride, which is also thermodynamically unstable relative to the hydrogen difluoride and free amine. The formation of the strongly hydrogen bonded hydrogen difluoride anion provides the driving force to shift these equilibria.

Experimental Section

Eastman Kodak White Label 10% tetrapropylammonium hydroxide solution and Baker reagent grade 48% hydrofluoric acid were used as supplied. Fluoride was determined by precipitation as PbClF. Infrared spectra were recorded on a Beckman IR-12 using NaCl and Nujol mulls. The hydrates were handled under dry nitrogen at all times; polyethylene labware was used in all reactions.

Hydrates of Tetrapropylammonium Fluoride. A. Hexahydrate. A solution of tetrapropylammonium hydroxide (1.031 g, 5.07 mmol) in water (10 ml) was brought to pH 7.00 by addition of hydrofluoric acid. The solvent water was removed *in vacuo* with a rotary evaporator at room temperature for 28 hr. This afforded a white, low-melting (about 30°) crystalline mass containing a quantity of water (0.549 g, 30.5 mmol) corresponding to 6.01 mol of water for each mole of tetrapropylammonium fluoride.

B. Dihydrate. Additional heating of the hexahydrate sample from A *in vacuo* at 55° for 24 hr reduced the water content to 3.64 mol of water per mole of salt. The sample was then heated *in vacuo* at 80° for 1 hr to give a white, semicrystalline slush containing a quantity of water (0.190 g, 10.5 mmol) corresponding to 2.08 mol of water for each mole of tetrapropylammonium fluoride. Titration with base showed a negligible amount of residual acid.

C. Trihydrate. A solution of tetrapropylammonium fluoride (1.036 g, 5.07 mmol) in water (about 15 ml) was prepared exactly as in A. The solvent water was removed *in vacuo* with a rotary evaporator at room temperature for 24 hr, and then the resulting hexahydrate was heated *in vacuo* at 35° for 60 hr. This afforded a white, semicrystalline slush containing a quantity of water (0.273 g, 15.1 mmol) corresponding to 2.99 mol of water for each mole of tetrapropylammonium fluoride.

Elimination Reaction of Tetrapropylammonium Fluoride. A flask containing a crystalline slush of tetrapropylammonium fluoride (1.507 g, 7.329 mmol) and water (0.477 g, 26.5 mmol), which had been prepared as in B above, was connected to a Dry Ice cooled trap fitted with inlet and outlet stopcocks and a fitting to attach an infrared gas cell. The flask was heated rapidly to about 140°, at which point a vigorous decomposition set in. In a few minutes the slush had changed to a hard, white, crystalline mass, with obvious evolution of gas. The flask was found to contain a 99.0% yield of tetrapropylammonium hydrogen difluoride (0.819 g, 3.63 mmol) as white microcrystals. *Anal.* Calcd fo $C_{12}H_{29}NF_2$: F^-, 16.88; HF, 8.88. Found: F^-, 17.08; HF, 9.10.

The trap was removed from the system and allowed to warm in an ice bath to 0° with the stopcocks closed; it was then opened to an infrared gas cell. The vapor was shown to consist solely of propene, identified by its characteristic infrared spectrum. The trap also contained a mixture of two immiscible liquids with the odor of amine; this strongly basic mixture was rinsed from the trap with water; titration with standard hydrochloric acid showed an 88.75% yield of tripropylamine (0.467 g, 3.253 mmol). In a similar experiment the amine was separated from the water in the trap by use of a fine dropper, and identified by its nmr spectrum: δ ($CHCl_3$) triplet, 2.42, 2.30, 2.18 (area 2); sextuplet 1.75–1.05 (area 2); triplet 0.93, 0.83, 0.72 (area 3).

Identification of the Decomposing Species. A sample of tetrapropylammonium fluoride trihydrate (1.309 g, 5.07 mmol) was connected to the vacuum system with a Dry Ice cooled trap and heated *in vacuo* at 42° for 50 hr. After this time the flask contained 1.127 g of a crystalline slush; the infrared spectrum of this material showed, in addition to cation bands, the characteristic infrared spectra of the dihydrate and the hydrogen difluoride (see Discussion). Titration of the solid with sodium hydroxide showed it to contain a 17.3% yield of tetrapropylammonium hydrogen difluoride (0.098 g, 0.438 mmol).[6] Titration of the amine from the trap showed a 16.5% recovery of tripropylamine (0.60 g, 0.418 mmol). If we assume that the quantity of hydrogen difluoride represents one-half of the tetrapropylammonium ions involved in the decomposition reaction (eq 1) the sample now contains 82.7% of the original cations as tetrapropylammonium fluoride (0.857 g, 4.195 mmol) and by difference a quantity of water (0.172 g, 9.6 mmol) corresponding to 2.2 mol of water per mole of fluoride salt.

Discussion

The hydrates of tetrapropylammonium fluoride are extremely stable species, even though they are not highly

crystalline at room temperature. Although specific measurements were not carried out, the behavior of the materials on drying suggests that only the hexahydrate might have a vapor pressure of water high enough to measure by manometric means at a temperature where the material was crystalline. The formation of strongly bound anion–molecule complexes without concurrent lattice stability has been observed before with the larger tetraalkylammonium ions; thus we found[7] that tetrapropyl- and tetrabutylammonium hydrogen dibromides are extremely tightly bound stoichiometric salts which are liquids at or just above room temperature.

The solid state infrared spectrum of the hexahydrate is typical of those of the clathrate hydrates[2] such as tetramethylammonium hydroxide pentahydrate[8a,9] or fluoride tetrahydrate,[8b,9] and shows, in addition to cation bands, a broad stretching band of hydrogen-bonded water centered at 3300 cm^{-1} and a bending band at 1650 cm^{-1}; no rocking modes of strongly coordinated water are present. The infrared spectrum of the tetrapropylammonium fluoride dihydrate, on the other hand, shows a stretching region for unusually strongly hydrogen-bonded water centered at 2900 cm^{-1}, a bending band at 1630 cm^{-1} which is now nearly as intense as the stretching band, and a broad, strong rocking band stretching from 600 to 1100 cm^{-1}[9]. Thus this dihydrate, like tetramethylammonium fluoride monohydrate and hydroxide monohydrate,[2,9] contains a water–anion moiety in which the water oxygen is apparently tricoordinate and involved in very strong hydrogen bonds.

The symmetrical hydrogen difluoride anion in potassium hydrogen difluoride shows ν_3 (asymmetric stretch) as a broad band at 1450 cm^{-1} and ν_2 (bending) as a fairly sharp single band at 1222 cm^{-1}.[10] The ν_1 (symmetic stretch) mode is not observed under $D_{\infty h}$ symmetry. We have reported [5]that the hydrogen difluoride anion in *p*-toluidinium hydrogen difluoride, which is known[11] to be a linear, unsymmetrical species of $C_{\infty v}$ symmetry, shows ν_3 as a very broad, strong band centered at 1740 cm^{-1}, and ν_2 appears as a pair of bands at 1080 and 1230 cm^{-1} as a result of the lifting of the degeneracy of this band in the asymmetric crystal environment. Subsequently we have found that ν_1 can be observed in this salt, as predicted by theory, as a broad and reasonably intense band centered at 450 cm^{-1}; there is no absorption in this area in the infrared spectrum of *p*-toluidinium hexachlorostannate.

In tetrapropylammonium hydrogen difluoride ν_3 (1900 cm^{-1}) and ν_2 (1255 and 1315 cm^{-1}) resemble the corresponding bands in the *p*-toluidinium salt; however, ν_1 does not appear in the spectrum. The ion thus is presumably still of $D_{\infty h}$ symmetry, since in either $C_{\infty v}$ or C_{2v} ν_1 would be infrared active; however, it lies in a crystal site that lifts the degeneracy of the $\Pi_u\nu_2$ bending mode. Low-temperature infrared studies of this and related hydrogen difluorides are under investigation.

Dehydration of solutions of tetramethylammonium fluoride in water yields a monohydrate; further removal of water can be effected by heating *in vacuo* at 140°.[12] Preparation of the anhydrous fluoride by this method is always accompanied by some decomposition to trimethylamine and methyl fluoride, and the decomposition is complete at higher temperatures.[13] With tetrapropylammonium fluoride it is clear that either there is no monohydrate, or it decomposes at the temperature necessary to remove water from the dihydrate to form it. The solid material which remains after the elimination reaction has been run partially to completion gives an infrared spectrum which is the composite of those of the dihydrate and the hydrogen difluoride, with no new absorptions attributable to a monohydrate, and the matter balance of the reaction shows that there are essentially 2 mol of water remaining for each mole of fluoride salt. Whether proton abstraction by fluoride occurs within the lattice of the dihydrate or in the anhydrous salt left after water is removed cannot be established at this time.

The elimination reaction of quaternary ammonium fluorides would at first appear to have limited synthetic application when compared to that of the hydroxides, since one-half of the starting amine salt is retained as the hydrogen difluoride.[14,15] However, since the fluoride salts could be prepared in neutral solution, such as by reaction of sulfates with barium fluoride or halides with silver fluoride, this process affords a means to achieve, if desirable, the results of a Hofmann elimination reaction without the need to expose a molecule to solution in aqueous base.

Acknowledgments. We wish to acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, the National Science Foundation, and the Biomedical Support Committee of Oakland University for support of this work. Two of us (I. A. G. and S. L. M.) held NSF–URP summer fellowships.

Registry No.—Tetrapropylammonium fluoride hexahydrate, 51934-09-9; tetrapropylammonium fluoride dihydrate, 51934-10-2; tetrapropylammonium fluoride trihydrate, 51934-11-3; tetrapropylammonium fluoride, 7217-93-8; tetrapropylammonium hydrogen difluoride, 52003-47-1.

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On the Products of Hydroboration of 1-Chlorononorbornene

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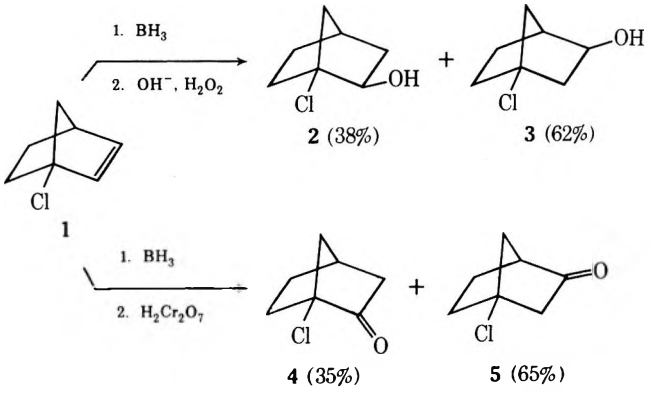
Received January 22, 1974

For the penultimate step in a synthesis of 1-deuterio-*exo*-norborneol, we repeated a procedure by Fry and Farn-

ham for the preparation of 1-chloro-2-*exo*-norbornanol from the hydroboration of 1-chloronorbornene.[1] Fry and Farnham reported that reaction of 1-chloronorbornene (1) with diborane in THF gave a mixture of 38% 1-chloro-2-*exo*-norbornanol (2) and 62% 1-chloro-3-*exo*-norbornanol (3) when the borane intermediates were oxidized with alkaline hydrogen peroxide and a mixture of 35% 1-chloro-2-norbornanone (4) and 65% 1-chloro-3-norbornanone (5) when the borane intermediates were oxidized with chromic acid (Scheme I).

Scheme I



Structural assignments for chloro ketones 4 and 5 were based on the facts that 5 had ir and nmr spectra identical with those of 1-chloro-3-norbornanone prepared according to Wiberg[2] and that 4 had ir and nmr spectra compatible with those expected for the isomeric chloro ketone.

Structural assignments for 2 and 3 were based mainly on the fact that the ratio of chloro alcohols 2 and 3 from the hydroboration were the same, within experimental error, as the ratio of chloro ketones 4 and 5. This similarity of product composition seemed reasonable, since the diborane addition step must determine the orientation for formation of the borane intermediates in both reactions. Exo configurations for the previously unknown 2 and 3 were assigned by analogy with products of hydroboration of other norbornenes[3] and from the characteristic α-hydroxy proton absorption in the nmr spectra of both chloro alcohols.[4]

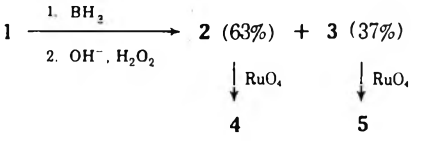
We repeated the hydroboration of 1-chloronorbornene as described by Fry and Farnham except that the solvent was removed by distillation through a Vigreux column rather than with a rotary evaporator. The concentrated ether solution was examined by glpc and found to contain, in order of increasing retention time, 8% starting material, a peak of 57% (hereafter referred to as the major chloro alcohol), an unidentified peak of 1%, and a peak of 34% (hereafter referred to as the minor chloro alcohol).[5]

Because we had on hand a small amount of 1-chloro-2-*exo*-norbornanol[6] we injected a sample into the chromatograph expecting the peak to have the same retention time as that of the minor chloro alcohol of the hydroboration mixture. Instead, the retention time was identical with that of the major chloro alcohol, the two peaks being well separated under the conditions used.

The chloro alcohol mixture was separated by preparative glpc and each chloro alcohol[7] was oxidized with ruthenium tetroxide[8] to the corresponding ketone. The major chloro alcohol on oxidation gave a ketone whose ir and nmr spectra were identical with those of 1-chloro-2-norbornanone prepared by ozonolysis of 1-chloro-2-methylenenorbornane.[9] The minor chloro alcohol on oxidation gave a ketone whose ir and nmr spectra were identical with those for 1-chloro-3-norbornanone prepared by the method of Wiberg.[2,10]

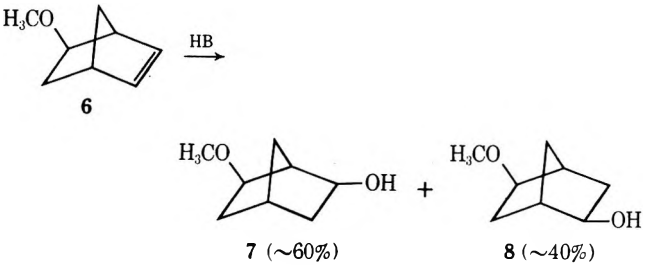
Hydroboration of 1-chloronorbornene (1) followed by oxidation with alkaline hydrogen peroxide thus gives 1-chloro-2-*exo*-norbornanol (2) as the predominant alcohol (Scheme II).[11,12] This observation is in agreement with the results of a number of hydroboration reactions, which show a marked tendency for boron to add nearer to chlorine in allylic chlorides, owing to the stabilizing −I effect on that position in the four-centered transition state.[13,14]

Scheme II



Another apposite example of the −I effect of a substituent on orientation is seen in the hydroboration of 5-*exo*-methoxy-2-norbornene (6), which gives ~60% 7 and ~40% 8 (Scheme III).[3] Here again, the boron becomes attached preferentially to the carbon closer to the substituent. Oxymercuration of 6 gives the opposite orientation as expected, a predominance (~92%) of 8 and ~8% of 7.[3]

Scheme III



There remains the unanswered question of why hydroboration of 1-chloronorbornene (1) gives a predominance (65%) of 1-chloro-3-norbornanone (5) when the borane intermediates are oxidized with chromic acid.[15] In hydroboration of an unsymmetrical chloroallylic system, orientation of the borane intermediates is determined at the stage of addition of diborane to the double bond. While it has been demonstrated that oxidation of organoborane intermediates with alkaline hydrogen peroxide is quantitative and that the resulting alcohols reflect the initial orientation of addition,[16] the yields of ketones derived from oxidation of organoboranes with chromic acid are less than quantitative (65–85%).[17] Considering that hydroboration of 1 followed by alkaline hydrogen peroxide oxidation leads to a predominance of 2 (Scheme II) and that oxymercuration (which gives orientation opposite to that of hydroboration) of 1 followed by oxidation with Jones reagent gives 5 solely,[15] the unexpected *observed* predominance of 5 in the hydroboration of 1 followed by oxidation with chromic acid (Scheme I) must be due to some factor unique to the chloroborane intermediates and/or the chromic acid medium.

One possible explanation for the observed predominance of 5 is that the rate of chromic acid oxidation for the borane precursor of 4 was slower than that for 5, resulting in a lesser degree of conversion (and a lower yield) to the chloro ketone. This hypothesis receives some support from the observation that 2 is converted to the chloro ketone more slowly than 3 by ruthenium tetroxide.[9] Furthermore, it is well known that ketones are not stable to strong oxidiz-

ing acids and that the contact time must be controlled carefully to maximize the yield of ketone. It may be that **4** is more labile to the acid medium than **5**.

Unfortunately, experimental verification for both hypotheses is lacking since no mass balance was reported for the reaction.

Experimental Section

Hydroboration of 1-Chloronorbornene (1).[1] Aldrich 1 *M* diborane in THF (13.8 ml) was added to a stirred solution of 6.9 g (0.0537 mol) of **1** in 13.8 ml of freshly distilled THF under nitrogen. After 20 min, 5.7 ml of 3 *N* sodium hydroxide was added dropwise (caution, frothing) to the stirred solution followed by 4.2 ml of 50% hydrogen peroxide (slowly, reaction exothermic). The reaction mixture was stirred for 2 hr.

Water (20 ml) and some sodium chloride were added and the mixture was extracted three times with ether (30 ml, 2 × 20 ml). The combined ether extracts were washed with water (3 × 50 ml) and dried over magnesium sulfate. The ether solution was concentrated to about 30 ml by slow distillation through a small Vigreux column and examined by glpc (Perkin-Elmer Column K, 15% Carbowax 20M, 170°, 40 psi). The analysis showed, in order of increasing retention time, 8% **1**, 57% **2**, 1% of an unidentified substance, and 34% **3**.

The chloro alcohol mixture was separated by preparative glpc (column: 20 ft × 0.375 in. 20% SE-30 on Chromosorb P 45/60, 185°, 29 psi): 1-chloro-2-*exo*-norbornanol (**2**), mp 84.5–85.5°, ir (CCl_4) hydroxyl 3550 cm^{-1}, the nmr ($CDCl_3$) consisted of a multiplet centered at τ 6.36 (α-hydroxy proton) and a multiplet between τ 7.65 and 9.0, in the ratio of 1:10; 1-chloro-3-*exo*-norbornanol (**3**), mp 76.5–77.5°, ir (CCl_4) hydroxyl 3590 cm^{-1}, the nmr ($CDCl_3$) consisted of a multiplet at τ 6.1 (α-hydroxy proton) and a very complex multiplet between τ 7.7 and 8.95, in the ratio of 1:10.

Oxidation of 1-Chloro-3-*exo*-Norbornanol (3).[8] Ruthenium tetroxide [2.9 ml of *ca* 0.137 *M* solution in Freon 11 (Matheson)] was added with a chilled syringe to a stirred solution of 50 mg (0.00034 mol) of **3** in 2 ml of Freon 11 and 2 ml of pentane at 5–10°. It was necessary to add an equal volume of pentane to bring the chloro alcohol into solution; at 0° the chloro alcohol was only partially soluble. The reaction mixture was stirred at 0° for 20 min.

The excess oxidant was consumed by addition of 2 ml of anhydrous ether and the black ruthenium dioxide was removed by filtration. The solvent was removed by careful evaporation with nitrogen and sublimation of the residue afforded 25 mg of **5**, ir (CCl_4) carbonyl 1775 cm^{-1}, the nmr ($CDCl_3$) showed three multiplets centered at τ 7.3, 7.47, and 7.87.

Oxidation of 1-Chloro-2-*exo*-norbornanol (2).[8] Alcohol **2** (30 mg) in 2 ml of Freon 11 (**2** was completely soluble in Freon 11 at 0°) was oxidized with 1.9 ml (0.00026 mol) of 0.137 *M* ruthenium tetroxide solution at 0° as in the procedure above except that the reaction mixture was stirred at room temperature for 18 hr.[9] Work-up identical with that given above afforded 17 mg of **4**, ir (CCl_4) carbonyl 1780 cm^{-1}, the nmr ($CDCl_3$) showed two multiplets, one centered at τ 7.33 and the other between τ 7.5 and 8.8, with the relative areas of 1:9.4.

Acknowledgment. We wish to thank the National Science Foundation for financial support. We are grateful to Professor A. J. Fry for sending us copies of private correspondence and a number of spectra which were helpful in making this clarification. Gratitude is also expressed to Dr. Raymond Weglein for consultation on several aspects of this work.

Registry No.—**1**, 15019-71-3; **2**, 19916-70-2; **3**, 19916-71-3; **4**, 51417-65-3; **5**, 51417-66-4.

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(6) The reduction of 1-chlorononcamphor with sodium borohydride gave a 3:1 mixture of 1-chloro-2-*endo*-norbornanol and 1-chloro-2-*exo*-norbornanol. Satisfactory analyses were obtained for both chloro alcohols. R. J. Muller and B. L. Murr, unpublished results.
(7) The ir spectra of the major and minor chloro alcohols were identical with those of the first and second chloro alcohol peaks, respectively, from the preparative glpc carried out by Fry and Farnham. We are grateful to Professor Fry for sending copies of these spectra.
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(10) We are grateful to Professor R. Sauers for sending copies of these spectra.
(11) The ir spectra of **4** and **5** (prepared from **1** by hydroboration and chromic acid oxidation) sent to us by Professor Fry were identical with the ir spectra of the chloro ketones prepared from the oxidation of **2** and **3**, respectively.
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Conformation of Acyloxy Groups in *I,I*-Diacyloxyiodobenzenes. A Dipole Moment Study

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Received December 27, 1973

In the compounds of general formula R-X-Y-X-R, where X and Y stand for any divalent group, the two bonds Y-X are equivalent and *a priori* the same conformation on both may be expected. Summarizing the results of our dipole moment studies and those obtained from other methods, we reached the conclusion[1] that the actual conformation can be predicted from the conformation of the simpler model compound R-Y-X-R. If it is planar, the electronic configuration on the central atom Y is usually sp^2 and the bonds Y-X acquire partial double bond character. The whole molecule R-X-Y-X-R is then also planar, or nearly planar (carbonates and their analogs, anhydrides,[2] diacyl sulfides,[1] boronic esters[3]). When the central atom Y has a tetrahedral sp^3 configuration, the model molecule R-Y-X-R as well as the bifunctional molecules R-X-Y-X-R are nonplanar. The latter has more frequently C_2 than C_s symmetry (acetals,[4] *gem*-disulfones,[4] sulfonic acid anhydrides,[1] dialkylphosphinic esters,[5] trisulfides).

Table I
Polarization Data of *I,I*-Diacyloxyiodobenzenes (Benzene, 25°)

Compd	$P_2(\infty)$, cm³	R_D,[a] cm³	μ(5%),[b] D	μ(15%),[b] D
Ia $C_6H_5I(OCOCH_3)_2$	514.6	63.3	4.68[c]	4.61
Ib 4-$ClC_6H_4I(OCOCH_3)_2$	338.0	68.2	3.61	3.56
Ic $C_6H_5I(OCOC_6H_5)_2$	570.2	105.1	4.74	4.69
Id $C_6H_5I(OCOC_6H_4CH_3$-4)$_2$	561.8	114.4	4.65	4.59
Ie $C_6H_5I(OCOC_6H_4F$-4)$_2$	634.8	104.7	5.06	5.02
If $C_6H_5I(OCOC_6H_4Br$-4)$_2$	660[d]	120.8	5.1[d]	5.1[d]

[a] Calculated using Vogel's atomic increments[9] including the common value for iodine. Suitable exaltations, 1.25 and 0.1 cm³, were added to account for Ph–CO and Ph–Hal conjugation, respectively. [b] Correction for the atomic polarization of 5 or 15% of the R_D value, respectively. [c] Reference 10 gives 4.9 D without correcting for the atomic polarization. [d] These values are less precise owing to the unexplained instability of the solutions.

The polyvalent iodine derivatives offer the rare opportunity to study compounds with the dsp³ configuration on the central atom Y and with the two X–Y bonds practically collinear, oriented to the two apices of the trigonal dipyramid.[6,7] Since the alkyl derivatives are not available, we used in this study the *I,I*-diacyloxyiodobenzenes Ia–f (Table I). We are aware that the replacement of alkyl by acyl may influence the results; *e.g.*, the conformations of acylals[8] and acetals[4] are not the same. Since the two rotating groups are relatively distant (Figure 1) we may anticipate that the conformation is controlled by the interactions on each I–O bond (see the Newman projection II); any comparison with simpler model compounds does not seem to be possible.

We followed the same experimental approach as previously.[1-5] The experimental dipole moments (Table I) are also influenced by the estimated molar refraction, which is uncertain owing to an unknown increment for tervalent iodine atom. Since the measured moments are large, they would be not affected even by an inaccuracy of 1 cm³ in molar refraction. The expected dipole moments for individual conformations have been calculated assuming the exactly linear conformation O–I–O and common geometry of the acyl group (∠O–C=O = 124°, ∠C–C=O = 116°, ∠C–O–I = 113° as in esters). We used the bond moments well tried in previous work[1-5,8] on similar compounds, *viz.*, C_{al}–H 0.3 D, C_{ar}–H 0 D, C–O 0.74 D, C=O 2.5 D, C_{ar}–Cl 1.60 D, C_{ar}–Br 1.58 D, C_{ar}–F 1.35 D. In the actual conformation the bond moments C–Hal are almost insignificant and the I–O moment is completely irrelevant; the C=O and C–O bonds have been confirmed on many acyl derivatives.[1,2,8] Most problematic is the formal moment C–I, including also the two lone electron pairs. Its value should be intermediate between that in iodobenzene dichloride (equal to its dipole moment,[10] 2.6 D) and aliphatic iodides (*ca.* 1.45 D). We got reasonable results with the moment of 1.9 D, but the final conclusions are not affected by its exact value.

The expected moments have been calculated for various dihedral angles $\tau_{1,2}$ = ∠C–I–O–C in the two moieties and for various planar conformations on the C–O bond, *i.e.*, *E* or *Z*. From these only the *Z* conformation in both moieties (Figure 1) yielded dipole moments comparable to the experimental ones. The *Z* conformation is clearly the only reasonable one, since it is found in all compounds containing the COO– grouping (see, *e.g.*, ref 1, 2, and 8). The computed and experimental values are compared using the previously introduced[8] graphical method (Figure 2). In Figure 2 only the symmetrical conformations are shown: $\tau_1 = \tau_2$, *i.e.*, the two acyl groups symmetrically

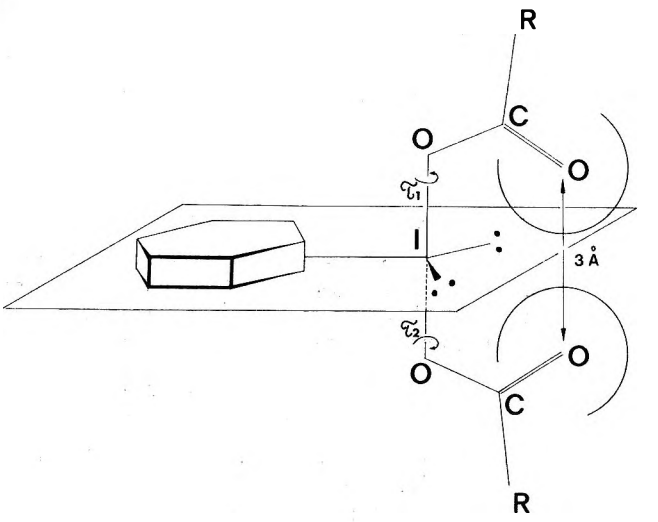


Figure 1. Steric arrangement of the molecule of *I,I*-diacyloxyiodobenzene. The actual conformation with $\tau_1 = \tau_2 = 0$ is shown.

situated when looking along the O–I bond (full lines), and $\tau_1 = -\tau_2$, *i.e.*, the two acyl groups eclipsed (broken lines).

Figure 2 shows in a convincing manner that only the planar conformation IIa with $\tau_1 = \tau_2 = 0$ in which the dipole moment is a maximum is compatible with experiment. The dipole moment method is, of course, unsufficiently sensitive to the presence of other, little populated

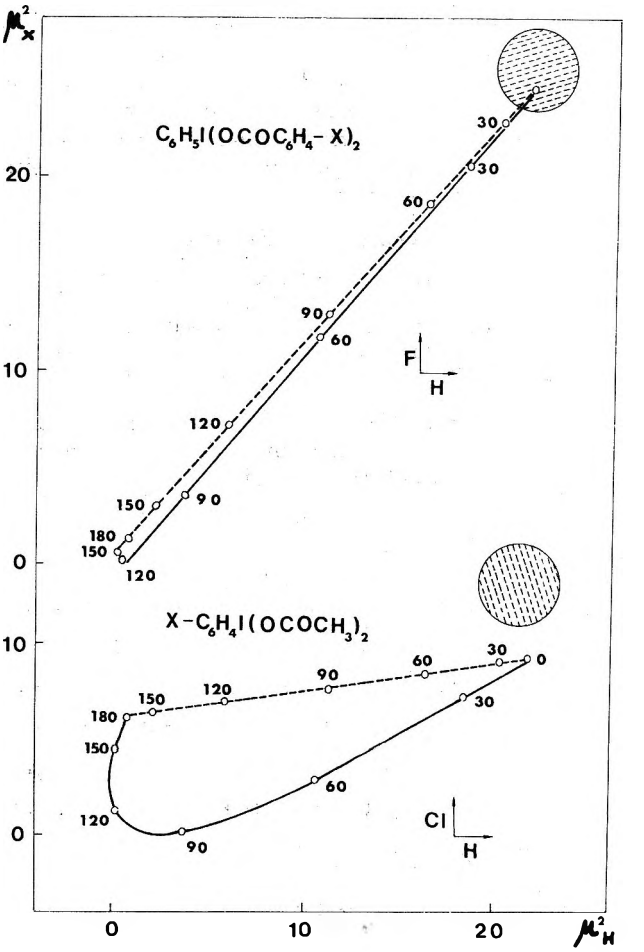
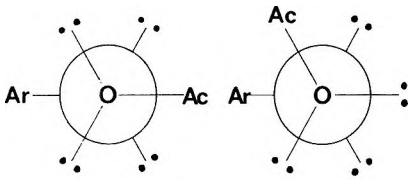


Figure 2. Comparison of dipole moments of *I,I*-diacyloxyiodobenzenes, experimental and calculated for various conformations. Values of μ^2 for the unsubstituted compounds (Ia, Ic) are plotted on the *x* axis, and values for the para derivatives (Ib, Ie) on the *y* axis. Computed values are plotted as a function of the dihedral angle τ = ∠C–I–O–C; the experimental points are shadowed.



IIA IIB

forms. Neither have such forms been revealed by the nmr spectra of several derivatives from Table I. Within the temperature interval −50 to 55°, which was limited by the solubility and stability of the compounds, no additional signals or shifts were observed. We conclude that the conformation IIa is the prevailing one, or even the only one present.

The result shows that the interaction of the two acyl groups is negligible as anticipated, but it is somewhat surprising with respect to the interactions about the I–O bonds. If we compare the two staggered conformations IIa and IIb in terms of Wolfe's theory[11] of gauche interaction, we would give IIb the preference. It has the bonds I–C and O–C in the gauche positions and in addition there is a double Edward–Lemieux effect[11] (a polar bond between two electron pairs) destabilizing the form IIa. We could conclude that Wolfe's concept is not applicable to dsp^3-hybridized atoms;[12] *e.g.*, the C_1–I–O angle of 90° could produce greater repulsion between phenyl and carbonyl groups, not fully compensated by the C–I and I–O bond lengths. Alternatively, the apparent exception could be caused by the presence of acyl groups. On the other hand, we do not find any clear reason why the repulsion between phenyl and carbonyl should exceed that between phenyl and, *e.g.*, alkyl. In addition, disagreement was found even with other compounds[13] where similar arguments do not apply. Hence, there is a more probable explanation that the whole theory,[11] although promising, is not valid without exceptions in its simplified form.

Experimental Section

Materials. *I,I*-Diacyloxyiodobenzenes were prepared by the known procedure[14] and found to be 99% pure by iodometry.

Physical Measurements. The same method was used as previously,[1-5,8] except that the concentration of benzene solutions was lowered to 10^{-3}–10^{-2} *M* owing to the low solubility.

Acknowledgment. Thanks are due to Mrs. M. Kuthanová for technical assistance in physical measurements and to Dr. V. Jehlička for the control.

Registry No.—Ia, 3240-34-4; Ib, 6973-73-5; Ic, 6597-18-8; Id, 51716-26-8; Ie, 38469-36-2; If, 38469-37-3.

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A Facile Method for the Transformation of Ketones into α-Substituted Aldehydes

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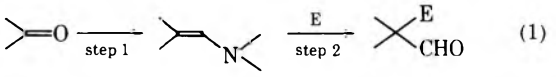
Received April 25, 1974

The introduction of dissimilar geminal substituents with concomitant creation of a quaternary carbon center remains a problem in the synthesis of natural products, where fully substituted carbon atoms commonly occur. Recent approaches to geminal alkylation involve the use of the thio-Claisen rearrangement,[2] the base-induced decomposition of methyl dialkylcyanodiazenecarboxylates,[3] the acid-catalyzed rearrangement of cyclopropyl ethers,[4] the [2,3] sigmatropic rearrangement of allylic sulfonium ylides[5] and allylic ammonium ylides,[6] the [2,3] sigmatropic rearrangement of sulfur-stabilized carbenoids,[7] the addition of organocopper or organolithium reagents to α, β-ethylenic sulfur compounds,[8] and the spiro annelation procedure based upon the rearrangements of oxaspiropentanes.[9] Unfortunately, these methods typically involve multistep procedures with the isolation of intermediates. We now wish to report an efficient, one-pot procedure for the one-carbon homologation of ketones to α-allyl aldehydes which may, in principle, be extended to the synthesis of other α-substituted aldehydes and ketones.

It is well known that enamines of aliphatic α-disubstituted aldehydes react readily with electrophilic reagents such as allyl bromide to afford, upon hydrolysis, α-allyl dialkylaldehydes.[10] It occurred to us that the conversion of a ketone with one-carbon homologation to the enamine of an α-disubstituted aldehyde, and the subsequent reaction of the thus formed enamine *in situ* with an appropriate electrophilic reagent (E), would provide an efficacious synthesis of a quaternary carbon atom possessing two substituents of differing functionality (eq 1). We envisioned that a

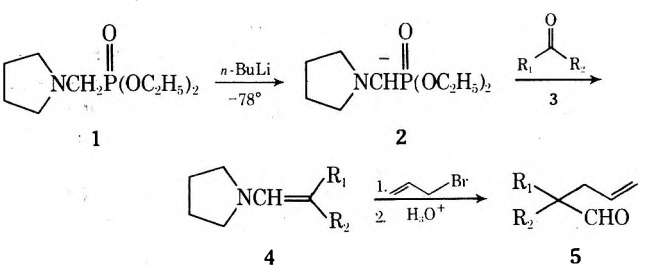


(1)

modified Wittig reaction of a dialkylaminomethylphosphonic acid ester with a ketone would effect the conversion indicated in step 1.[11]

Treatment of diethyl pyrrolidinomethylphosphonate[12] (1) with 1 equiv of *n*-butyllithium in tetrahydrofuran at −78° afforded the anion **2**, which reacted smoothly with ketones **3** to give the corresponding enamines **4** (Scheme I). Subsequent reaction of **4** with an excess of allyl bromide and hydrolysis of the intermediate immonium salt afforded the α-allyl aldehydes **5** in good yields. These results are depicted in Table I.

Scheme I



The enamines **4a–e** which were generated are very useful synthetic intermediates which undergo a wide variety of transformations.[13] For example, in a preliminary experi-

Table I
Conversion of Ketones into α-Allyl Aldehydes

Ketone 3	Enamine 4[a]	Yield of 5, %[b]
4-Heptanone (**3a**)	+	61
3-Methyl-2-butanone (**3b**)	+	38
Cyclohexanone (**3c**)	+	39
2-Methylcyclohexanone (**3d**)	+	57[c]
Norbornanone (**3e**)	+	54
Acetophenone (**3f**)	+	*d*
Cyclooctanone (**3g**)	−	
Fenchone (**3h**)	Trace	

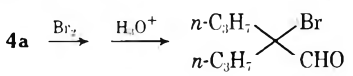
[a] +, enamine formation; −, no enamine formation. [b] No attempt was made to fully optimize yields. [c] A mixture of diastereomers (*ca.* 4:1) was obtained. [d] A mixture of alkylated and unalkylated aldehydes (*ca.* 1:1) was obtained.

Table II
α-Allyl Aldehydes 5

Compd	Bp, °C[a] (mm)	Mp, °C,[b] of 2,4-DNPH[c]
5a	83–85 (10)	164–165
5b	90–92 (50)	125–126
5c	109–111 (40)[d]	156–157[e]
5d	90–92 (10)	114–115
5e	112–114 (25)[f]	148–149[g]

[a] Uncorrected. [b] The melting points were determined using a Reichert hot stage apparatus and are uncorrected. [c] Satisfactory elemental analysis was obtained for all new aldehydes as their 2,4-dinitrophenylhydrazones. *Anal.* Calcd for $C_{17}H_{24}N_4O_4$ (**5a**): C, 58.61; H, 6.94; N, 16.08. Found: C, 58.87: H, 6.76; N, 16.18. Calcd for $C_{15}H_{20}N_4O_4$ (**5b**): C, 56.24; H, 6.29; N, 17.49. Found: C, 56.46; H, 6.48; N, 17.34. Calcd for $C_{17}H_{22}N_4O_4$ (**5d**): C, 58.95; H, 6.40; N, 16.17. Found: C, 59.10; H, 6.40; N, 16.19. [d] Lit.[14] bp 105–107° (32 mm). [e] Lit.[14] mp 156–157°. [f] Lit.[14] bp 120° (26 mm). [g] Lit.[14] mp 146–148°.

ment the enamine **4a** was brominated to give, after careful hydrolysis, the α-bromo aldehyde **6** in 33% yield (eq 2).



(2)

6

Since these α-bromo aldehydes may be readily converted α,β-unsaturated aldehydes, the direct bromination of the *in situ* generated enamines constitutes a useful modification of this method.

Further investigations to extend the scope and utility of this new synthetic method are in progress.

Experimental Section

α-Allyl Dialkylaldehydes 5a–e. General Procedure. A well-stirred solution of diethyl pyrrolidinomethylphosphonate[12] (1, 3.65 g, 16.5 mmol) in 75 ml of anhydrous tetrahydrofuran was treated with *n*-butyllithium (8.7 ml of a 1.9 *N* hexane solution, 16.5 mmol) at −78° under dry nitrogen. After 1 hr, a solution of the appropriate ketone **3a–e** (15.0 mmol) in 10 ml of anhydrous tetrahydrofuran was added dropwise over a 10-min period, and the stirring was continued for 4 hr at −78° and then overnight at room temperature to give a solution of the enamine **4a–e.** Allyl bromide (13.0 ml) was added, the mixture was refluxed for 24 hr, 30 ml of 1 *N* hydrochloric acid was added, and the refluxing was continued for an additional 3 hr. After cooling, the reaction mixture was poured into water and the aqueous layer was extracted with ether. The combined organic layers were washed successively with 2 *N* hydrochloric acid and 10% sodium bicarbonate, and the aqueous washings were backwashed once with ether. The combined organic layers were dried ($MgSO_4$), the excess solvent was removed under reduced pressure, and the residue was distilled to afford the α-allyl dialkylaldehydes **5a–e.** See Table II for physical constants.

Acknowledgment. We wish to thank the Alexander von Humboldt-Stiftung of West Germany for their generous financial support of this program.

Registry No.—**1,** 51868-96-3; **3a,** 123-19-3; **3b,** 563-80-4; **3c,** 108-94-1; **3d,** 583-60-8; **3e,** 497-38-1; **3f,** 98-86-2; **5a,** 51868-97-4; **5a** 2,4-DNPH, 51868-98-5; **5b,** 51868-99-6; **5b** 2,4-DNPH, 51911-65-0; **5c,** 29517-58-6; **5c** 2,4-DNPH, 51869-00-2; *cis*-**5d,** 51869-01-3; *cis*-**5d** 2,4-DNPH, 51869-02-4; *trans*-**5d,** 51869-03-5; *trans*-**5d** 2,4-DNPH, 51869-04-6; **5e,** 29517-67-7; **5e** 2,4-DNPH, 51869-05-7.

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Catalytic Dehydrator. A Simplified Isolation Procedure for Acetals and Ketals

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Received May 31, 1973

The catalytic dehydrator is defined as a combination of an ion exchange resin (a sulfonated polymer) and a drying agent, and it promotes acid-catalyzed, equilibrium reactions in which water is one of the products. At the present time, it has been applied to the synthesis of esters,[1] ketals, and acetals.[2] We now wish to present additional data on the use of the catalytic dehydrator for the synthesis of acetals and ketals together with a simplified preparative isolation procedure.

In regard to structural effects, aldehydes produce higher yields of acetals than comparable ketones form ketals. As the data of Table I indicate, the 1,2-ethanediol–acetal yield from phenylacetaldehyde is greater than the 1,2-ethanediol–ketal yield from phenylacetone. Similarly the acetal yield from diphenylacetaldehyde is higher than the ketal yield from 1,1-diphenylacetone. Similar results have been observed using a cation-exchange resin and a water separator.[3] For example, Astle, *et al.*, obtained a 92% yield of 2-propyl-1,3-dioxolane from butanal and 1,2-ethanediol but

Table I
Substituent Effect on Acetal and Ketal Formation Using the Catalytic Dehydrator

Compd	Registry no.	Carbonyl, mmol	1,2-Ethanediol, mmol[b,c]	Resin, g	$CaSO_4$, g	Yield,[a] %	Registry no.	Lit. yield, %	D_{total}
Cyclohexanone	108-94-1	9.7	53.9	0.5–1.0	0.97–1.77	74–89	177-10-6	75–85[d]	1.8–3.6
Acetophenone	98-86-2	8.6	53.9	0.5	1.5	22–24	3674-77-9	80–85[e,f]	2.3
Benzaldehyde	100-52-7	11.0	53.9	0.5	1.5	67–70	936-51-6	83[g]	1.8
Phenylacetone	100-79-7	9.0	53.9	0.5	1.5	62–68	4362-18-9	90[f]	2.2
Phenylacetaldehyde	122-78-1	9.4	53.9	0.5	1.5	81–83	101-49-5	58[g]	2.1
1,1-Diphenylacetone	781-35-1	9.0	53.9	0.5	1.5	48–51	52002-91-2	45[h]	2.2
Diphenylacetaldehyde	947-91-1	9.6	53.9	0.5	1.5	70–74	4359-35-7	70[i]	2.1

[a] These yields were determined by glpc analysis of the ether extract solution. [b] There was an error committed in our previous report.[2] The amount of 1,2-ethanediol used in that data was 53.9 mmol rather than 5.39 mmol as reported. [c] Registry no., 107-21-1. [d] R. A. Daignault and E. L. Eliel, *Org. Syn.*, **47**, 37 (1967). [e] M. Sulzbacher, E. Bergmann, and E. R. Pariser, *J. Amer. Chem. Soc.*, **70**, 2827 (1948). [f] F. Alderweireldt and M. Anteunis, *Bull. Soc. Chim. Belg.*, **74**, 488 (1965). [g] Prepared by a base process on a dichloride: V. M. Naidan, N. V. Dzumedzei, and A. V. Dombrovskii, *Zh. Org. Khim.*, **1**, 1377 (1965); *Chem. Abstr.*, **64**, 721c (1966). [h] Prepared in our laboratory using *p*-toluenesulfonic acid and the benzene azeotrope. [i] R. Soulier and J. Soulier, *Bull. Soc. Chim. Fr.*, 2048 (1969).

only a 21% yield of 2-propyl-2-methyl-1,3-dioxolane from 2-pentanone and 1,2-ethanediol. At higher temperatures, the cation-exchange resin alone produces similar results, *i.e.*, a 79% yield of the 1,2-ethanediol–acetal from 2-methylpropanal and a 42% yield of corresponding ketal from 3-methyl-2-butanone.[4]

When the carbonyl group is conjugated with an aromatic ring, the yields are also reduced. Using 1,2-ethanediol, benzaldehyde produces 67–70% of the corresponding acetal (Table I) whereas phenylacetaldehyde gives its acetal in 81–83% yield under comparable conditions. Further, phenylacetone is converted to its ketal in 62–68% yield by the catalytic dehydrator whereas acetophenone gives only 22–24% of its ketal. Thus it appears that the additional conjugation of the carbonyl with its concomitant reduction in the carbonyl reactivity serves to inhibit the formation of ketals and acetals. This preferential phenomenon is of potential advantage when preparing monoacetals in compounds where several competing carbonyl groups are present.

The yields of acetals and ketals are sensitive to changes in substituents on the α carbon atom of the aldehyde or ketone. Phenylacetaldehyde yields 81–83% of 2-benzyl-1,3-dioxolane with the catalytic dehydrator whereas diphenylacetaldehyde produces 70–74% of 2-diphenyl-1,3-dioxolane. Similarly phenylacetone yields 62–68% of 2-benzyl-2-methyl-1,3-dioxolane while 1,1-diphenylacetone gives 48–51% of 2-diphenylmethyl-1,3-dioxolane.

Though optimum particle size for the calcium sulfate in the catalytic dehydrator has not been systematically studied, we have observed that the smaller the particle size, the higher the yield of products for a given reaction time. Presumably this is due to the increased surface area per gram on the smaller sized particles. If the work-up involves filtration as previously recommended for preparative work, then there is a point of diminishing returns on particle size because powder greatly retards filtration by clogging filter pores. The problem of slow filtration combined with the adsorption–inner diffusion process whereby the product is partially lost to the inner regions of the calcium sulfate[2] is now solved by a modified work-up procedure. At the termination of the reaction, the calcium sulfate particles are partially dissolved in a water solution and extracted with ether. Emulsions result if the quantity of water added is too small.

Preferably, the solvents should be dry before use. Minor amounts of water in the solvents and reactants can be tolerated; however, more catalytic dehydrator is required when the water content of the initial reaction mixture is significant.

Experimental Section

The ion exchange resins used were sulfonated polystyrene copolymers with total exchange capacities on the dry basis of 4.5 mequiv/g [Rexyn 101 (H) R-231] and 4.8 mequiv/g [Rexyn 101 (H) R-204] sold by Fisher Scientific Co., Fair Lawn, N. J. The ion exchange resins were dried at 100° for 24 hr and stored in a desiccator prior to use, and the $CaSO_4$ (Drierite) was dried and stored at 200°. The glpc analyses were performed on a flame ionization Varian Model 1200-2 instrument equipped with columns containing 20% Carbowax 20–5% KOH on Chromosorb W.

General Procedure Illustrated for Cyclohexanone. A dry 500-ml erlenmeyer flask was fitted with an efficient mechanical stirrer. To the flask were added 28.4 g (30.0 ml, 0.29 mol) of cyclohexanone, 100.4 g (90 ml, 1.62 mol) of 1,2-ethanediol, 3.0 g of an anhydrous ion-exchange resin, and 46.5 g (0.342 mol) of finely ground anhydrous calcium sulfate. The viscous mixture was stirred for 6 hr. Diethyl ether (75 ml) was then added, and the mixture was allowed to stir for an additional 10 min. Water (150 ml) was added, and the mixture was stirred again for 10 min. The layers were separated using a separatory funnel and the water layer was washed with 75 ml of diethyl ether. The combined ether layers were dried with anhydrous calcium sulfate and filtered and the solvent was removed by distillation. The product was obtained by distillation through a 90-cm spinning band column. After distillation, 1,4-dioxaspiro[4.5]decane was obtained as a colorless liquid, bp 51–52° (3 mm), $n^{22}D$ 1.4572. The yield was 31.9 g (79%).

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Acknowledgments. This investigation was supported in part by a Public Health Service Career Development Award (1-K4-6M 9888:V.I.S.)

A Novel α Elimination in the Mild Thermal Treatment of α-Chloroboronic Esters. A New Route to Olefins

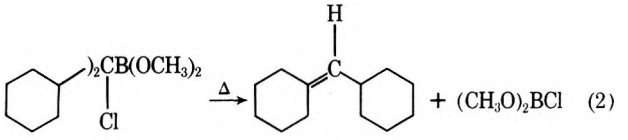
Summary: Mild thermal treatment of α-chloroboronic esters, readily available from the base-induced reaction of borinic esters with dichloromethyl methyl ether, converts them in high yield into the chloroborate ester and the corresponding internal olefin.

Sir: α-Chloroboronic esters are now readily available by the base-induced reaction of borinic esters with DCME[1] (eq 1).

$$R_2BOR' + CHCl_2OCH_3 + LiOCEt_3 \xrightarrow[30\ min]{THF,\ 25^\circ} R_2CClB(OCH_3)OR' + Et_3COH + LiCl \quad (1)$$

1

At elevated temperatures, the products 1 were observed to undergo an essentially quantitative decomposition to the corresponding internal olefin (eq 2). This was of interest



2 3

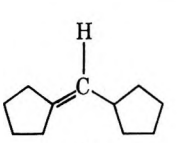
and we undertook to explore the thermal behavior of these α-chloroboronic esters.[2]

Dimethyl dicyclohexylchlorocarbinylboronate (**2**, 1.98 g, 5.68 mmol), in a distilling flask, was heated for 2 hr in an oil bath which was maintained at 240–250°. There was obtained as distillate 0.48 g (89%) of dimethyl chloroborate, $(CH_3O)_2BCl$.[3] Remaining in the flask was 0.98 g (97%) of pure cyclohexylidenecyclohexane (**3**). Benzene was added as an internal standard. Examination of the product by nmr established that **3** had been formed in a yield of 94%.

Thermal treatment of the α-chloroboronic esters in a Kügelrohr oven[4] under aspirator vacuum provided an even simpler technique with the reaction being essentially complete in 10–20 min. In all cases, excellent yields of olefins were realized with no evidence for any isomerization of the double bond.

The following procedure is representative. In the Kügelrohr flask was placed 1.60 g (5.58 mmol) of dimethyl (dicyclohexylchlorocarbinyl)boronic ester **2**.[1] Aspirator vacuum was applied and the oven temperature raised to 240°; the decomposition was complete in 10 min. No residue was observed. The product was collected in an U-tube cooled at −78°. Nmr examination of the distillate prior to any work-up indicated the quantitative presence of vinyl protons. The distillate was washed out with 10 ml of pentane and stirred vigorously for 2–3 hr with a mixture of 5 ml of 3 *M* NaOH and 5 ml of brine, 10 ml pentane was then added, the organic layer was separated, and the mixture was dried over anhydrous magnesium sulfate. The solvent was removed. There was obtained 0.86 g, (86.5% yield) of cyclohexylidinecyclohexane **3**: $n^{20}D$ 1.4948; ≥95% pure by nmr (only a trace of the endocyclic isomer was present at δ 5.4 ppm) (CCl_4, TMS) δ 0.8–2.5 (m, 21 H), 4.83–4.96 (d, 1 H, *J* = 8 Hz) ppm; exact mass calcd for $C_{13}H_{22}$, 178.1722; found, 178.1690.

No difficulty was experienced in extending the reaction to the *n*-butyl, cyclopentyl, and *exo*-norbornyl derivatives. Thus, olefins **4** and **5** were readily obtained.



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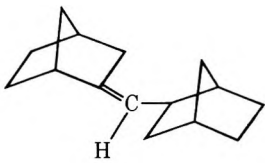
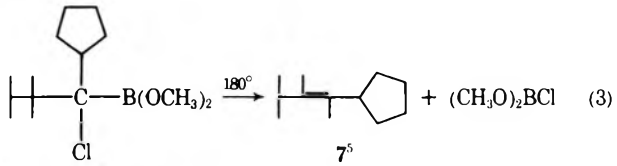


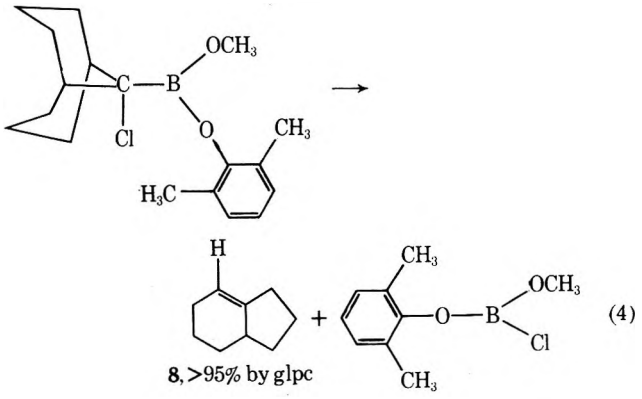
5

An unexpected development was the observation that the α elimination proceeds with exceptional ease in the case of dimethyl thexylcyclopentylchlorocarbinylboronate (**6**). Moreover, the olefin product (**7**) arises not from migration of the tertiary hydrogen, as in other cases, such as **3**, **4**, and **5**, but from migration of a methyl group (eq 3).



6 7[5]

Finally, the promise of this new synthetic route to olefin is indicated by the result realized in the thermal treatment of the α-chloro derivative from 9-borabicyclo[3.3.1]-nonane. There was obtained a 70% yield of bicyclo[4.3.0]-non-1(2)-ene (**8**, eq 4). The earlier routes to this bicyclic

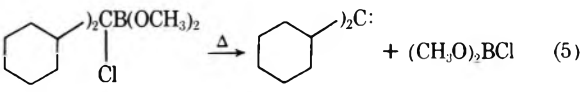


8, >95% by glpc

olefin involved either the acid treatment of hydrindan alcohols[6] or solvolysis of hydrindan *p*-nitrobenzoate esters;[7] however, a mixture of all isomers were obtained.

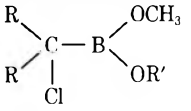
The results are summarized in Table I.

It is tempting to suggest that the reaction proceeds through a concerted α elimination to give the carbene (eq 5). A simple migration of the tertiary hydrogen atom would



give **3**. However, a remarkable feature of these eliminations is the simplicity of the product and the nearly quantitative yields. We have failed to detect any cyclopropyl derivatives such as are accepted as characteristic of dialkylcarbenes.[8]

Table I
Preparation of Internal Olefins from Pyrolysis of α-Chloroboronic Esters

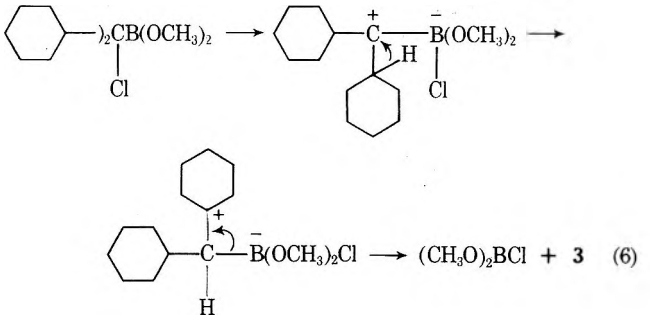


R	R	R′	Temp, °C	Olefin	Yield,[a] % (isolated)
n-Butyl	*n*-Butyl	2,6-Dimethylphenyl	240	4-Nonene[b]	80
Cyclopentyl	Cyclopentyl	2,6-Dimethylphenyl	220	Cyclopentylidene-cyclopentane (**4**)[c]	80
Cyclohexyl	Cyclohexyl	Methyl	240–250	Cyclohexylidene-cyclohexane (**3**)[c]	86.5
exo-Norbornyl	*exo*-Norbornyl	Methyl	220	2-Norbornylidene-*exo*-norbornane (**5**)[c,d]	88
2,3-Dimethyl-2-butyl	Cyclopentyl	Methyl	180	1-Cyclopentyl-1,2,3-trimethyl-1-butene (**7**)[e]	85
9-Bicyclo[3.3.1]nonanyl		2,6-Dimethylphenyl	190	Bicyclo[4.3.0]non-1(2)-ene[f]	70

[a] All olefins gave satisfactory ir, nmr, and mass spectral data. [b] 78% cis-22% trans determined by glpc. [c] All cyclic olefins were exocyclic, as evidenced by nmr analysis (doublets $J \sim 8$–9 Hz). [d] Exists as a pair of "in-out" isomers, as demonstrated by an overlapping pair of doublets ($J = 10$ Hz) at $\delta = 4.83$ and 5.03 ppm. [e] Almost no vinylic proton resonance was observed at δ 5.2 ppm. Microozonolysis of the olefinic product confirmed the structure **7**. Methyl isopropyl ketone was the predominant product and only a small amount (≤5%) of cyclopentanone was observed. No stereochemistry implied. [f] Spectroscopic data were in agreement with the reported values.[6]

Consequently, it is necessary to conclude either that the carbenes in this reaction undergo unusually clean conversion to olefin or that the elimination is not a concerted process.

In the latter case, the reaction could be a carbonium ion process involving transfer of the tertiary chloride from carbon to boron, followed by consecutive transformation as shown in eq 6.



$$\text{C}(\text{OCH}_3)_2\text{Cl} \cdot \text{B}(\text{OCH}_3)_2\text{Cl} \longrightarrow (\text{CH}_3\text{O})_2\text{BCl} + \mathbf{3} \quad (6)$$

Even though it is not possible at this time to give a definitive mechanism, the reaction provides a remarkably simple elimination leading to a wide variety of olefinic structures. Irrespective of whether the reaction proceeds through a dialkylcarbene (eq 5) or through an intermediate carbonium ion (eq 6), it is evident that this reaction offers promise of new, very simple mechanistic pathways.

References and Notes

(1) B. A. Carlson, J.-J. Katz, and H. C. Brown, *J. Organomet. Chem.*, **67**, C39–C42 (1974).
(2) The mass spectral examination of **2** revealed interesting features. The molecular ion was not observed. The highest mass was 250 (rel intensity 0.2), corresponding to loss of hydrogen chloride. The ion of highest intensity was 178 (rel intensity 100), corresponding to the ionized olefin. Similar spectra were realized with the other derivatives.
(3) E. Wiberg and W. Sütterlin, *Z. Anorg. Allgem. Chem.*, **202**, 1 (1931); **222**, 92 (1935).
(4) Available from Büchi. A pyrolysis tube was used and filled with glass beads.
(5) See Table I, note *e*.
(6) C. Arnal, J. M. Bessière, H. Cristol, and R. Vanel, *Bull. Soc. Chim. Fr.*, 2479 (1967).
(7) R. C. Fort, R. E. Hornish, and Gao A. Liang, *J. Amer. Chem. Soc.*, **92**, 7558 (1970).
(8) W. Kirmse, "Carbene Chemistry," 2nd ed, Academic Press, New York, N. Y., 1971.
(9) Graduate research assistant on Grant GM 10937 supported by the National Institutes of Health.
(10) Graduate research assistant on Grant GP 27742X supported by the National Science Foundation.

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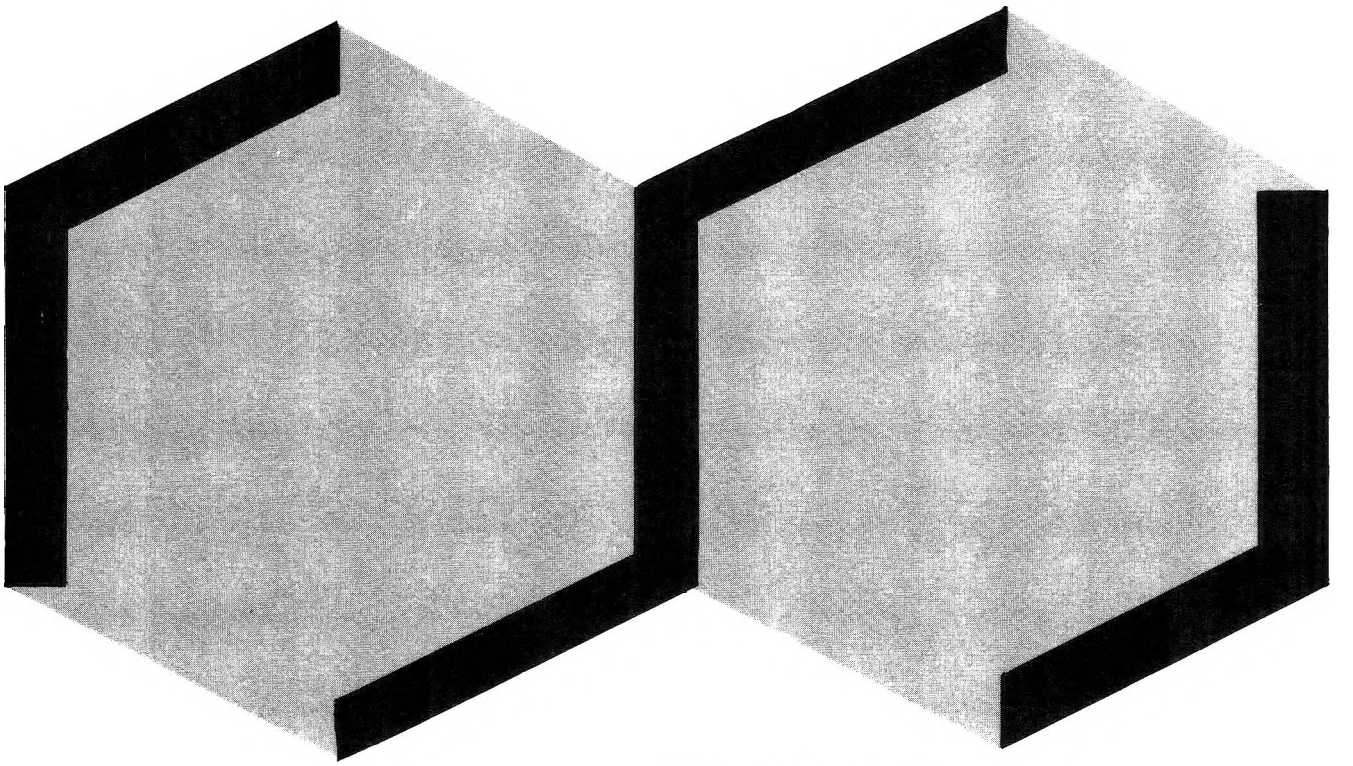

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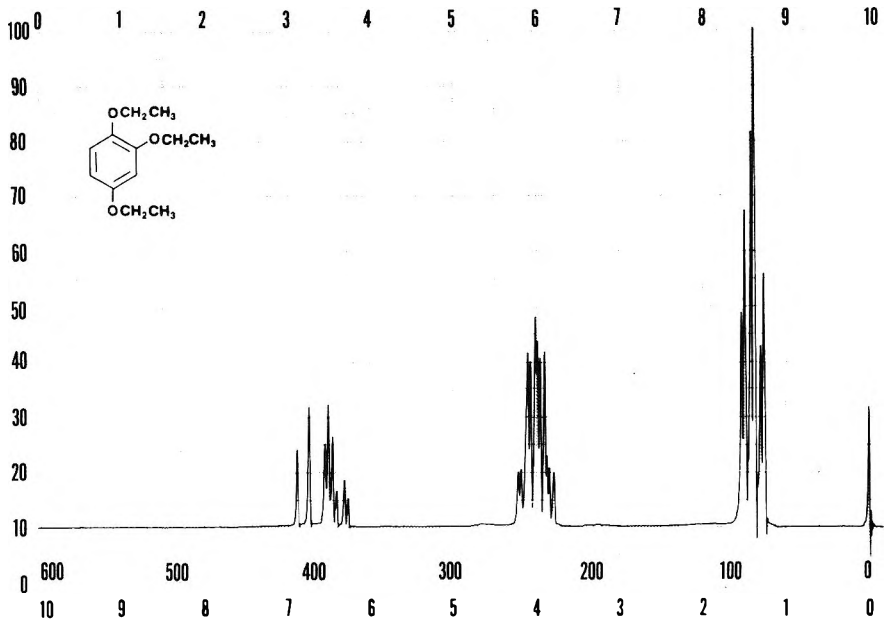

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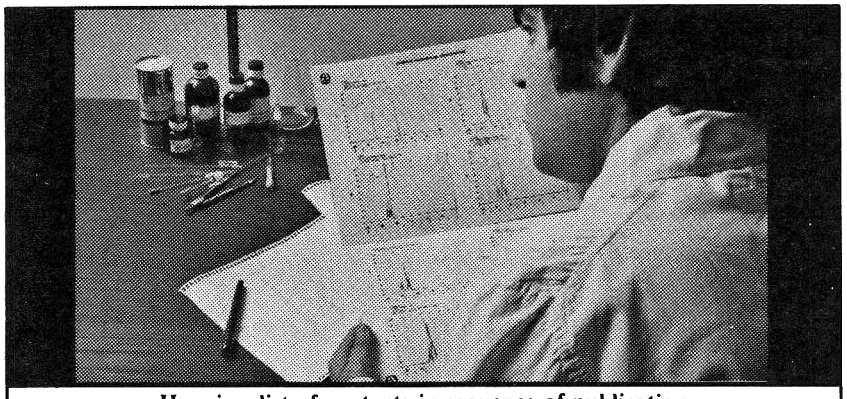

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