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Reactive Triflate Alkylating Agents

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Trifluoromethanesulfonate esters of α-hydroxycarbonyl compounds, several derivatives of allyl alcohol, formaldehyde cyanohydrin, and propargyl alcohol have been prepared. In most cases, the triflates can be isolated by distillation or crystallization. All of the triflates prepared are reactive toward sulfides and can be used for convenient synthesis of substituted sulfonium salts. The allylic triflates are exceptionally reactive and attack a variety of S-, P-, N-, or O-containing molecules. The triflate of 2-ethoxyprop-2-en-1-ol has been characterized by formation of the corresponding triphenylphosphonium salt. The latter is a source of 2-ethoxyallylidenetriphenylphosphorane.

Synthetic projects under way in our laboratory require the conversion of highly functionalized allylic sulfides or amines into carbonyl-stabilized ylides. We had hoped to prepare ylides such as **1** or **2** by alkylation of the appropriate sulfide or amine using ethyl bromoacetate, followed by deprotonation with base. However, it quickly became apparent that ethyl bromoacetate is not sufficiently reactive for this purpose. Alkylation of α-branched sulfides and amines requires heating the reactants and complex product mixtures are formed in typical cases. To avoid high-temperature alkylations, we have prepared several trifluoromethanesulfonates (triflates) of α-hydroxy esters, ketones, and nitriles. As expected,[1] these reagents are far more reactive than the analogous bromides. Alkylation of branched sulfides and amines with the triflate reagents becomes a routine operation and the corresponding ylides can be obtained easily (path a, below).[2] We have also prepared and isolated several substituted allyl triflates which allow synthesis of **1** and **2** from α-thiomethyl or α-dialkylamino carbonyl compounds (path b). Not surprisingly, the allyl triflates are extremely reactive alkylating agents toward a variety of sulfur-, nitrogen-, phosphorus, or oxygen-containing molecules.

The trifluoromethanesulfonate ester (**3**) of ethyl glycolate is representative of triflates derived from α-hydroxycarbonyl compounds. This reagent is most conveniently prepared by slow addition of ethyl diazoacetate to trifluoromethanesulfonic acid in liquid sulfur dioxide at −78 °C. Wentrup and Dahm have used a similar method to prepare the analogous fluorosulfonate ester.[3] Under optimized conditions, **3** can be isolated in 73% yield as an air-stable, easily crystallized (mp 22 °C), and mildly lachrymatory liquid. Ether can be substituted for the sulfur dioxide solvent, but the yield of triflate is only 30–40%. Several related triflates have been prepared similarly from the diazo compounds in liquid SO_2, as summarized in Table I.

Table II lists triflates which have been prepared from alcohols and trifluoromethanesulfonic anhydride. This method appears suited for α-hydroxycarbonyl compounds (entries VII–X), although it is less convenient (and more expensive) than the diazo ester procedure for preparation of **3**. In several cases (notably, entries VIII and X) we have found that a 5% excess of pyridine is essential for good yields. Accordingly, a stoichiometry of 1:1.05 m of anhydride/pyridine per 0.8–1.0 mol of alcohol has been adopted as the standard procedure using inert solvents such as liquid sulfur dioxide or halogenated hydrocarbons.

As indicated in Table II, it is possible to prepare exceedingly reactive allylic triflates. The propenyl and propargyl derivatives **8** and **9** have been reported previously, although neither triflate was isolated in pure form.[4] We have found that trifluoromethanesulfonates **8–11** can be purified by distillation if a sufficiently low-boiling solvent is used for the experiment. Thus, allyl triflate **8** can be prepared in methyl chloride solution, and solvent removal followed by product distillation affords **8** as a colorless liquid. The most reactive triflates **8–12** all decompose if stored at room temperature. In one instance, a neat sample of **8** which had been placed in a sealed ampule exploded upon reaching ambient temperature. It is essential to store purified samples of **8–12** at −78 °C, and to exercise precautions during distillation of the triflates.

All of the allylic triflates are extremely reactive toward typical compounds containing covalent oxygen, nitrogen,

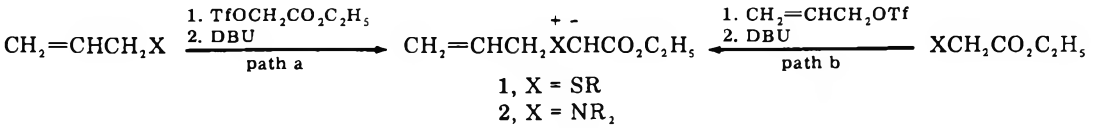


Table I. Triflates from Diazo Esters, Ketones, and Nitriles

Entry	Starting diazo comp	Registry no.	Triflate	Registry no.	Isolated yield, %
I	$C_2H_5O_2CCHN_2$	623-73-4	$C_2H_5O_2CCH_2OTf$ (3)	61836-02-0	73
II	$C_6H_5COCHN_2$[15]	3282-32-4	$C_6H_5COCH_2OTf$ (4)	62861-51-2	75
III	$NCCHN_2$[8]	13138-21-1	$NCCH_2OTf$ (5)	62861-52-3	23
IV	CH_3COCHN_2[15]	2684-62-0	CH_3COCH_2OTf (6)	62861-53-4	37
V	$Cl_3CCOCHN_2$[9]	20485-55-6	Cl_3CCOCH_2OTf (7)	62861-54-5	36

Table II. Triflates from Alcohols and Trifluoromethanesulfonic Anhydride–Pyridine

Entry	Starting alcohol	Registry no.	Triflate	Registry no.	Yield, %
I	$CH_2{=}CHCH_2OH$	107-18-6	8	41029-45-2	69[a]
II	$CH{\equiv}CCH_2OH$	107-19-7	9	41029-46-3	28[a]
III	$CH_2{=}C(Cl)CH_2OH$	5976-47-6	10	62861-56-7	79[a]
IV	$Me_3SiCH{=}CHCH_2OH$		11	62905-84-4	72[a]
V	$CH_3O_2CCH{=}CHCH_2OH$	4508-99-0	12	62861-57-8	80[d]
VI	$CH_2{=}C(OC_2H_5)CH_2OH$	62861-55-6	13	62905-85-5	60[b]
VII	$C_2H_5O_2CCH_2OH$	623-50-7	3		77[a]
VIII	$C_6H_5C(=O)CH(OH)C_3H_7$	20907-23-7	14	62905-86-6	44[a,c]
IX	$CH_3O_2CCH(OH)C_5H_{11}$	54340-91-9	15	62861-58-9	89[a]
X	$C_2H_5C(=O)CH(OH)CH_3$	5704-20-1	16	62861-64-7	75[a]

[a] Isolated yield of purified triflate. [b] Yield based on salt formation with triphenylphosphine. [c] Initial yield 75% by NMR; partial decomposition during isolation. [d] Yield of oil after solvent removal, pure by NMR.

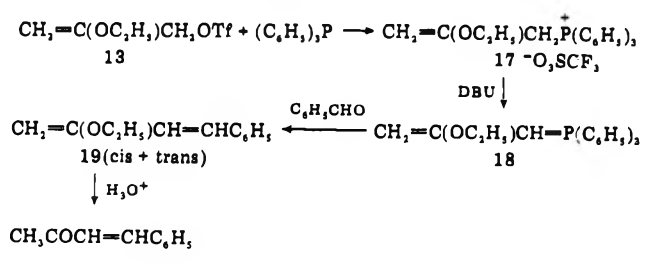
Table III. Half-Lives for Diphenyl Sulfide Alkylation by Triflates[a]

Triflate	$T_{1/2}$	Triflate	$T_{1/2}$
$TfOCH_2CO_2C_2H_5$	5 h	$TfOCH_2CN$	8 h
$TfOCH_2COCH_3$	8 h	$TfOCH_2CH{=}CHCO_2CH_3$	<5 min
$TfOCH_2COC_6H_5$	2 h	$TfOCH(C_5H_{11})CO_2CH_3$	4.5 days
$TfOCH_2COCCl_3$	0.7 h	$TfOCH(CH_3)COC_2H_5$	12 h

[a] Experiments performed in CD_3CN: half-life indicates disappearance of one-half of triflate at 25 °C according to NMR integration; sixfold excess diphenyl sulfide (~1 M).

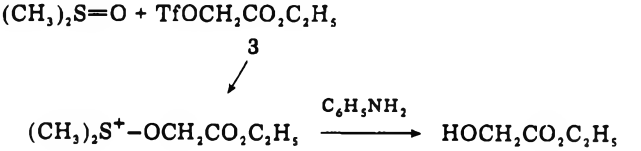
sulfur, or phosphorus. Only the α,β-unsaturated ester derivative 12 has a sufficient lifetime in acetonitrile at 20 °C to allow use of this solvent for preparation of sulfonium salts from the triflate. The other allylic triflates attack acetonitrile within minutes at room temperature, and react violently with solvents such as Me_2SO or DMF. Typical sulfides are alkylated with considerable evolution of heat using any of the reagents 8–11, and even diphenyl sulfide is completely alkylated after 1–2 min at room temperature in chloroform.

Entry VI, Table II, refers to the trifluoromethanesulfonate ester 13 of 2-ethoxyprop-2-en-1-ol. This triflate is too unstable for isolation by the usual distillation procedure and decomposes in methylene chloride solution above −20 °C. In order to characterize the triflate, we have treated filtered solutions of 13 with nucleophiles at −40 °C. Noncrystalline salts are formed with diphenyl sulfide, thioanisole, or pyridine, but the triphenylphosphonium salt 17 is easily obtained as the pure solid in 61% yield. The structure of 17 is based on spectral and



analytical data, as well as on Wittig condensation with benzaldehyde in the presence of DBU to form the dienyl ether 19. Acid hydrolysis of 18 affords the enone in good yield. Prior to our work, the ethoxyallylidenetriphenylphosphorane (18) had not been described in the literature. However, we have recently learned that Martin and Desai have generated the same phosphorus ylide from a different precursor.[6]

The trifluoromethanesulfonate esters of α-hydroxycarbonyl compounds are considerably less reactive than the allylic reagents, but the triflates are far more effective alkylating agents than the α-bromocarbonyl analogues. For example, tetrahydrothiophene is alkylated rapidly at −20 °C by the triflate 3 derived from ethyl glycolate, while the corresponding reaction with ethyl bromoacetate requires several hours at 25 °C. The triflate 3 does not alkylate acetonitrile or dimethylformamide to an appreciable extent at 25 °C after 24 h, but extensive decomposition of 3 occurs in these solvents at 40 °C. Dimethyl sulfoxide is O-alkylated cleanly at room temperature. The moisture-sensitive alkoxysulfonium salt 20 could not be



crystallized, but the assigned structure is supported by spectral data and by cleavage to ethyl glycolate (89%) upon treatment with aniline.

Table III compares the relative reactivity of representative triflates toward diphenyl sulfide. Qualitative half-lives are listed for disappearance of starting triflate in the presence of a sixfold excess of diphenyl sulfide (deuterioacetonitrile, NMR analysis). To a first approximation, alkylation rates increase with increasing electron demand from substituents and decrease with increased substitution at the triflate α carbon. These observations are compatible with S_N2 attack by sulfide on triflates derived from hydroxy esters, ketones, or nitriles.

The triflate reagents described in Tables I and II provide easy access to a variety of stabilized sulfur or nitrogen ylides. We have already published some examples of the utility of

triflate 3 for synthesis of ester-stabilized ylides, which undergo facile fragmentation to alkenes.[2] By comparison, the carbenoid decomposition of ethyl diazoacetate in the presence of sulfide or amine gives poor yields of ylide-derived products and numerous side products in several cases that we have examined. Other synthetic applications of the triflate reagents involving ring expansion by repeatable 2,3-sigmatropic shifts will be described elsewhere.

Experimental Section

Preparation and Purification of Starting Materials. Trifluoromethanesulfonic acid was obtained from 3M Company, distilled, and kept in a flask equipped with a three-way stopcock under N_2 atmosphere. Trifluoromethanesulfonic anhydride was prepared according to the method of Burdon, Sarazmand, Stacy, and Tatlow[7] from trifluoromethanesulfonic acid and P_2O_5. Ethyl diazoacetate was obtained from the Aldrich Chemical Co. and was used without further purification.

Methylene chloride was distilled from P_2O_5 and stored over 4A molecular sieves.

Carboethoxymethyl Trifluoromethanesulfonate (3). Procedure A. To a solution of trifluoromethanesulfonic acid (6.0 g, 40 mmol) in sulfur dioxide (SO_2) (100 mL) at −78 °C was slowly added ethyl diazoacetate (4.56 g, 40 mmol) over a 20-min period. The mixture was stirred for 1 h at −78 °C and then the solvent was evaporated by removing the dry ice bath. The residue was cooled to 0 °C and ice water (15 mL) was added. The mixture was extracted with hexane (three 40-mL portions) and the combined hexane extracts were dried over Na_2SO_4. Norit (~100 mg) was added and the hexane solution was passed through a thin silica gel plug (1.5 cm). More hexane (50 mL) was used to further wash the silica gel plug. The hexane solution was then cooled in the freezer overnight and the hexane decanted from the colorless crystals (6.9 g, 73%): mp 22–23 °C; NMR ($CDCl_3$, δ) 1.35 (3 H, t, J = 7.0 Hz), 4.34 (2 H, q, J = 7.0 Hz), 4.98 (2 H, s); IR (cm^{-1}, film) 2990 (m), 2950 (w), 1769 (s), 1418 (s), 1385 (m), 1304 (m), 202 (s), 1145 (s), 930 (w), 864 (m), 813 (s), 760 (m), 610 (s).

Procedure B. Pyridine (166 mg, 2.1 mmol) in methylene chloride (7 mL) was cooled to −22 °C and trifluoromethanesulfonic anhydride (564 mg, 2.0 mmol) was added. After 5 min, ethyl glycolate (208 mg, 2.0 mmol) was added and the mixture was warmed to ambient temperature with a 22 °C water bath. The mixture was then filtered, the solvent evaporated, and the residue passed through a silica gel plug (~2 cm) with hexane. Evaporation of the solvent and crystallization from hexane at 0 °C gave a colorless liquid (364 mg, 77%), identical with material prepared previously.

Phenacyl Trifluoromethanesulfonate (4). Trifluoromethanesulfonic acid (900 mg, 6.0 mmol) was dissolved in SO_2 (20 mL) at −78 °C. diazoacetophenone[15] (877 mg, 6.0 mmol) was added slowly to the colorless acid solution. The yellow diazoacetophenone upon addition quickly dissolved and N_2 evolution was apparent. The reaction was stirred for 20 min at −78 °C and then warmed to 0 °C to evaporate the solvent. The residue was extracted with hexane, and Norit treatment followed by evaporation of solvent gave phenacyl trifluoromethanesulfonate. The product was recrystallized from hexane to give fine white needles (1.207 g, 75%): mp 55.5–56 °C; NMR (CDCl, δ) 5.7 (2 H, s), 7.5–9.0 (5 H, m); IR (cm^{-1}, CHCl) 3042 (w), 2961 (w), 1715 (s), 1601 (m), 1588 (w), 1455 (m), 1419 (s), 1372 (m), 1238 (s), 1145 (s), 1049 (s), 1020 (m), 960 (s), 829 (m), 687 (m).

Cyanomethyl Trifluoromethanesulfonate (5). A methylene chloride solution of diazoacetonitrile was prepared according to the procedure of Curtius[8] from aminoacetonitrile hydrochloride (1.296 g, 14 mmol), sodium acetate trihydrate (21.4 mg, 0.17 mmol), sodium nitrite (1.47 g, 21.2 mmol), and 10% H_2SO_4 (0.464 mL). The methylene chloride extracts were combined and dried over Na_2SO_4. After filtering, the solution was concentrated to about one-third of the original volume. (CAUTION: Neat diazoacetonitrile is extremely explosive.) The crude reaction mixture was added dropwise to trifluoromethanesulfonic acid (1.80 g, 12 mmol) in SO_2 (20 mL) at −78 °C. After 20 min at −78 °C, the mixture was warmed to 0 °C and then quenched with ice water (10 mL). Extraction of the reaction mixture with ether (three 15-mL portions) gave a yellow oil after combining extracts, drying over Na_2SO_4, and evaporating. The oil was taken up as much as possible in hexane (two 15-mL portions) and the combined hexane washings were cooled to −78 °C. The triflate crystallized and the hexane was decanted at 0 °C. The crystals quickly melt when removed from a 0 °C ice bath. A colorless liquid (522 mg, 23%) was obtained; NMR ($CDCl_3$, δ) 5.10 (2 H, s); IR (film, cm^{-1}) 2260 (w), 1750 (w), 1420 (s), 1200–1250 (s), 1130 (s), 980 (s), 800 (w), 750 (m), 610 (s).

2-Oxopropyl Trifluoromethanesulfonate (6). This triflate was prepared from trifluoromethanesulfonic acid (2.37 g, 1.55 mmol) and 1-diazo-2-propanone[15] according to procedure A described for the preparation of carboethoxymethyl trifluoromethanesulfonate. The usual workup gave a yellow oil which was crystallized from hexane at −78 °C. The material crystallized as fine white needles (1.22 g, 37%): NMR ($CDCl_3$, δ) 2.21 (3 H, s), 4.90 (2 H, s); IR (cm^{-1}, CHCl) 3040 (w), 2979 (w), 1755 (s), 1736 (sh), 1420 (s), 1370 (w), 1252 (s), 1232 (s), 1146 (s), 1024 (s), 934 (s), 810 (m), 610 (s); mp 43.5–45 °C.

3,3,3-Trichloro-2-oxopropyl Trifluoromethanesulfonate (7). Trifluoromethanesulfonic acid (800 mg, 5.32 mmol) was dissolved in SO_2 (10 mL) at −78 °C. To this solution was added 1-diazo-3,3,3-trichloro-2-propanone[9] (1.00 g, 5.32 mmol). The diazo compound was instantly decolorized and N_2 evolution was apparent. The mixture was stirred for another 20 min at −78 °C and then warmed to 0 °C. The usual workup followed by several recrystallizations from hexane gave 3,3,3-trichloro-2-oxopropyl trifluoromethanesulfonate (450 mg, 36%); mp 36–38 °C; NMR ($CDCl_3$, δ) 5.70 (2 H, s); IR ($CHCl_3$, cm^{-1}) 2985 (w), 1780 (s), 1430 (s), 1370 (w), 1410 (s), 1215 (s), 1140 (s), 1020 (s), 885 (w), 825 (w), 760 (m), 610 (s).

Prop-2-enyl Trifluoromethanesulfonate (8). Freshly distilled trifluoromethanesulfonic anhydride (14.1 g, 50.0 mmol) was dripped slowly into a mechanically stirred solution of dry pyridine (4.05 mL, 50.0 mmol) in refluxing chloromethane (70 mL, Matheson, unpurified) under a slight positive N_2 pressure (dry ice condenser). Neat 2-propen-1-ol (3.40 mL, 50.0 mmol) was then added dropwise to the white, viscous suspension over a 10-min period. The solvent was then allowed to boil away and the stirring apparatus replaced by a short-path distillation head. The triflate was distilled (ambient temperature, safety shield) and the product was trapped into a cooled (dry ice–EtOH) receiver (6.54 g, 69%, density 1.47 g/mL at 20 °C). The colorless oil must be stored at −78 °C in a vented flask. CAUTION: an explosion occurred on accidental warming of sealed ampules. Care should be exercised to avoid contact with or inhalation of this volatile, extremely reactive alkylating agent. The neat reagent has a half-life of ~10 min at room temperature: IR (neat, cm^{-1}) 2970 (w), 1413 (m), 1281 (s), 1248 (s), 1194 (s), 1149 (m), 913 (m); NMR (CCl_4, δ) 5.8–6.2 (1 H, m), 5.4–5.6 (2 H, m), 4.95 (2 H, d, J = 6 Hz).

Prop-2-ynyl Trifluoromethanesulfonate (9). Freshly distilled trifluoromethanesulfonic anhydride (2.82 g, 10.0 mmol) was dripped slowly into a mechanically stirred solution of dry pyridine (791 mg, 10.0 mmol) in methylene chloride (20 mL) at −23 °C (dry ice-CCl_4) under positive nitrogen pressure. Neat propargyl alcohol (449 mg, 8.0 mmol) was added dropwise over a 10-min period. The suspension was allowed to warm and was quickly filtered and evaporated under the aspirator. The resultant oil was extracted with hexane (three 20-mL portions) and the hexane was quickly removed under the aspirator (20 °C). The residue was immediately distilled (ambient temperature, 0.1 mm) through a short-path apparatus and the volatile product was trapped in a cooled (dry ice–EtOH) receiver (0.80 g, 53%). The colorless oil must be stored at −78 °C in a vented flask: IR (CCl_4, cm^{-1}) 3330 (m), 2970 (w), 2142 (w), 1430 (s), 1251 (m), 1220 (s), 1148 (s), 1008 (w), 981 (m), 945 (s); NMR (CCl_4, δ) 5.06 (2 H, d, J = 2 Hz), 2.76 (1 H, t, J = 2 Hz).

2-Chloroprop-2-enyl Trifluoromethanesulfonate (10). This triflate was prepared according to the method described for the preparation of 8, using 2-chloroprop-2-en-1-ol (184 mg, 2.0 mmol, Chemical Samples Co.), trifluoromethanesulfonic anhydride (593 mg, 2.1 mmol), and pyridine (174 mg, 2.2 mmol) in methyl chloride solution. The solvent was removed at 0 °C by a stream of dry N_2 and the residue was distilled through a short-path distillation apparatus. A colorless liquid (354 mg, 79%) was trapped in a dry ice–ethanol cooled flask; NMR ($CDCl_3$, δ) 5.01 (2 H, s), 5.64 (1 H, d, J = 2.2 Hz), 5.70 (2 H, d, J = 2.2 Hz); IR (cm^{-1}, $CHCl_3$) 2987 (w), 1639 (m), 1415 (s), 1250 (s), 1211 (s), 1142 (s), 1005 (m), 975 (m), 950 (s), 928 (s), 848 (m), 818 (m), 763 (m), 618 (s); bp <22 °C [bath temperature 22 °C (0.25 mm)].

(*E*)-3-Trimethylsilylprop-2-enyl Trifluoromethanesulfonate (11). This material was prepared using a procedure identical with that for allyl triflate (8). Thus, the combination of trifluorosulfonic anhydride (2.82 g, 10.0 mmol), pyridine (791 mg, 10.0 mmol), and 3-trimethylsilylprop-2-enol[10] in methylene chloride (40 mL) yielded 11 (1.50 g, 57%) after distillation [34 °C (0.25 mm)]: NMR (δ, CCl_4) 6.2 (2 H, m), 5.1 (2 H, m), 0.13 (9 H, s); IR (cm^{-1}, neat) 2970 (w), 1620 (w), 1410 (m), 1280 (s), 1248 (s), 1190 (s), 995 (w). The product was stored at −78 °C in a vented flask, and turned dark within an hour at 20 °C.

(*E*)-3-Trimethylsilylprop-2-enol.[10] According to a procedure provided by Professor Stork, 3-trimethylsilylprop-2-ynol (50 mmol) was dripped into a suspension of $LiAlH_4$ (57.5 mmol) and sodium

methoxide (105 mmol) in THF (95 mL) at reflux. Freshly opened $LiAlH_4$ gave 61% of *E* alcohol (>90% *E*) using the recommended 3 h reaction time and workup with water (20 °C, careful addition), followed by 15% aqueous sodium hydroxide and distillation [bp 34 °C (0.1 mm)]. Our first attempts using the conventional procedure of dripping the alcohol into an ether–lithium aluminum hydride suspension (2:1 molar ratio, $LiAlH_4$-alcohol) at varying temperatures gave mixtures of what appear to be the *Z* and the *E* alcohols (2–3:1, *Z*/*E*) in reasonable yield (60–70%). Our evidence for the identity of the "*Z*" product consists only of the following data extracted from an NMR spectrum of the mixture [NMR (δ, $CDCl_3$) 6.31 (1 H, d of t, J = 14, 6 Hz), 5.53 (1 H, d, J = 14 Hz), 4.07 (2 H, d, J = 6 Hz), 2.8 (1 H, s), 0.12 (9 H, s)], which is to be compared with the NMR spectrum of the *E* isomer [NMR (δ, $CDCl_3$) 6.03 (1 H, d, J = 19 Hz), 5.85 (1 H, d of t, J = 19, 3 Hz), 4.02 (2 H, d, J = 3 Hz), 3.20 (1 H, s), 0.03 (9 H, s).

(3-Carbomethoxy)prop-2-enyl Trifluoromethanesulfonate (12). A solution of pyridine (1.22 mL, 15.0 mmol) in methylene chloride (25 mL) was treated with trifluoromethanesulfonic anhydride (3.95 g, 14.0 mmol) at −23 °C (dry ice–CCl_4) with vigorous mechanical stirring under a slight nitrogen pressure. Methyl (3-hydroxy)but-2-enoate[14] (1.39 g, 12.0 mmol) dissolved in methylene chloride (5 mL) was slowly dripped into the white suspension. The reaction was then allowed to warm to 20 °C and quickly filtered. The filtrate was evaporated and the yellow oil was extracted with hexane (two 15-mL portions). The washings were then evaporated, leaving **12** as a pale yellow oil which appeared pure by NMR (2.23 g ~80%). Attempted distillation (<0.1 mm) resulted in decomposition and attempts at crystallization failed: IR (CCl_4, cm^{-1}) 2960 (w), 2850 (w), 1729 (s), 1671 (w), 1648 (w), 1421 (s), 1244 (s), 1219 (s), 1205 (s), 1144 (s), 933 (m); NMR (CCl_4, δ) 6.92 (1 H, dt, J = 16, 5 Hz), 6.17 (1 H, dm, J = 16 Hz), 5.12 (2 H, dm, J = 5 Hz), 3.78 (3 H, s).

2-Ethoxyprop-2-en-1-ol. Ethyl 2-ethoxypropenoate[11] (3.0 g, 20.8 mmol) in ether (5 mL) was slowly added to lithium aluminum hydride (780 mg, 20.8 mmol) in refluxing ether (100 mL). After refluxing the mixture for 18 h and cooling to ambient temperature, Glauber's salt (Na_2SO_4, 10 H_2O) was continuously added to decompose the excess $LiAlH_4$. An excess of Glauber's salt was used and the mixture was stirred for 2 hr before filtering. The filtrate was concentrated and distilled to give a colorless oil (1.80 g, 86%); bp 30–35 °C (0.5 mm); NMR ($CDCl_3$, δ) 1.28 (3 H, t, J = 7.0 Hz), 3.5 (1 H, broad OH), 3.75 (2 H, q, J = 7.0 Hz), 3.94 (2 H, s), 3.99 (1 H, d, J = 2 Hz), 4.13 (1 H, d, J = 2 Hz); IR (cm^{-1}, film) 3360 (s), 2975 (s), 2922 (m), 1662 (s), 1625 (m), 1442 (m), 1378 (m), 1294 (s), 1256 (s), 1090 (s), 1030 (s), 970 (w), 808 (s); exact mass determined, 102.068 08; calcd for $C_5H_{10}O_2$, 102.06820.

Preparation and Trapping of 2-Ethoxyprop-2-enyl Trifluoromethanesulfonate 13 with Pyridine. Pyridine (166 mg, 2.1 mmol) in dichloromethane (7 mL) was cooled to −22 °C and trifluoromethanesulfonic anhydride (564 mg, 2.0 mmol) was added to form the crystalline pyridinium adduct at −22 °C. The solution was cooled to −42 °C and 2-ethoxyprop-2-en-1-ol (204 mg, 2.0 mmol) was added slowly with vigorous stirring. The mixture was stirred for 10 min after the addition was complete and during this time most of the precipitate had dissolved. Dry hexane (8 mL) was slowly added via syringe to precipitate the dissolved salts. The solution was filtered through a sintered glass frit built into the reaction vessel directly into a solution of pyridine (158 mg, 2.0 mmol) in dry methylene chloride (1 mL) at 0 °C and the mixture was stirred for 20 min at 0 °C. After warming to ambient temperature and removing the solvents, the residue was washed with ether to remove neutral materials and pumped dry under vacuum (0.25 mm). A pyridinium salt (523 mg, 81%) was obtained which failed to crystallize; NMR ($CDCl_3$, δ) 1.20 (3 H, t, J = 7.6 Hz), 3.74 (2 H, q, J = 7.6 Hz), 4.30 (1 H, d, J = 3.1 Hz), 4.65 (1 H, d, J = 3.1 Hz), 5.24 (2 H, s), 8.15 (2 H, m), 8.62 (1 H, m), 8.94 (2 H, d, J = 6.2 Hz); IR (cm^{-1}, $CHCl_3$) 3070 (m), 2985 (w), 1640 (s), 1580 (w), 1489 (s), 1444 (m), 1438 (m), 1270 (s), 1225 (s), 1160 (s), 1074 (m), 1030 (s), 984 (w), 822 (w), 772 (m), 752 (m), 688 (m), 634 (s).

Preparation and Trapping of 2-Ethoxyprop-2-enyl Trifluoromethanesulfonate 13 with Thioanisole. Following the above procedure the sulfonium salt was prepared from pyridine (166 mg, 2.1 mmol), trifluoromethanesulfonic anhydride (564 mg, 2.01 mmol), 2-ethoxyprop-2-en-1-ol (204 mg, 2.0 mmol), and thioanisole (248 mg, 2.0 mmol). The salt (494 mg, 76%) was an oil which failed to crystallize; NMR ($CDCl_3$, δ) 1.2 (3 H, t, J = 6.8 Hz), 3.4 (3 H, s), 3.65 (2 H, m), 4.28 (1 H, d, J = 3 Hz, 4.44 (1 H, d, J = 3 Hz), 4.50 (2 H, AB, J = 12.0 Hz), 7.7 (3 H, m), 8.0 (2 H, m); IR (cm^{-1}, $CHCl_3$) 2970 (m), 1645 (s), 1570 (w), 1450 (m), 1405 (m), 1280 (s), 1150 (s), 1035 (s), 980 (w), 750 (m), 695 (m), 638 (s).

Preparation of 2-Ethoxyprop-2-enyltriphenylphosphonium Trifluoromethanesulfonate (17). 2-Ethoxyprop-2-enyl trifluoromethanesulfonate was prepared as above from 2-ethoxyprop-2-en-1-ol (204 mg, 2.0 mmol), pyridine (166 mg, 2.1 mmol), and trifluoromethanesulfonic anhydride (564 mg, 2.0 mmol). The hexane–dichloromethane solution of the triflate at −42 °C was filtered through a frit in the side arm of the flask directly into a solution of triphenylphosphine (470 mg, 1.8 mmol) in dry dichloromethane (1 mL) at −42 °C. During the addition the phosphonium salt precipitates out. The mixture was stirred at −42 °C for 10 min and warmed to ambient temperature (30 min). After solvent removal and recrystallization from THF–ether, colorless, fine needles (541 mg, 61% based on triphenylphosphine) were obtained: mp 87–88.5 °C; NMR ($CDCl_3$, δ) 0.88 (3 H, t, J = 7.0 Hz), 3.45 (2 H, q, J = 7.0 Hz), 4.10 (1 H, m), 4.38 (1 H, m), 4.30 (2 H, d, J = 14.4 Hz), 7.7 (15 H, m); IR (cm^{-1}, $CHCl_3$) 3010 (m), 1630 (m), 1586 (w), 1484 (w), 1440 (m), 1382 (w), 1272 (s), 1220 (m), 1156 (m), 1108 (m), 1055 (w), 1029 (s), 995 (w), 866 (w), 680 (m), 632 (s). Anal. Calcd for $C_{24}H_{24}F_3PO_4S$: C, 58.05; H, 4.88; S, 6.44. Found: C, 58.06; H, 4.83; S, 6.50.

Preparation of (*E*)- and (*Z*)-(3-Ethoxybutadienyl)benzene (19) and Hydrolysis to 4-Phenylbut-3-en-2-one. (2-Ethoxyprop-2-enyl)triphenylphosphonium trifluoromethanesulfonate (17) (124 mg, 0.25 mmol) was dissolved in THF (3 mL) and cooled to −78 °C, and DBU (24 mg, 0.25 mmol) was added. With the addition of base the solution turned from colorless to deep yellow. Benzaldehyde (27 mg, 0.25 mmol) was added and the mixture was stirred at −78 °C for 15 min, at 0 °C for 1 h, and then overnight. After refluxing for 6 h, the mixture was diluted with water (5 mL) and extracted with hexane (three 20-mL portions). The hexane extracts were combined, dried over Na_2SO_4, and evaporated. PLC of the residue on silica gel using 40% ether in hexane gave a pale yellow oil, R_f 0.6 (28 mg, 64%): NMR ($CDCl_3$, δ) [mixture of *E*/*Z* isomers 7.6:1 based on NMR integration] *E* isomer 1.37 (3 H, t, J = 7 Hz), 3.85 (2 H, q, J = 7 Hz), 4.2 (2 H, s), 6.50 (1 H, d, J = 17 Hz), 6.93 (1 H, d, J = 17 Hz), 7.2 (5 H, m); *Z* isomer 1.05 (3 H, t, J = 7 Hz), 3.70 (2 H, q, J = 7 Hz), 4.12 (2 H, s), 5.95 (1 H, d, J = 13 Hz), 6.45 (1 H, d, J = 13 Hz), 7.2 (5 H, m); IR (cm^{-1}, film) 2980 (m), 1640 (w), 1595 (m), 1580 (m), 1490 (m), 1445 (m), 1373 (w), 1310 (s), 688 (s); exact mass determined, 174.104 46; calcd for $C_{12}H_{14}O$, 174.104 43. Treatment of the diene in methanol (2 mL) and water (1 mL) with 10% HCl (2 drops) for 4 h at ambient temperature gave 4-phenylbut-3-en-2-one, identical with authentic material.

1-(1-Phenylcarbonyl)butyl Trifluoromethanesulfonate (14). Pyridine (41 mg, 0.52 mmol) in dry CH_2Cl_2 (1.8 mL) was cooled to −22 °C and trifluoromethanesulfonic anhydride (144 mg, 0.51 mmol) was added. A white pyridinium salt immediately precipitated. After stirring the mixture for 5 min, 2-hydroxy-1-phenylpentan-1-one[11] (89 mg, 0.5 mmol) in CH_2Cl_2 (0.5 mL) was added. Stirring was continued for 10 min and then the reaction mixture was brought to ambient temperature with a water bath (~22 °C). The mixture was quickly filtered and the white precipitate was washed with CH_2Cl_2 (2 mL). The solvent was evaporated and the crude oil which remained was extracted with hexane. After concentrating the hexane extracts to 5 mL, the solution was left in the freezer overnight to give fine white crystals (71 mg, 44%); mp 46–47.5 °C; NMR ($CDCl_3$, δ) 1.1 (3 H, t, J = 8.0 Hz), 1.65 (2 H, m), 2.02 (2 H, m), 6.00 (1 H, t, J = 6.0 Hz), 7.3–7.7 (3 H, m), 7.95 (2 H, dd, J = 2.0, 8.0 Hz); IR (cm^{-1}, $CHCl_3$) 3080 (w), 2050 (w), 2980 (m), 2970 (m), 2890 (m), 1708 (s), 1601 (m), 1586 (w), 1456 (m), 1461 (s), 1250 (s), 1215 (s), 1156 (s), 1008 (w), 938 (s), 764 (s), 699 (s), 668 (m).

1-(1-Carbomethoxy)hexyl Trifluoromethanesulfonate (15). To a solution of pyridine (181 mg, 2.3 mmol, distilled from BaO and stored over KOH) in CH_2Cl_2 (6.6 mL) at −22 °C was slowly added freshly distilled trifluoromethanesulfonic anhydride (586 mg, 2.2 mmol). The white suspension which formed was stirred vigorously for 5 min and then methyl 2-hydroxyheptanoate (320 mg, 2.0 mmol) in CH_2Cl_2 (1 mL) was slowly added. Stirring was continued for 15 min at −22 °C. A 20 °C water bath was used to warm the reaction mixture quickly to ambient temperature. The reaction turned light tan at this point and the precipitate was filtered and washed with more dichloromethane (two 3-mL portions). After evaporating the combined filtrates, the residue was extracted with hexane (three 15-mL portions), dried over Na_2SO_4, and passed through a silica gel plug (1.5 cm). The plug was thoroughly washed with more hexane (20 mL). Evaporation of the solvent gave a colorless liquid (522 mg, 89%): NMR ($CDCl_3$, δ) 0.91 (3 H, t, J = 7.1 Hz), 1.40 (6 H, m); IR (cm^{-1}, film) 2972 (m), 2948 (m), 1770 (s), 1435 (m), 1425 (s), 1362 (w), 1295 (w), 1250 (s), 1215 (s), 1149 (s), 1011 (w), 948 (s), 875 (w), 620 (s).

3-Oxo-pent-2-yl Trifluoromethanesulfonate (16). A solution of pyridine (2.02 mL, 25 mmol) in CH_2Cl_2 (50 mL) was treated with trifluoromethanesulfonic anhydride (7.04 g, 25 mmol) at −23 °C (CCl_4–dry ice) under slight N_2 pressure with mechanical stirring. Freshly distilled 2-hydroxy-3-pentanone[13] (2.00 g, 19.6 mmol) was dripped in over a 5-min period and the reaction immediately allowed

Table IV. Crystalline Diphenylsulfonium Derivatives of Triflate Reagents

Triflate	Solvent for alkylation	Mp of salt, °C	Chemical shift of HCS^+Ph_2, ppm	Registry no.
4	CH_3CN	168–169.5	6.52 (CD_3COCD_3)	62861-59-0
6	CH_3CN	119–120	5.97 (CD_3COCD_3)	62861-61-4
7	CH_3CN	163–165.5	5.18 ($CDCl_3$)	62861-66-9
9	$CHCl_3$	118–120	5.12 (CD_3CN)	62861-63-6
10	$CHCl_3$	104–105	5.35 ($CDCl_3$)	62861-68-1

Table V. Crystalline Triphenylphosphonium Salts from Triflates

Triflate	Solvent for alkylation	Mp of salt, °C	Chemical shift of HCP^+Ph_3, ppm	Registry no.
8	$CHCl_3$	131–133	4.21 ($CDCl_3$)	62861-69-2
12	$CHCl_3$	150–153	4.55 ($CDCl_3$)	62861-70-5
16	$CHCl_3$	137–139	5.87 ($CDCl_3$)	62861-72-7

to warm to 20 °C. The red oil resulting from evaporation of the methylene chloride was extracted with three 10-mL portions of 10% ether–hexane. Evaporation and distillation [bp 35 °C (0.8 mm), 3.43 g, 75%] of the combined extracts yielded a colorless oil which crystallized on standing in a freezer. These crystals melt at approximately 5 °C: IR (CCl_4, cm^{-1}) 2995 (w), 2955 (w), 1731 (m), 1422 (s), 1248 (m), 1215 (s), 1148 (s), 940 (m), 915 (s); NMR (CCl_4, δ) 5.14 (1 H, q, J = 5 Hz), 2.61 (2 H, q, J = 6 Hz), 1.65 (2 H, d, J = 5 Hz), 1.12 (3 H, t, J = 6 Hz).

General Method for Preparation of Diphenylsulfonium Salts from Trifluoromethanesulfonates. Preparation of (Carboethoxymethyl)diphenylsulfonium Trifluoromethanesulfonate. To carboethoxymethyl trifluoromethanesulfonate (**3**) (472 mg, 2.0 mmol) in dry acetonitrile (4 mL) was added diphenyl sulfide (558 mg, 3.0 mmol). This mixture was stored at room temperature, in the dark, and under a static nitrogen atmosphere for 2 days. The solvent was evaporated and the residue washed with hexane (two 5-mL portions) to remove excess sulfide. The residue was taken up in a minimum amount of THF and then ether was slowly added until the mixture became cloudy. At this point, the triflate crystallized. The mixture was left in the freezer overnight and then the salt was filtered and recrystallized from THF–ether (490 mg, 58%): mp 120.5–121 °C; NMR ($CDCl_3$, δ) 1.20 (3 H, t, J = 7.1 Hz), 4.20 (2 H, q, J = 7.1 Hz), 5.40 (2 H, s), 7.71 (6 H, s), 8.08 (4 H, m); IR (cm^{-1}, $CHCl_3$) 3030 (m), 1735 (s), 1580 (w), 1480 (m), 1448 (m), 1400 (w), 1372 (m), 1315 (m), 1255 (s), 1215 (s), 1165 (m), 1035 (s), 750 (s), 660 (m), 635 (m). Anal. Calcd for $C_{17}H_{17}O_5S_2F_3$: C, 48.45; H, 4.06; S, 15.15. Found: C, 48.48; H, 4.08; S, 15.23.

The same method was used to prepare crystalline diphenylsulfonium salts for additional characterization of triflates **4**, **6**, and **7** (Table IV). The more reactive triflates **9** and **10** also gave crystalline diphenylsulfonium salts, but the reaction could not be performed in acetonitrile due to solvent alkylation. Chloroform was used for these alkylations. The diphenylsulfonium salts from **5**, **8**, **11**, **12**, **15**, and **16** did not crystallize. Characterization of **8**, **12**, and **16** by way of the crystalline triphenylphosphonium salts was successful (Table V). Thus, 0.25 mmol of triflate was added to 0.28 mmol of triphenylphosphine in 1–2 mL of dry chloroform. After 1 h, the residual oil after solvent removal and ether trituration was crystallized from tetrahydrofuran–ether.

Alkylation of Dimethyl Sulfoxide with Carboethoxymethyl Trifluoromethanesulfonate (3) and Proof of O-Alkylation. Dimethyl sulfoxide (78 mg, 1.0 mmol) was dissolved in dry acetonitrile (1.6 mL) and carboethoxymethyl trifluoromethanesulfonate (236 mg, 1.0 mmol) (**3**) was added. The mixture was stirred overnight and the solvent was evaporated. A colorless oil (301 mg, 96%) which failed to crystallize was obtained after washing with hexane: NMR ($CDCl_3$, δ) 1.30 (3 H, t, J = 7.1 Hz), 3.48 (6 H, s), 4.30 (2 H, q, J = 7.1 Hz), 4.95 (2 H, s); ^{13}C NMR ($CDCl_3$, ppm) 168.157 (C=O), 71.05 (OCH_2), 62.888 (CH_2C=O), 35.608 (CH_2=CH_3), 13.912 (Me_2S^+); IR (cm^{-1}, film) 3470 (m), 3030 (m), 2940 (m), 1735 (s), 1435 (w), 1387 (m), 1260 (s), 1230 (s), 1169 (s), 1100 (m), 1055 (m), 1034 (s), 980 (m), 870 (w), 760 (w), 640 (s).

The colorless oil (314 mg, 1.0 mmol) was dissolved in dry chloroform and freshly distilled aniline (75 mg, 0.95 mmol) was added. The reaction mixture quickly turned yellow and within a few minutes a white precipitate formed. After 15 min, ether was added until cloudy and the precipitate was filtered and washed with more ether. The filtrate was passed through a silica gel plug and the solvent was evaporated. PLC of the residue on silica gel using 50% ether in hexane gave a colorless oil (92 mg, 89%) identified as ethyl glycolate.

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Registry No.—**13** pyridinium salt, 62861-74-9; **13** thioanisole salt, 62861-76-1; **17**, 62861-78-3; (*E*)-**19**, 1902-98-3; (*Z*)-**19**, 1981-43-7; **20**, 62861-79-4; trifluoromethanesulfonic acid, 1493-13-6; trifluoromethanesulfonic anhydride, 358-23-6; 3-trimethylsilylprop-2-ynol, 5272-36-6; (*Z*)-3-trimethylsilylprop-2-enol, 62861-80-7; (*E*)-3-trimethylsilylprop-2-enol, 59376-64-6; ethyl 2-ethoxypropenoate, 22121-86-4; pyridine, 110-86-1; thioanisole, 100-53-8; triphenylphosphine, 603-35-0; (carboethoxymethyl)diphenylsulfonium trifluoromethanesulfonate, 62861-81-8; diphenyl sulfide, 139-66-2; dimethyl sulfoxide, 67-68-5.

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A General One-Step Synthesis of Nitriles from Ketones Using Tosylmethyl Isocyanide. Introduction of a One-Carbon Unit[1]

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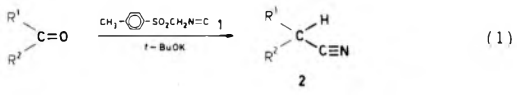
Ketones are converted efficiently, in one step, to nitriles ($R_2CO \rightarrow R_2CHC{\equiv}N$) at temperatures between 0 and 45 °C by the use of TosMIC (tosylmethyl isocyanide) and base. This conversion is effectively a reductive cyanation, unlike the classical cyanohydrin reaction. The reaction is shown to be generally applicable.

Tosylmethyl isocyanide (TosMIC, 1) is a synthon with diverse and steadily expanding applications. Thus far emphasis in the chemistry of TosMIC has centered mainly on heterocyclic synthesis. The preceding paper in this series deals with the synthesis of imidazoles from TosMIC and aldimines,[2a] and summarizes other azole (and azoline) syntheses.[2] The present paper will show, however, that the application of TosMIC by no means is restricted to the domain of heterocyclic synthesis only.

We here wish to concentrate on the use of TosMIC in an efficient, direct conversion of ketones to nitriles:[3]



(1)

TosMIC adds one carbon unit to a ketone, as in the classical cyanohydrin reaction,[4] but without the simultaneous formation of an α-hydroxy group. In this sense the reaction of TosMIC is a "reductive cyanation". Reaction 1 is unique because it allows the ketone → nitrile conversion to be carried out in a single operation.[5,6]

Obviously, the nitriles can be exploited further, for instance, by conversion to carboxylic acids or derivatives thereof.[6,7] A reaction of TosMIC with aldehydes and ketones leading in two steps via *N*-(1-tosyl-1-alkenyl)formamides to carboxylic acids has been reported independently by Schöllkopf et al.,[8a] and this reaction has later been shown to proceed through nitriles (as in eq 1).[8b]

Dehydration of aldoximes also leads to nitriles, however, with the same number of carbon atoms as in the starting aldehydes,[9] and therefore is a process quite different from reaction 1.

Results and Discussion

The synthesis of nitriles according to eq 1 is applicable to a wide variety of different ketones (Table I). The substrates range from simple aliphatic and aromatic ketones to sterically hindered ones, including camphor and β,β-dimethyl-α-tetralone (to give **2c** and **2g**, respectively). Also, the cyanation can be realized with 3- and 17-steroidal ketones (**2h–k**). So far only the severely hindered carbonyl of di-*tert*-butyl ketone has resisted reaction, whereas *tert*-butyl methyl ketone (pinacolone) and diisopropyl ketone are convertible (**2q** and **2p**).

Reaction Conditions. The conditions of reaction 1 were adapted to differences in reactivity of the ketones concerned. Typically, for ketones of normal reactivity *t*-BuOK was added at 0 °C to a solution of a ketone and 1.0–1.5 equiv of TosMIC in 1,2-dimethoxyethane (containing a little *t*-BuOH or EtOH). The reaction went to completion in 1–2 h at room temperature (**2a,b,d,e,i–k,m–o**). Under these mild conditions, however, camphor and diisopropyl ketone gave only trace amounts of nitrile (**2c,p**), and *tert*-butyl methyl ketone gave no more than 36% of 2-cyano-3,3-dimethylbutane (**2q**).

The best way to convert camphor to 2-cyanocamphane (**2c**) was with 3 equiv of TosMIC in dimethyl sulfoxide (containing some MeOH) at a slightly elevated temperature (45 °C). Thus, 80% of **2c** was obtained after 70 h. In hexamethylphosphoric triamide (HMPT) the same reaction went faster (17 h), but the product was less pure. Comparable reaction conditions were used with success for other sterically hindered ketones (nitriles **2g,p,q**). Benzophenone and α-tetralone,[10] which did not react in DME, were also converted to the corresponding nitriles (**2l,f**) in Me_2SO and HMPT, respectively.

Reaction Scheme. A rationale for reaction 1 is given in

Scheme I. Proposed Mechanism for Conversion of Ketones to Nitriles with TosMIC According to Equation 1

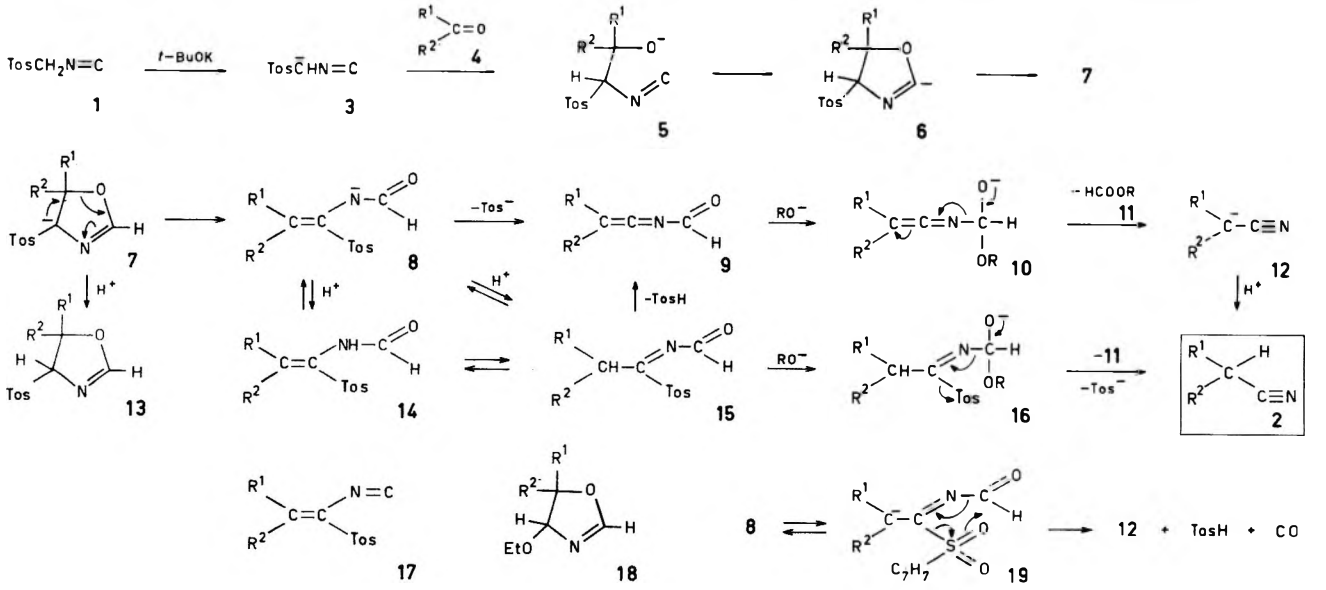


Table I. Nitriles Synthesized from Ketones and Tosylmethyl Isocyanide (TosMIC) According to Equation 1

Substrate[a] and product	Registry no.	TosMIC, equiv	Base (equiv) and solvent[b]	Time, h	Temp,[c] °C	Isolated yield, %	Bp or mp, °C	Lit. data
Adamantanone*	700-58-3							
2-Cyanoadamantane (**2a**)		1.3	*t*-BuOK (2.4), DME	1.5	35	93	~180	166–175[24]
2-Cyanoadamantane (**2a**)		1.3	*t*-BuOK (3.5), Me_2SO	17	20	84		
2-Norbornanone*	497-38-1							
2-Cyanonorbornane (**2b**)[d]		1.3	*t*-BuOK (3.5), Me_2SO	17	20	73	48–51 (endo)	51[25]
2-Cyanonorbornane (**2b**)[e]		1.3	EtONa (1.3), DME	2.5	20	62		
(+)-Camphor*	464-49-3							
2-Cyanocamphane (**2c**)[f]		3	*t*-BuOK (7), Me_2SO	70	45	80	135–148	[26]
2-Cyanocamphane (**2c**)		3	*t*-BuOK (7), HMPT	17	45	73		
2-Cyanocamphane (**2c**)		1.1	*t*-BuOK (2), DME	1.5	20	<5		
Cycloheptanone	502-42-1							
Cyanocycloheptane (**2d**)		1.1	*t*-BuOK (2), DME	1.5	20	80	85–86 (10 mm)	85–86 (10 mm)[33]
Cyclohexanone	108-94-1							
Cyanocyclohexane (**2e**)		1.0	*t*-BuOK (2), DME	1.5	20	80	62–67 (12 mm)	67 (10 mm)[33]
α-Tetralone	529-34-0							
1-Cyano-1,2,3,4-tetrahydronaphthalene (**2f**)		3	*t*-BuOK (5), HMPT	21	20	47	Chromat[g]	109–111 (1.5 mm)[34]
β,β-Dimethyl-α-tetralone*	2977-45-9							
1-Cyano-2,2-dimethyl-1,2,3,4-tetrahydronaphthalene (**2g**)		3	*t*-BuOK (7), HMPT	40	45	76	*h*	
Estrone 3-methyl ether	1624-62-0							
17β-Cyano-1,3,5(10)-estratrien-3-ol methyl ether (**2h**)		1.3	*t*-BuOK (3.5), Me_2SO	17	20	69	205–207	207–210[6b]
Androsta-1,4-diene-3,17-dione*	897-06-3							
17-Cyanoandrosta-1,4-dien-3-one (**2i**)[i]		1.3	EtONa (1.2), DME	2	20	47	159–164	
5α-Cholestan-3-one	566-88-1							
3-Cyano-5α-cholestane (**2j**)[j]		1.3	*t*-BuOK (2.5), DME	5	20	85	114–121	*k*
5β-Cholestan-3-one	601-53-6							
3-Cyano-5β-cholestane (**2k**)[l]		1.5	*t*-BuOK (3), DME	5	20	53	57–72	[36]
Benzophenone*	119-61-9							
Diphenylacetonitrile (**2l**)		1.3	*t*-BuOK (3.5), Me_2SO	17	20	69	67–71	74[30]
Acetophenone	98-86-2							
2-Phenylpropionitrile (**2m**)		1.0	*t*-BuOK (2), DME	1.5	20	68	74–78 (2 mm)	100 (8 mm)[37]
p-Bromoacetophenone*	99-90-1							
2-*p*-Bromophenylpropionitrile (**2n**)		1.0	*t*-BuOK (2), DME	1.5	20	79	112–116 (1 mm)	
Di-*n*-propyl ketone	123-19-3							
4-Cyanoheptane (**2o**)		1.2	*t*-BuOK (2.5), DME	1.5	20	74	*m*	183–184[33]
Diisopropyl ketone	565-80-0							
3-Cyano-2,4-dimethylpentane (**2p**)		3	*t*-BuOK (7), HMPT	70	45	65	$n^{21}D$ 1.4177[n]	170–171 } [38]
3-Cyano-2,4-dimethylpentane (**2p**)		1.0	*t*-BuOK (2), DME	1.5	20	<5		$n^{23}D$ 1.4158 }
tert-Butyl methyl ketone[p]	75-97-8							
2-Cyano-3,3-dimethylbutane (**2q**)		1.3	*t*-BuOK (3.5), Me_2SO	17	20	70	40–42 (15 mm) }	151–152 } [39]
2-Cyano-3,3-dimethylbutane (**2q**)		1.0	*t*-BuOK (2), DME	1.5	20	36	$n^{25}D$ 1.4099 }	$n^{25}D$ 1.4092 }
Di-*tert*-butyl ketone	815-24-0							
3-Cyano-2,2,4,4-tetramethylpentane	62796-07-0	3	*t*-BuOK (7), HMPT	170	45	*o*		67–78 (10 mm)[40]

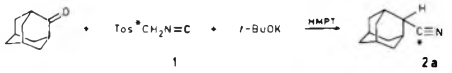
[a] Substrates are marked with an asterisk when further details are given in the Experimental Section. [b] Alcohol (1–2 equiv) was added in all cases (see text and Experimental Section). [c] All reactions were started around 0 °C, and usually after 15 min continued at the temperature indicated. [d] Endo–exo = 4:3. [e] Endo–exo = 1:1. [f] Endo–exo = 4:1 or 1:4. [g] Hydrolyzed (NaOH, 30% H_2O_2) to amide, mp 163–165 °C (lit.[34] 165–167 °C). [h] See Experimental Section. [i] α:β = 1:1 (see Table II, Experimental Section). [j] α:β = 0.7 (Table II). [k] Lit.[35] 3α—C≡N, mp 166–168 °C; 3β—C≡N, mp 142–144 °C. [l] α:β = 0.9 (Table II). [m] Short-path distilled, bath temperature 64 °C (12 mm). [n] As *m*, 65 °C (13 mm). [o] 65% of ketone recovered. [p] Pinacolone.

Scheme I. An important aspect of the proposed mechanism is the ring opening of **7** to **8**; beyond that stage the mechanism is more speculative. The following observations are consistent with Scheme I: (1) A ^{14}C label in the methylene group of **1** appears integrally in the nitrile **2a** (cf. eq 2). (2) In addition to **2a**, ethyl formate (**11**) has been detected qualitatively ($RO^- = EtO^-$), which accounts for the fate of the isocyano carbon of **1**. (3) The reaction can be interrupted at the stage of **7** as well as **8** to give **13** or **14**. (4) Under the conditions of reaction 1 both **13** and **14** can be converted to **2**, and further also **13** to **14** ($R^1 - R^2$ = pentamethylene). (5) Rapid H–D exchange is observed in **13** ($R^1 = R^2$ = Me) at C(4) only (with K_2CO_3 in CD_3OD–DME). For further details concerning these arguments and the (as yet unsolved) question of a one-step or two-step cycloaddition of **3** to **6**, we refer to previous discussions[2a,3,8,11] and the Experimental Section of the present paper.

An alternative mechanism involving a base-catalyzed condensation of **1** and a ketone to give **17** (Scheme I), followed by addition of water to **14** and eventually formation of **2** (and **13**), is highly unlikely. Compounds **17** have not been detected, even though they are expected not to be hydrated to **14** under the conditions of the reaction.[12]

In the second part of Scheme I attack of a nucleophile at the carbonyl of **9** or **15** is assumed.[3a,8b] The postulated intermediates **9** and **15** both possess a second carbon center that might well be more electrophilic than the carbonyl. (This may be true in particular for the N=C-Tos group[13] of **15**; also, nucleophilic reactions of ketenimines are well known[14].) However, initial nucleophilic attack at these other centers does not necessarily preclude the formation of **2**. In addition to the nucleophiles RO^- (R = Me, Et, or *t*-Bu) reacting with **9** or **15**, TosMIC anion (**3**) may act as such in some cases.[15]

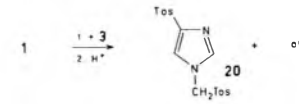
Occasionally, reaction 1, when carried out in Me_2SO or HMPT, was accompanied by evolution of gas. For the reaction of **1** with adamantanone in HMPT the gas was shown spectroscopically (MS and IR) to be carbon monoxide. This reaction gave 73% of 2-AdC≡N and 44% of CO (determined gravimetrically and volumetrically after CuO oxidation to CO_2). Carbon monoxide might be formed by decomposition of the hypothetical mixed anhydride p-$CH_3C_6H_4S(O)OCHO$ (or the isomeric TosCHO), which could result from nucleophilic action of Tos^-, possibly through **19**. Alternatively, CO could arise from decomposition of *tert*-butyl formate (**11**, R = *t*-Bu) in the medium used here.[16] These assumptions at least account for the fact that the CO was not radiolabeled when the reaction was performed with $Tos^{14}CH_2N{=}C$ (eq 2).



1 2a (2)

Competing Reactions. 4-Tosyl-2-oxazolines (**13**, and **7**, Scheme I) play a crucial role in the reaction of TosMIC with ketones (and aldehydes).[17] Compounds **13** can be converted not only to nitriles **2** but also to tosylalkenylformamides **14** as discussed above. With EtONa or EtOTl in EtOH (or EtOH–DME) **13** will give 4-ethoxy-2-oxazolines[18] **18**, which are convenient precursors for the synthesis of α-hydroxy aldehydes.[19] By a proper choice of the conditions of the reaction of TosMIC with ketones either of the products **2**, **13**, **14**, or **18** can be obtained exclusively; therefore special attention should be given to these conditions.

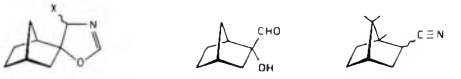
The tosyloxazolines **13** are obtained in protic solvents using weak bases (e.g., K_2CO_3 in MeOH,[2b,20] or NaCN in EtOH[8a]). In an aprotic medium (*t*-BuOK in THF) at −10 °C the reaction goes one step further to give **8** (**14**),[8] but at temperatures of 20–45 °C the reaction slowly continues to go all the way to nitriles **2**. This last process is speeded up considerably by addition of 1–2 equiv of an alcohol (*t*-BuOH or better MeOH or EtOH) to the aprotic solvent (DME).[21] However, the addition of more alcohol should be avoided, otherwise 4-alkoxy-2-oxazolines (**18**) will be formed as well. The role of the added alcohols is explained (in part) by their contribution to the reaction step **9** → **12** (or **15** → **2**).



(3)

TosMIC itself is known to undergo a base-catalyzed cyclodimerization to give inter alia imidazole **20** (eq 3).[2a] This explains the low yields of nitriles **2** obtained previously with the less reactive (usually sterically hindered) ketones (Table I, e.g., **2c,p,q**, reactions in DME). The cyclodimerization of TosMIC, visualized as a reaction of TosMIC anion (**3**) with TosMIC,[2a] can be suppressed effectively by working in Me_2SO (or HMPT) with 2 equiv of *t*-BuOK with respect to TosMIC. Thus, TosMIC will be transformed completely into its anion **3**.[22] These conditions then allow reaction 1 to be carried out at 45 °C for prolonged periods to achieve a high yield conversion of the less reactive ketones without appreciable loss of TosMIC.

Stereochemistry. The endo–exo ratio of 2-cyanonorbornane (**2b**) is nearly 1:1 (by GLC and NMR). This ratio may well reflect thermodynamic control through **12** (Scheme I), but most certainly is not the result of indiscriminatory attack of TosMIC anion (**3**) on norbornanone from both the exo and endo side. In fact, we have established previously that the large TosMIC anion attacks norbornanone only from the exo side, as expected, to give **13b** (4). This was concluded from the stereochemistry of the derivative **18b** and its subsequent hydrolysis to 2-*endo*-hydroxynorbornane-2-*exo*-carboxaldehyde (**21**) exclusively.[18,19]



13b X = Tos
18b X = EtO 21 2c (4)

Camphor with its hindered exo side required accordingly a rather long reaction time to provide 80% of 2-cyanocamphane (**2c**, a mixture of unassigned endo and exo isomers, ratio of 4:1). Likewise, mixtures of α- and β-cyanosteroids were obtained for **2i–k**, although from estrone 3-methyl ether only the 17β-cyano compound (**2h**) was found (after crystallization[6b]). The ratio of the epimers **2i–k** was determined by ^1H NMR (Table II, in Experimental Section).

Experimental Section

General remarks are as in ref 2a. Carbon-14 radioactivity was measured with a Nuclear Chicago Unilux III Scintillation Counter.

Starting Materials. Commercially available ketones were used as such. Estrone 3-methyl ether and 5α-cholestan-3-one were purchased from Steraloids Inc., Pawling, N.Y. Samples of androsta-1,4-dien-3-one and 5β-cholestan-3-one were donated by Gist-Brocades N.V., Delft, Holland. TosMIC (**1**) was prepared as described in ref 2a or purchased from Ofichem, Gieten, Holland. ^{14}C-Labeled formaldehyde was obtained from NEN Chemicals, Frankfurt, Germany.

Synthesis of Nitriles from Ketones and TosMIC (1). The following selected procedures are illustrative. Table I summarizes the conditions used in the reactions not described in detail.

2-Cyanoadamantane (2a). Solid *t*-BuOK (28.0 g, 0.24 mol, 95%, Merck) was added portionwise to a stirred and cooled solution of adamantanone (15.0 g, 0.10 mol) and TosMIC (25.0 g, 0.13 mol) in a mixture of 350 mL of DME and 10 mL of absolute EtOH while keeping the temperature between 5 and 10 °C. Stirring was continued, first for 30 min without cooling, then for 30 min at 35–40 °C. The suspension thus obtained was cooled to room temperature with stirring. The precipitate (TosK) was removed and extracted with DME. The combined DME solutions were concentrated to 25–35 mL and purified by flushing the concentrate over a 5-cm thick layer of alumina (ca. 200 g, on a Buchner funnel) with 250 mL of petroleum ether (bp 40–60 °C). Removal of the solvent provided 14–15 g (87–93%) of

near-white **2a**, melting range 160–180 °C (sealed tube). Despite the wide melting range, this material is over 99.8% pure according to GLC (2-m SE-30 column, 190 °C). Charcoal treatment gave completely white material, melting in the same range. The melting point of **2a** is an unreliable criterion for purity; a value as high as 184–187 °C has been found occasionally.[23]

The same reaction has been carried out successfully with EtONa,[3] and also with *t*-BuOK in Me_2SO or HMPT. Hydrolysis of **2a** with HBr in AcOH provided adamantane-2-carboxylic acid (95%, mp 143–144 °C, lit.[24] 62%).

2-Cyanonorbornane (2b). To an ice-cooled solution of TosMIC (1.3 g, 6.5 mmol) in dry Me_2SO (7.5 mL) was added all at once 2.25 g (ca. 18 mmol) of solid *t*-BuOK. After stirring for 5 min under N_2 0.25 mL of MeOH was added, then 0.55 g (5.0 mmol) of 2-norbornanone, and the mixture was stirred for 17 h at room temperature. (After 10 min some foaming was observed, indicating the evolution of CO, cf. **2a**, below.) The reaction mixture was diluted with water (150 mL), acidified with 2 N HCl to pH ~6, and extracted with petroleum ether (bp 40–60 °C). The combined extracts were washed once with saturated NaCl solution and dried (Na_2SO_4). Short path distillation (at 20 mm) gave 0.44 g (73%) of **2b**, consisting of a mixture of endo:exo = ca. 4:3 as determined by analytical GLC (Carbowax 20M, 120 °C). Partial separation by GLC (same column) provided a sample of pure *endo*-**2b**, mp 48–51 °C (sealed tube) (lit.[25] mp 51 °C).

2-Cyanocamphane (2c). A reaction mixture was prepared analogously to **2b** from TosMIC (3.0 g, 15 mmol), (+)-camphor (0.76 g, 5.0 mmol), *t*-BuOK (4.5 g, ca. 36 mmol), 15 mL of Me_2SO, and 0.25 mL of MeOH. The mixture was stirred under N_2 for 1 h at room temperature and then for 70 h at 45 °C. (The camphor carbonyl was still present in IR after 17 h.) Workup as for **2b** gave after removal of the petroleum ether a semisolid brown residue, which was sublimed (150 °C, 20 mm) to give 0.65 g (80%) of **2c**, mp 135–148 °C (sealed tube).[26] This mixture of endo and exo isomers (4:1 or 1:4 by GLC on Carbowax 20M; 140 °C) gave one sharp C≡N band in IR (Nujol) at 2270 cm^{-1}. Anal. (of endo–exo mixture). Calcd for $C_{11}H_{17}N$: C, 80.93; H, 10.50; N, 8.58. Found: C, 80.9; H, 10.5; N, 8.4.

In the separatory funnel some impure insoluble material was left behind, and was shown to contain ca. 1 g of unreacted TosMIC.

1-Cyano-2,2-dimethyl-1,2,3,4-tetrahydronaphthalene (2g) was prepared similarly to **2b** from β,β-dimethyl-α-tetralone[27] (1.74 g, 10 mmol), TosMIC (6.0 g, 30 mmol), *t*-BuOK (9.0 g, ca. 72 mmol), and 40 mL of HMPT (dried over sieves) and 0.5 mL of MeOH, initially at 0 °C, then 40 h at 45 °C. The residue was submitted to short path distillation (at ca. 120 °C, 14 mm) yielding 1.41 g (76%) of impure **2g** as a colorless liquid: IR (neat) 2260 cm^{-1}; ^1H NMR (CCl_4) δ 1.09 (s, 3, CH_3), 1.16 (s, 3, CH_3), 1.4–1.8 (m, 2, 3-CH_2), 2.73 (t, 2, 4-CH_2), 3.50 (s, 1, CHC≡N), 6.8–7.4 (m, 4, aromatic). For characterization **2g** (0.92 g) was hydrolyzed by 17 h of reflux in AcOH (2.5 mL) and 48% HBr (10 mL) to give 0.14 g (15%) of 2,2-dimethyl-1,2,3,4-tetrahydronaphthalene-1-carboxamide, mp 121–122 °C (from the Me_2CO–pentane), IR (Nujol) 1650 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.8; H, 8.5; N, 6.8.

Mixture of 17α- and 17β-Cyanoandrosta-1,4-dien-3-one (2i). To a stirred solution of androsta-1,4-diene-3,17-dione (1.14 g, 4.0 mmol) and TosMIC (0.98 g, 5.0 mmol) in 20 mL of dry DME, cooled in ice–salt to 0 °C, was added a freshly prepared solution of sodium (0.12 g, 5.0 mmol) in 2 mL of absolute EtOH and 4 mL of DME at such a rate that the temperature did not exceed 3 °C. After stirring for 1 h at 0 °C and then 1 h at room temperature, the reaction mixture was diluted with water, extracted with Et_2O, and dried ($MgSO_4$). After removal of the solvent, the sticky residue was chromatographed by preparative TLC (silica gel, benzene–MeOH 10:1) providing 0.55 g (47%) of **2i**. Crystallization from Et_2O–pentane (1:1) gave analytically pure **2i**: mp 159–164 °C; IR (Nujol) 2240 (C≡N), 1660 (C=O), 1620 and 1610 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 0.92 and 1.02 (two singlets of equal intensity, total 3 H, 18β-CH_3), 1.27 (s, 3, 19β-CH_3), 1.3–2.7 (br m, 15), lines at 7.25, 7.10, and 6.40, 6.35, 6.20, 6.15 (AB q, partially split into a doublet, 3, vinyl H's). The peaks at 0.92 and 1.02 account for a ratio 17β-C≡N:17α-C≡N ~ 1:1. Anal. Calcd for $C_{20}H_{25}NO$ (mixture of epimers): C, 81.25; H, 8.52; N, 4.74. Found: C, 80.4; H, 8.4; N, 4.7.

Diphenylacetonitrile (2l) was prepared analogously to **2b** from 1.82 g (10 mmol) of benzophenone. By extraction with Et_2O 2.6 g of solid material was obtained. The solid was extracted with a boiling mixture of 150 mL of petroleum ether (bp 40–60 °C) and 50 mL of Et_2O. The residue provided 0.48 g (21%) of 4-tosyloxazole,[15] mp 157–162 °C (from EtOH), reported[6b] mp 166 °C. The concentrated filtrate gave after crystallization from petroleum ether 1.33 g (69%) of **2l**, mp 67–71 °C (lit.[30] mp 74 °C).

2-*p*-Bromophenylpropionitrile (2n). A solution prepared by dissolving *t*-BuOK (2.25 g, 18 mmol) in 7 mL of warm *t*-BuOH was added to a stirred solution of *p*-bromoacetophenone (2.0 g, 10 mmol) and TosMIC (2.0 g, 10 mmol) in 35 mL of dry DME cooled in ice–salt, at such a rate that the temperature did not exceed 0 °C. After 15 min the mixture was warmed to room temperature and stirring was continued for 1 h. The mixture was concentrated to 20% of the original volume, diluted with water, and extracted with pentane. After drying ($MgSO_4$), distillation gave 1.65 g (79%) of **2n** as a colorless liquid: bp 112–116 °C (1 mm); IR (neat) 2245 cm^{-1} (C≡N); ^1H NMR ($CDCl_3$) δ 1.60 (d, 3, CH_3, J = 7 Hz), 3.85 (q, 1, CH, J = 7 Hz), 7.15, 7.30 and 7.45, 7.60 (AB q, 4, aromatic).

Table II. ^1H NMR Data of Cyano Steroids 2i–k

Compd		Chemical shift (rep), δ ppm 18-Me	19-Me	3-H	α/β
2i	17α-C≡N	0.92	1.27		1
2i	17β-C≡N	1.02	1.27		
2j	3α-C≡N	0.65 (0.65)	0.78 (0.79)	2.90 (2.95)[a]	0.7
2j	3β-C≡N	0.65 (0.65)	0.85 (0.82)	2.34 (2.34)[a]	
2k	3α-C≡N	0.65	0.91[b]	2.90	0.9
2k	3β-C≡N	0.65	0.94[b]		

[a] The values in parentheses are from the literature.[28] [b] Comparable δ values for the 18-Me and 19-Me in 3α-hydroxy-5β-androstane are 0.65 and 0.91; for 3β-hydroxy-5β-androstane they are 0.65 and 0.98.[29]

Analysis of CO Evolved in Reaction 2a. The evolution of gas observed in a number of the above reactions when carried out in Me_2SO or HMPT was identified qualitatively as carbon monoxide by mass spectral analysis and IR. For the quantitative determination (as CO_2) in essence a microanalytical elemental analysis unit was used. The reaction was carried out by adding all at once 150 mg (1.0 mmol) of adamantanone to a stirred and ice-cooled mixture of TosMIC (260 mg, 1.3 mmol), HMPT (1.5 mL), MeOH (0.05 mL), and *t*-BuOK (450 mg, ca. 3.6 mmol) in a slow stream of He (15–20 mL/min). During 6 h the gas stream was passed through a trap cooled at −196 °C, then through a tube with CuO heated at 800 °C, and finally through a preweighed tube containing Colorcarb (Perkin-Elmer). An increase in weight of 18.3–20.3 mg was found, corresponding to 42–46% of CO (calculated on adamantanone). The reaction mixture contained 73% of **2a** and 7% of starting ketone.

Synthesis of ^{14}C-Labeled TosMIC. Tos$^{14}CH_2N$=C was prepared in two steps following the procedure in ref 2a on a 1/10 scale. To the reaction mixture was added ca. 0.02 mL of a 1% solution of $^{14}CH_2O$ with a specified activity of 0.05 mCi. The yield was 15.6 g (49%) of Tos$^{14}CH_2NHCHO$, mp 107–110 °C, specific activity 0.08 μCi/mmol. Dehydration of 2.67 g of this material provided 1.20 g of Tos-$^{14}CH_2N$=C, mp 111–114 °C.

Reaction of Adamantanone with ^{14}C-Labeled TosMIC. The reaction with Tos$^{14}CH_2N$=C was carried out in HMPT as above (three times that scale). To absorb the $^{14}CO_2$, the He–CO_2 stream from the CuO tube was now passed through 2 mL of a 1 M solution of Hyamine hydroxide[31] in methanol in a 10-mL volumetric flask. After shutting off the gas stream the flask was filled up to 10.00 mL with MeOH and the quantity of CO_2 was determined by titration. The specific activity of the CO_2 (20% yield) was <0.0001 μCi/mmol. 2-Cyanoadamantane (55%) had a specific activity of 0.08 μCi/mmol.

5,5-Pentamethylene-4-tosyl-2-oxazoline (13e).[32] A mixture of TosMIC (0.65 g, 3.3 mmol), cyclohexanone (0.33 g, 3.4 mmol), and K_2CO_3 (0.24 g, 1.7 mmol) was stirred for 1.5 h in 8 mL of MeOH at room temperature, then diluted with ice–water, and the precipitate was crystallized from acetone–water, providing 0.81 g (83%) of **13e**: mp 131.5–132 °C; IR (KBr) 1622 (C=N), 1330–1300 and 1150 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 2.44 (s, 3, CH_3), 1.68 (br s, c-Hex), 4.68 (d, 1, 4-CH, J = 1.5 Hz), 7.05 (d, 1, 2-CH, J = 1.5 Hz), 7.35 and 7.84 (two d, 4, aromatic, J = 8.5 Hz). Anal. Calcd for $C_{15}H_{19}NO_3S$: C, 61.41; H, 6.53; N, 4.77; S, 10.93. Found: C, 61.3; H, 6.5; N, 4.8; S, 11.0.

Cyanocyclohexane (2e) from 13e and from 14e. A solution of **13e** (0.58 g, 2.0 mmol) in 15 mL of DME and 0.1 mL of absolute EtOH was stirred for 1 h at 40 °C with *t*-BuOK (0.45 g, 3.6 mmol) and worked up as described for **2n** to give 0.13 g (60%) of **2e**, bp 64–66 °C (12 mm).

Similarly, *N*-(1-tosylcyclohexylidenemethyl)formamide[8a] (**14e**, 1.75 g, 5.9 mmol) was converted with *t*-BuOK (1.23 g, 10 mmol) in 20 mL of DME and 5 mL of *t*-BuOH to give 0.59 g (90%) of **2e**.

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Registry No.—**2a**, 35856-00-9; *endo*-**2b**, 3211-87-8; *exo*-**2b**, 3211-90-3; *endo*-**2c**, 62796-09-2; *exo*-**2c**, 62796-08-1; **2d**, 32730-85-1; **2e**, 766-05-2; **2f**, 56536-96-0; **2g**, 62796-10-5; **2h**, 57764-88-2; 17α-**2i**, 62796-11-6; 17β-**2i**, 62796-12-7; 3α-**2j**, 1251-67-8; 3β-**2j**, 1251-66-7; 3α-**2k**, 62796-13-8; 3β-**2k**, 62796-14-9; **2l**, 86-29-3; **2m**, 1823-91-2; **2n**, 42186-06-1; **2o**, 13310-75-3; **2p**, 62391-96-2; **2q**, 21101-85-9; **13e**, 52568-58-8; **14e**, 39031-25-9; 2,2-dimethyl-1,2,3,4-tetrahydronaphthalene-1-carboxamide, 62796-15-0; 4-tosyloxazole, 57764-94-0; $Tos^{14}CH_2N{=}C$, 62796-16-1; $^{14}CH_2O$, 3046-49-9; $Tos^{14}CH_2NHCHO$, 62796-17-2; TosMIC, 36635-61-7.

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Aminations with Ammonia and Formamide. Synthesis of Terephthalamic Acid and of *p*-Nitroaniline

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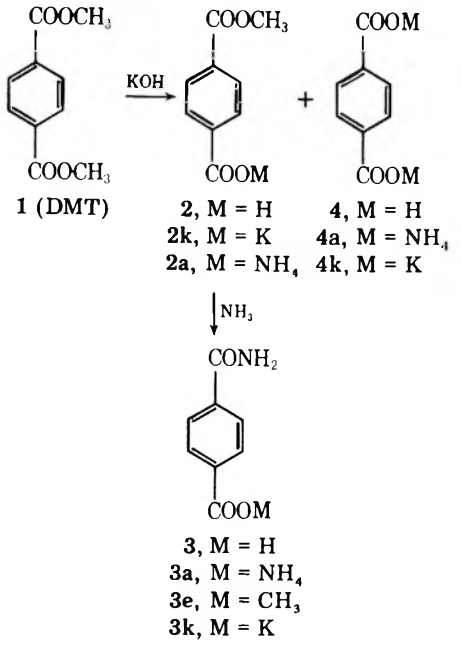
Ammonolysis of potassium methyl terephthalate (**2k**) to potassium terephthalamate (**3k**) is markedly accelerated by formamide solvent. No corresponding acceleration is seen with other amides, such as mono- or dimethylformamide or acetamide. Negligible hydrolysis to ammonium terephthalate (**4a**) occurs. An efficient procedure for the Hofmann conversion of potassium terephthalamate (**3k**) to *p*-aminobenzoic acid is reported. Ammonolysis of *p*-nitrochlorobenzene occurs rapidly in formamide solvent at 200–220 °C to furnish high yields of *p*-nitroaniline. *p*-Chlorobenzotrifluoride and 1,2,4-trichlorobenzene are not aminated under these conditions.

We sought to develop an economical synthesis of *p*-aminobenzoic acid from commercial dimethyl terephthalate (DMT, 1).[1] Attempts to half-ammonolyze DMT to methyl terephthalamate (**3e**) were unsuccessful, since all conditions tried formed excessive amounts of terephthaldiamide. However, half-hydrolysis of DMT by potassium hydroxide in

Scheme I



methanol proved to be quite selective, and potassium methyl terephthalate (**2k**) was isolated in about 90% yield (Scheme I).[2,3] The ammonolysis of **2k** to potassium terephthalamate (**3k**) in various media was investigated in detail, and the results form the subject of this paper.

Ammonolysis in 28% aqueous ammonia was examined first. At room temperature, ammonium methyl terephthalate (**2a**) required 20–24 h for complete reaction to ammonium terephthalamate (**3a**); 5–10% of diammonium terephthalate (**4a**) was also formed. However, heating the mixture at 50–100 °C accelerated hydrolysis of the ester group much more than ammonolysis, so that up to one-third of the product became **4a**. Addition of anhydrous ammonia to raise the concentration to 40–60% ammonia in water retarded both the hydrolysis and ammonolysis, but did not increase the selectivity appreciably. With the more basic potassium salt **2k**, hydrolysis became still more prominent.

Many ammonolyses of esters reported in the literature use an organic cosolvent for either aqueous or anhydrous ammonia. Methanol usually gives the fastest rates and highest yields of amides.[4] In our hands, **2a** reacted sluggishly with anhydrous ammonia in methanol. At 130 °C about 80% conversion was obtained in 6 h, and about 5% of **4a** was also formed despite the anhydrous conditions. In dry dimethylformamide, conversion was nearly complete in 6 h at 130 °C, but 25% of the product was **4a**; the reaction was negligibly slow at 40 °C. The reaction was slightly faster in dimethyl sulfoxide at 130 °C and less **4a** was formed.

At this point it appeared that a protic solvent of high dielectric constant was required for rapid ammonolysis. Water fits this description, though hydrolysis is excessive at temperatures where the rate is practical. Formamide[5] was tried, and the search ended. When potassium (or ammonium) methyl terephthalate (**2k** or **2a**) was heated with excess anhydrous ammonia in formamide (500 mL/mol), almost complete conversion to **3k** (**3a**) was achieved in 2 h at 130 °C, or 1 h at 140 °C. Vigorous agitation is required. About 80% yield of almost pure **3k** was isolated merely by filtering the reaction mixture at room temperature. When the filtrate was used as solvent in a second reaction, the solubility losses disappeared and the yield reached 95%.

Curiously, although the **2k**, formamide, and ammonia were rigorously dry, the ammonolysis reaction invariably produced about 5% of terephthalic acid salt (**4**). This is not a simple hydrolysis by adventitious water, since addition of up to 5 mol of water/mol of **2k** did not increase the proportion of **4**. Indeed, the rate of ammonolysis was increased slightly, in keeping with literature statements.[6] In contrast to the acceleration caused by water, methanol caused a slight but definite retardation. In parallel experiments, **2k** with only ammonia and formamide gave 98% conversion, while a run to which 3 mol of methanol had been added (per mole of **2k**) gave only 85% conversion. Since methanol is a product of the ammonolysis, it is therefore desirable to strip out the methanol by heating under vacuum before reusing the filtrate.

Still faster rates would be desirable for a continuous commercial process, hence catalysts were sought. Imidazole is a powerful catalyst for many transformations of carboxylic acid derivatives.[7] In the formamide system, imidazole increased the rate considerably. Thus, in parallel runs at 130 °C for 30 min, conversion of **2k** to **3k** was 33% without catalyst and 82% with 7.3 mol % of imidazole. But when this additive was tested in the aqueous ammonia system first studied, no change in rate of either hydrolysis or ammonolysis was apparent either at 25 or 60 °C.

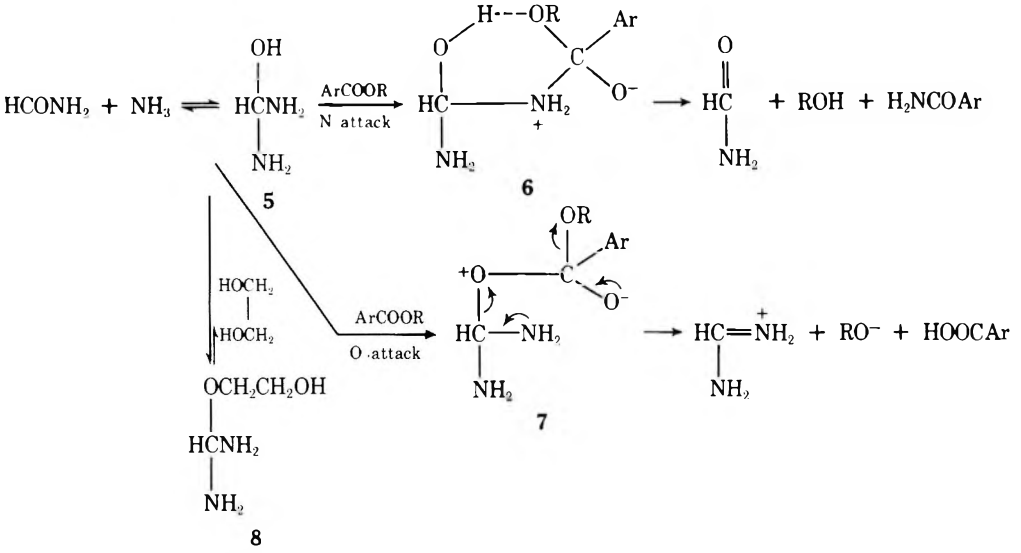
Polyhydric alcohols are known to promote ammonolysis of esters in aqueous dioxane;[4,8] ethylene glycol, glycerol, and sorbitol are increasingly effective. Day found it essential to have water present because of the low solubility of polyols in many anhydrous organic solvents. We found that both ethylene glycol and sorbitol are quite soluble in dry formamide. In parallel runs at 130 °C for 30 min, ethylene glycol gave 75% conversion and sorbitol 95%, compared to the 33% obtained without additive. Both polyols were used in the proportion of two hydroxyl groups per ester function. Unexpectedly, the "hydrolysis" to **4** observed in the formamide–ammonia system was almost completely suppressed by either polyol. Glycol has been used as solvent for the ammonolysis of polyesters such as poly(ethylene terephthalate).[9]

The remarkable ability of formamide to promote ammonolysis of esters seems to be restricted to this solvent alone. Acetamide (D = 65[10]) gave 20% conversion of **2k** to **3k** under conditions where formamide (D = 109) gave 95%; addition of 1 mol of water to the acetamide system increased the hydrolysis to **4** substantially, but did not improve the 20% conversion to **3k**. *N*-Methylamides have enormous dielectric constants, but *N*-methylformamide (D = 200), *N*-methylacetamide (D = 165), and *N*-methylpropionamide gave no detectable **3k** under the standard conditions where formamide itself gave 95% of **3k**. Pyrrolidinone (butyrolactam), with a very high dipole moment resulting from the enforced cis configuration, was likewise inactive. Apparently, two protons on nitrogen and a high dielectric constant are both necessary.

Acids, esters, and other acid derivatives may sometimes be converted to amides by heating with formamide, acetamide, or their N-substitution products with or without acid or base catalysis.[11] To test this possible explanation for our formamide–ammonia ammonolysis, **2k** was heated with formamide without ammonia at temperatures to 180 °C for times known to be sufficient for complete conversion in presence of ammonia. In none of these experiments was **3k** detected.

The active ammonolytic reagent is believed to be the ammonia adduct of formamide, diaminomethanol (**5**, Scheme II). If one of the amino groups adds to the carbonyl of the ester to form the tetrahedral intermediate **6**, departure of methanol should be strongly promoted by hydrogen bonding to the hydroxyl function. Alternatively, if the hydroxyl group of **5** adds to the ester carbonyl, the tetrahedral intermediate **7** would dissociate to methanol, carboxylic acid, and formamidine. Formation and collapse of **7** explain the "hydrolysis" of the ester in the absence of free water. Promotion by glycols may result from formation of **8**, in which additional possibilities for three-dimensional hydrogen bonding exist. Failure

Scheme II



of N- or C-substituted formamides may be a result of a very unfavorable equilibrium in the first step, formation of **5**.

Since equal conversions (within experimental error) were obtained with either the ammonium or potassium salts (**2a** or **2k**), the reaction does not appear to be strongly catalyzed by either acid or base. A detailed study to confirm the proposed mechanism of this unusual reaction lay outside the scope of the present research.

Silylation of Terephthalamic Acid and Other Amides. Analysis of Acid Mixtures. The various combinations of **1**, **2**, **3**, and **4** encountered in this work were analyzed by GC. Unexpected chemistry was also encountered. A mixture of trimethylsilyl chloride and hexamethyldisilazane in pyridine (commercial Tri-Sil) forms the volatile trimethylsilyl esters from these acids quantitatively in 1 min at room temperature.[12] The amide function in **3** reacts erratically with Tri-Sil; depending on the time and temperature of silylation, four different peaks with quite variable areas were obtained from pure **3**. An amide may be O-monosilylated, N-monosilylated, or N,O-disilylated.[13] Subsequently, one or more of these may decompose to a nitrile. The first peak from **3** has the same retention time as trimethylsilyl *p*-cyanobenzoate.

The more powerful reagent *O,N*-bis(trimethylsilyl)acetamide (BSA) was ultimately used as the preferred silylating reagent for analysis of mixtures containing **3**. Pure **3** gave mostly the nitrile (3.6 min), but also variable small amounts of the 15.2- and 17.6-min peaks (Scheme III). The amount of **3** in amidation mixtures was computed from the total areas under the three peaks, corrected for the response factors determined with authentic mixtures. The precision of the method for mixtures of **2**, **3**, and **4** is about 3% relative.

Dennis[14] reported that dehydration of amides to nitriles by silylating reagents required temperatures near 200 °C; our nitriles may have been formed in the hot injection port. Some other aromatic amides were tested qualitatively. Benzamide with BSA yielded only a little benzonitrile; the main product was a single monosilyl peak. *m*-Toluamide also yielded but little nitrile; the main peak was a poorly resolved doublet, presumably a mixture of *O*- and *N*-monosilyl derivatives. By contrast, *p*-nitrobenzamide yielded only *p*-nitrobenzonitrile. *p*-Carbomethoxybenzamide (**3e**) yielded mostly nitrile plus a little monosilylamide as a chromatographic doublet. Evidently, an electron-attracting group markedly increases the rate at which aromatic amides are dehydrated by BSA, either because that group increases the acidity of the amide and thus the rate of disilylation, or because it accelerates the breakdown of the disilylamide.

Several other silylating reagents[15] (used in excess) were tested with **3** in various solvents. Only trimethylsilyldiethylamine [$(CH_3)_3SiN(C_2H_5)_2$] yielded any significant amount of cyanobenzoic ester. The others gave varying proportions of the 12.5-, 15.2-, and 17.6-min peaks. This result suggests that nitrile formation indeed occurs during the silylation step, not in the injection port. Interestingly, the 12.5-min peak was never seen in the same chromatogram as the 15.2-min peak.

The column used in this work was 20% SE-30 silicone gum rubber on Chromosorb W AW-DMCS, 60–80 mesh. The carrier gas was helium; the temperature was 215 °C isothermal. The instrument was an Aerograph Model 202-B with a thermal conductivity detector.

Hofmann Degradation of 3 to *p*-Aminobenzoic Acid. The Hofmann degradation was first applied to terephthalamic acid by Toland and Heaton.[16] Since they began with a crude **3** of uncertain purity (prepared by oxidation of *p*-xylene with ammonium sulfate, hydrogen sulfide, and water), their yield of *p*-aminobenzoic acid based on **3** is uncertain; it averaged 75% based on chlorine. We studied the Hofmann reaction with **3k**, pure or containing known amounts of **4k**. *p*-Aminobenzoic acid was obtained consistently in 80–85% yield by careful attention to the factors discussed below.

The Hofmann reaction involves the following steps:

$$ArCONH_2 + NaOCl \rightarrow ArCONHCl \rightarrow ArCON(Cl)Na \rightarrow ArN{=}C{=}O$$

$$ArN{=}C{=}O + 2NaOH \rightarrow ArNH_2 + Na_2CO_3$$

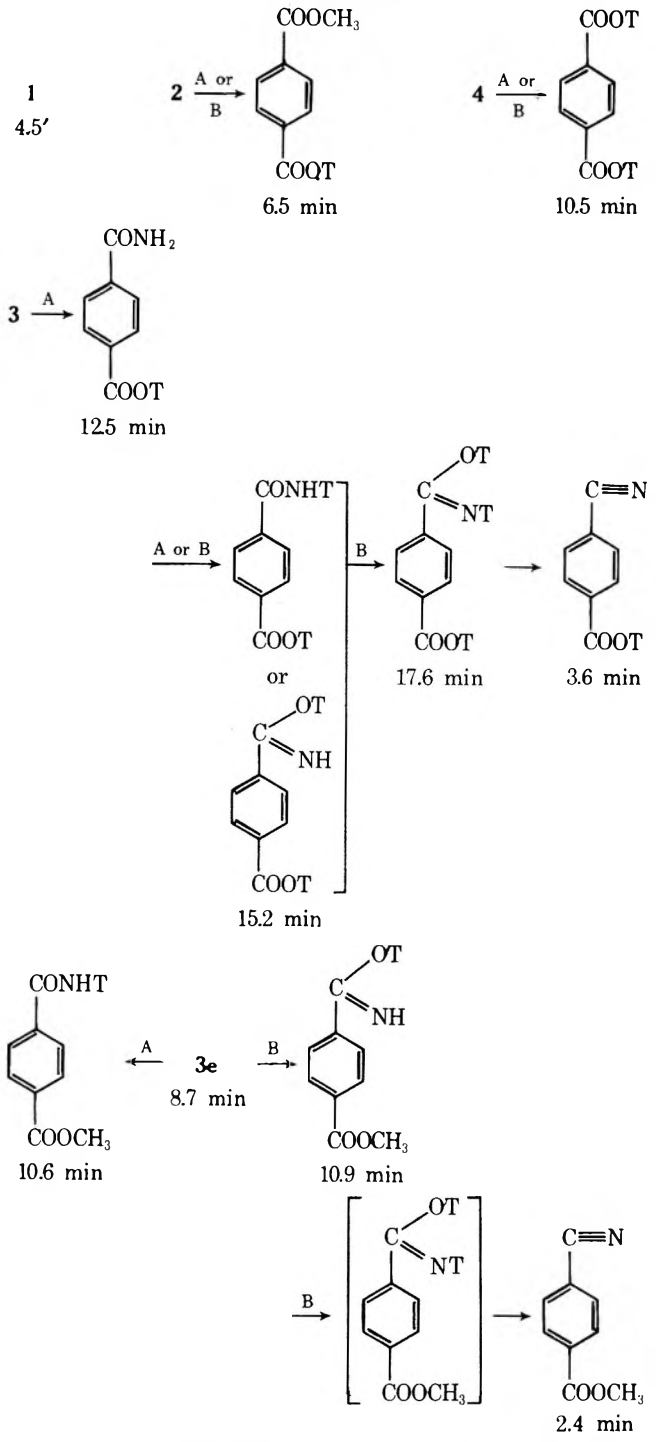
Overall:

$$ArCONH_2 + Cl_2 + 4NaOH \rightarrow ArNH_2 + Na_2CO_3 + 2NaCl + H_2O \quad (Ar = p\text{-}KOOCC_6H_4)$$

Since our terephthalamic acid was already the salt **3k**, we conducted the N-chlorination in basic medium, rather than in acid as preferred by Zengel and Bergfeld.[9] N-Chlorination of **3k** was complete in about 10 min at 15–25 °C. Longer contact times permit hydrolysis of the *N*-chloroamide to salts of **4**. Blank experiments showed that **3k** suffered very little hydrolysis in this period. The rearrangement itself set in at about 50 °C, and the heat of reaction raised the temperature to 90 °C in a few minutes. Reaction was complete in 5–15 min under these conditions. Accordingly, the preferred conditions detailed in the Experimental Section provide 10 min for N-chlorination and 10 min at 90 °C for the rearrangement.

The quantity of sodium hydroxide is critical. The overall reaction requires 4 mol, two to neutralize the chlorine and two to neutralize the carbon dioxide. However, with only 4 mol of base, the yields were consistently about 10% lower than when

Scheme III[a]



[a] Abbreviations: reagent A = Tri-Sil; reagent B = BSA; T = $(CH_3)_3Si$.

5 mol were used, and the product was much darker. With <4 mol, the yields dropped further. Zengel and Bergfeld observed a similar minimum requirement. Excess hypochlorite apparently oxidizes the amine to colored by-products. A slight deficiency of hypochlorite avoids this problem.

The concentration of **3** in the reaction mixture was examined briefly, since it is directly proportional to equipment productivity. With concentrations in the range 0.85–1.0 M, the reaction proceeds well, and the reaction heat brings the temperature quickly to the preferred 90 °C. In the range 0.5–0.6 M, heating takes longer, but the yields are the same. In the more dilute solutions, the product is somewhat lighter colored. The more concentrated solutions are preferred for their higher productivity, and also because the solubility losses are less.

Urea formation from the intermediate isocyanate and product amine, frequently encountered in other Hofmann degradations,[17] was unimportant in the present study.

The crude product was always somewhat discolored. Decolorizing carbons did not remove all colored products. Common reducing agents such as sodium dithionite and stannous chloride were ineffective. Then we found that a trace of sodium borohydride at pH 7–8 destroyed the colored materials very efficiently.[18] However, even this reagent did not completely decolorize products prepared with excess hypochlorite.

Amination of Aryl Halides. The unusual potency of the formamide–ammonia combination for ammonolyzing esters suggested its use in nucleophilic displacements. Matthews and Cookson showed that octyl bromide reacted with formamide–ammonia to yield *N*-octylformamide, not *n*-octylamine.[19] They also stated that aryl halides did not react. Bredereck et al., as part of an extensive study of the properties of formamide,[11] observed that alkyl halides could form either the *O*- or *N*-alkylformamide, which subsequently decomposed. Specifically, 2,4-dinitrochlorobenzene reacted with formamide in 16 h at 150 °C to yield (after hydrolysis) 55% of 2,4-dinitroaniline. However, *p*-nitrochlorobenzene failed to react in 20 h at 115 °C. Neither reaction was performed in the presence of ammonia.

We assumed that failure in the latter case was a result of the low temperature, and heated *p*-nitrochlorobenzene in formamide at 180 °C. Polymeric material plugged the condenser, which we attributed to reaction followed by acid-catalyzed decomposition of formamide. Accordingly, we added ammonia to repress formamide decomposition, and heated *p*-nitrochlorobenzene with formamide *and ammonia* in an autoclave at 180 °C. We did not expect the excellent conversion of the halide to *p*-nitroaniline which took place.

The reaction was then examined in detail; selected results are given in Table I. The first entry shows again that formamide alone is ineffective. In the runs tabulated, and in others not shown, it was evident that 2–3 mol of formamide and 3–4 mol of ammonia sufficed to give nearly quantitative conversions of the halide. Heating for 1 h at 220 °C or 2 h at 200 °C was sufficient. The true yields were about 5% higher than those shown, the loss occurring during the isolation procedure.

A *p*-nitro group is sufficient to activate ring chlorine toward displacement by ammonia in formamide. However, a *p*-trifluoromethyl group (in *p*-trifluoromethylchlorobenzene) or one or two chlorines (in *p*-dichlorobenzene or 1,2,4-trichlorobenzene) were not sufficiently activating, since negligible conversions to the amines were obtained in several experiments under the conditions where *p*-nitrochlorobenzene was quantitatively converted. This new method is clearly not a panacea for amination of all aryl halides.

Experimental Section

Hydrolysis of Dimethyl Terephthalate (1) to Potassium Methyl Terephthalate (2k).[20] Powdered **1**, 194 g, 1 mol, was dissolved in 3 L of boiling methanol; commercial briquets dissolve very slowly. A solution of 112.2 g of potassium hydroxide pellets (85% assay, 1.7 mol) in 1 L of methanol was added in 3–5 min to the boiling solution of **1**. After about 2 min, solid began to precipitate. After 30 min of boiling, the mixture was cooled rapidly to 40 °C and filtered. The solid **2k** was washed with two portions of 40 °C methanol, each sufficient to cover the crystals, and two portions of 10 °C methanol, then dried. The product weighed 173 g (80%), and it contained about 1–2% of **1** and 2–5% of **4k**. The **1** can be removed with a chloroform wash, if required. Alternatively, using only 1.06 mol of potassium hydroxide, hydrolysis required about 6 h. When *sodium* hydroxide was used, the salt was much more voluminous, was difficult to wash and handle, and it retained a great deal of methanol.

The free acid **2**, obtained by acidifying an aqueous solution of **2k**, can be recrystallized from acetone, in which **4** is virtually insoluble.

Table I. Amination of p-Nitrochlorobenzene (PNCB) with Ammonia in Formamide[a]

Vessel[b]	PNCB, mol	$HCONH_2$, ratio[c]	NH_3, ratio[c]	Temp, °C	Time, h[d]	% convn[e]	% yield[f]
B[g]	0.2	5.5	None	220	0.5	1.3	
A	0.5	9.0	8.0	220	0.5	High	
A	0.65	9.0	2.0	210	0.5	46	
A	1.0	3.5	2.0	220	0.5	68	
B[h]	0.2	5.0	4.0	210	0.5	90	
A	1.0	3.0	3.0	225	0.75	97	88
B	0.25	2.0	4.0	210	3.0	100	93
A	1.0	2.5	4.0	200	2.0	99	87
A	1.0	2.25	4.0	220	1.0	100	89
A	1.0	2.0	4.0	210	1.5	99.7	93

[a] Details of procedure in Experimental Section. [b] Vessel A: 432 mL capacity; vessel B, 100 mL capacity. [c] Expressed as mol/mol PNCB. [d] Excluding heating and cooling times. [e] Calculated from GC analysis for PNCB and p-nitroaniline. [f] Calculated from weight of crude washed product. No correction is made for the 5% handling losses during isolation. [g] Heating a similar mixture at 230 °C for 2 h caused 76% disappearance of PNCB, but formed a great deal of tar. [h] The same results were obtained when 0.01 mol of sorbitol was added to this recipe.

For preparation of large amounts of **2k** in multiple runs, the methanol filtrate and washes were used as solvent for subsequent runs; only 1 mol of new potassium hydroxide was then needed. The yield of **2k** was almost quantitative, since solubility loss was eliminated. We did not determine whether impurity buildup placed any limit on the number of times the filtrate could be recycled.

Ammonolysis of 2 and Its Salts. Preparation of 3.[21] Orienting experiments showed that equivalent results were obtained with pure **2** (thus its ammonium salt), its sodium salt, or with chloroform-washed **2k**. The latter was used in practically all the present work; it was analyzed to determine the amount of **4k** present. Typically, a mixture of 218 g, 1 mol, of **2k** containing 2–5% of **4k**, 450–500 mL of commercial formamide (pure dry solvent gave equivalent results), and 200 g, 11.8 mol, of anhydrous ammonia were heated in a 1-L bomb with *strong* agitation; slower reactions were obtained in a conventional rocking autoclave. In our apparatus, the time required to reach 130–140 °C varied from 45 to 75 min, depending upon the operator. Optimal results were obtained in 2 h at 130 °C or 1 h at 140 °C (excluding heating and cooling times). The excess ammonia was vented at room temperature, and the product slurry was filtered. The solids were washed with acetone to remove formamide, which would interfere with the Hofmann reaction; methanol was a less satisfactory wash solvent. The bomb was rinsed with water, and the combined water, filtrate, and acetone washes were further diluted and acidified to recover additional **3** as the free acid. In the best runs, the crude washed **3k** weighed 175 g, 86%, and it contained 10–15% of **4** salts. About 23 g, 14%, of **3** was obtained from the filtrate and washes, and it contained about 30% of **4**. Evidently **4** salts are more soluble in formamide than **3k**. Alternatively, the salts in the filtrate could be precipitated with acetone, though not with methanol.

In other experiments, the formamide filtrate was reused directly with fresh make-up formamide for a second amidation. Product from reused formamide contained more **4** salts.

The procedure was similar when imidazole, glycols, or other additives were included.

Pure **3** can be separated from **4** by fractional neutralization of an aqueous solution of the salts. On a large scale, successive crops were taken at pH 6.6, 6.0, 5.0, and 4.0. The first was free of **4**. The subsequent crops could be carried back through the cycle for further separation of **4**. Acetone recrystallization was more convenient for small-scale purification. However, it was unnecessary to remove **4** from **3k** destined for the Hofmann reaction.

***p*-Aminobenzoic Acid by Hofmann Degradation of 3k.** Sodium hypochlorite was prepared by passing chlorine from a *trapped* cylinder into a flask (on a balance) containing 128 g (1.6 mol) of 50% sodium hydroxide solution, 50 mL of water, and 200 g of ice until 28.2 g, 0.4 mol, had been absorbed. The ice melted during the exothermic chlorine addition and held the temperature below 5 °C. The resulting mixture was diluted to 400 mL.

To 300 mL, 0.3 mol, of the above solution, 65.4 g, 0.3 mol, of analyzed **3k** (also containing about 10% of **4k**) was added in one portion. The temperature rose from 15 to 18 °C during the 4 min required for the solid to dissolve. After no longer than 10 min, the flask was immersed in a large bath of boiling water, with magnetic stirring. At about 50 °C, a vigorous exothermic reaction carried the temperature to 65 °C in 15 s and to 92 °C in 15 s longer; the total time from 18 to 92 °C was usually just over 2 min with the concentrations specified. The mixture was held 5 min longer in the boiling water, then adjusted to pH 8.0 with sulfuric acid, stirred with 3.0 g of Darco G-60 for 10 min, then filtered. The light tan solution was mixed with 1.0 g of sodium borohydride, which decolorized the solution completely. The pH was then brought to 4.0 to precipitate terephthalic acid. At this point, pressure filtration through a heated filter would remove the **4**; the solution crystallized in a steam-heated Büchner funnel. In one experiment the mixture was diluted with 800 mL of boiling water before filtration, which removed 8.1 g, 16%, of **4**. The chilled filtrate deposited 28.5 g, 69%, of *p*-aminobenzoic acid, mp 183.5–186.0 °C (cloudy melt). The filtrate was extracted with three 100-mL portions of ethyl acetate, which was evaporated to give 3.1 g of amino acid, mp 184–186.5 °C. The total product, 31.6 g, represented 77% of 0.3 mol or 85% of the 0.27 mol of **3k** actually contained in the crude material. When the total product was dissolved in 400 mL of hot ethyl acetate, an additional 1.7 g of **4** was insoluble; the total **4** was 9.8 g, 0.059 mol, 19.7%.

This general procedure could be modified by adding more or less of the reagents or additional water. In most experiments, the total acids were collected after chilling the pH 4 solution, and the **4** was separated by dissolving the dried crude acid in hot ethyl acetate and filtering through a tared funnel. Experiments showed that about 7% of the amino acid remained in the filtrate from the (undiluted) pH 4 solution; it could be recovered by ethyl acetate extraction.

Amination of *p*-Chloronitrobenzene. The experiments in Table I were performed in shaker tubes lined with Hastelloy C. The 400-mL tube was charged with 0.5–1.0 mol of PCNB, 2.0–4.5 mol of formamide, and the specified amount of other additive, if any. The tube was sealed, pressure-tested, and evacuated. The tube was chilled in a −80 °C bath, connected to an ammonia cylinder through a flexible copper coil, and placed on a balance. The desired amount of ammonia was transferred to the shaker tube, and the weight was checked by back-weighing the ammonia cylinder. The tube was then mounted in its heating jacket on a horizontal shaker (180 strokes/min) behind a steel barricade, heated to 200–220 °C as specified in Table I, and held for the desired length of time. The tube was allowed to cool. The times in Table I do not include heating and cooling times.

The tube was vented at room temperature through a trap into a water scrubber. The product was washed out with water, and the precipitated *p*-nitroaniline was collected and washed with water until free from chlorides, then dried. It was analyzed by GC on a 20% SE-30 silicone gum rubber column, using an F&M 500 instrument with TC detector. Response factors were determined for known mixtures of PCNB and *p*-nitroaniline. When the isolation procedure was carried out with a known weight of pure *p*-nitroaniline, about 5% of the material was lost. The tabulated yield figures are not corrected for this isolation loss.

The bulk of the formamide can be recovered for reuse if the pasty reaction product is filtered and washed with several small portions of methanol or ethanol. When the alcohol has been stripped out in vacuum, the residue can be used for another run after addition of make-up formamide. The alcohol-washed filter cake is washed with water to remove ammonium chloride.

Acknowledgment. I am grateful to Mr. John Maciejczyk for skillful and imaginative technical assistance during most of this work.

Registry No.—Terephthalamic acid, 6051-43-0; *p*-nitrochloro-

benzene, 100-00-5; ammonia, 7664-41-7; formamide, 75-12-7; *p*-nitroaniline, 100-01-6; *p*-aminobenzoic acid, 150-13-0.

References and Notes

(1) The classical synthesis involves nitration of toluene (36% para), separation of isomers, oxidation of *p*-nitrotoluene, and reduction of the nitro group. It is not a route adaptable to large-scale manufacture of pure *p*-aminobenzoic acid because of heavy losses to unwanted isomers.
(2) The potassium salt was much easier to handle than the sodium salt.
(3) The crude product contained up to 5% each of unchanged DMT and potassium terephthalate.
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(18) Mr. John Maciejczyk devised this application of sodium borohydride.
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(20) This procedure is adapted from one originally devised by R. H. Sullivan.
(21) All pressure reactions must be conducted behind a suitable steel barricade with remotely actuated controls.

β-Thioxo Ketones. 2.[1] Preparation and Structure of Some Five- and Six-Membered 2-Acylcycloalkanethiones and 2-Thioacylcycloalkanones

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2-Acetylcyclohexanethione, 2-thioacetylcyclopentanone, and 2-benzoylcyclopentanethione have been synthesized by acid-catalyzed reaction of the corresponding β-diketones with H_2S, while 2-thioacetylcyclohexanone was obtained by Claisen condensation of cyclohexanone with ethyl thionoacetate. ^1H NMR, IR, and UV spectroscopic investigations have shown that these β-thioxo ketones exist as equilibrium mixtures of the tautomeric (*Z*)-enethiol and (*Z*)-enol forms, which interconvert very rapidly by intramolecular chelate proton transfer. The direction of enolization/enethiolization is determined by the relative stabilities of the respective endo- and exocyclic C=C double bonds. A small equilibrium concentration of the (*E*)-enethiol form was recognized only for 2-thioacetylcyclopentanone. Methylation as well as acetylation of the β-thioxo ketones resulted in exclusive formation of the respective *S*-methyl and *S*-acetyl derivatives.

It has been demonstrated recently[1,3] that thioacetylacetone[1,3] and similar open-chain α-unsubstituted β-thioxo ketones[1] exist in solution as equilibrium mixtures of the tautomeric (*Z*)-enol and (*Z*)-enethiol forms, which interconvert very rapidly by intramolecular chelate proton transfer. The two tautomers are distinguishable as individuals in the electron[1,3] and vibrational[1] spectra, whereas the very fast interconversion gives rise to a ^1H NMR spectrum where the positions of the resonance signals are weighted averages of the chemical shifts of the separate tautomers.[1] This suggests a very low activation energy barrier to the tautomeric interconversion. Furthermore, for all compounds investigated,[1,3] the equilibrium was found to depend distinctly on the nature of the solvent. It was therefore anticipated that properties which may influence the stability of the alternative types of C=C double bonds also must determine the position of the tautomeric equilibrium. Six-membered homocyclic compounds possessing an exocyclic C=C double bond are generally considerably less stable than prototropic isomers having an endocyclic C=C double bond, whereas the opposite is true for five-membered ring compounds.[4,5] It might therefore be expected that 2-acetylcyclohexanethione (**1**) would exist predominantly as the enethiol tautomer (**1C**), whereas the enol tautomer (**2D**) should predominate for the isomeric 2-thioacetylcyclohexanone (**2**).[3] For monothio analogues of 2-acylcyclopentanones a considerable contribution of the tautomer possessing an exocyclic C=C double bond would be expected. The purpose of the present work was primarily to demonstrate the fulfillment of these expectations, but also to extend generally our present knowledge of the tautomeric and structural properties of β-thioxo ketones.

Synthesis. 2-Acetylcyclohexanethione (**1**) was obtained as the only product by the acid-catalyzed reaction of 2-acetylcyclohexanone with H_2S under conditions very close to those applied successfully in the synthesis of thioacetylacetone.[1] It is noteworthy that no 2-thioacetylcyclohexanone (**2**) was formed by this reaction. The latter compound was, however, easily synthesized by Claisen condensation of cyclohexanone with ethyl thionoacetate.[6] 2-Thioacetylcyclopentanone (**3**) was obtained in a low yield by reaction of the corresponding β-diketone with H_2S in acidic acetonitrile solution. The product was isolated from the crude reaction mixture as its lead complex, which was decomposed to the free ligand by dilute sulfuric acid. The crude reaction mixture was not further investigated, but very probably a main component was 1,3-dimethyldicyclopentano[5,9,7,10]-2,4,6,8-tetrathiaadamantane (a formal dimer of 2-thioacetylcyclopentanethione), which in an earlier investigation[7] of this reaction was isolated as the only product. The reaction of 2-benzoylcyclopentanone with H_2S in acidic acetonitrile solution afforded as the only product 2-benzoylcyclopentanethione (**4**), which was also purified via its lead complex.

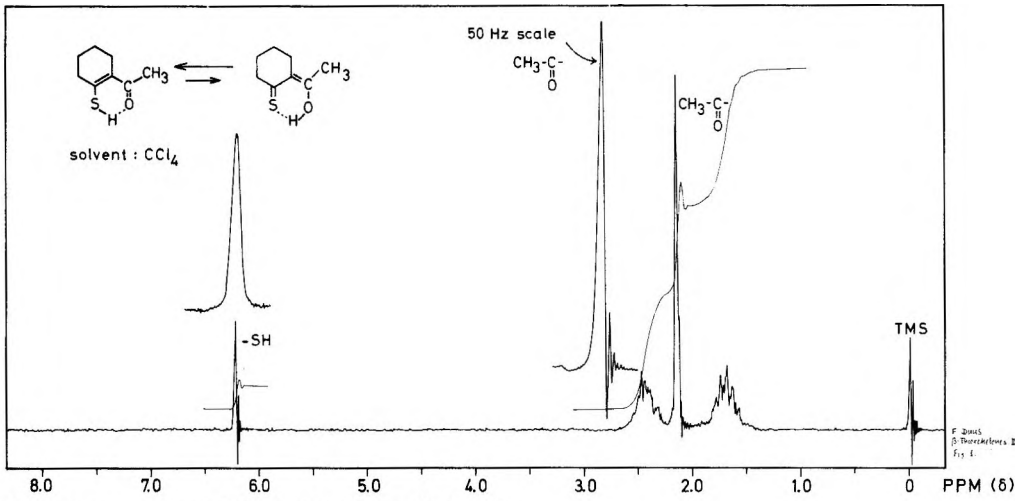
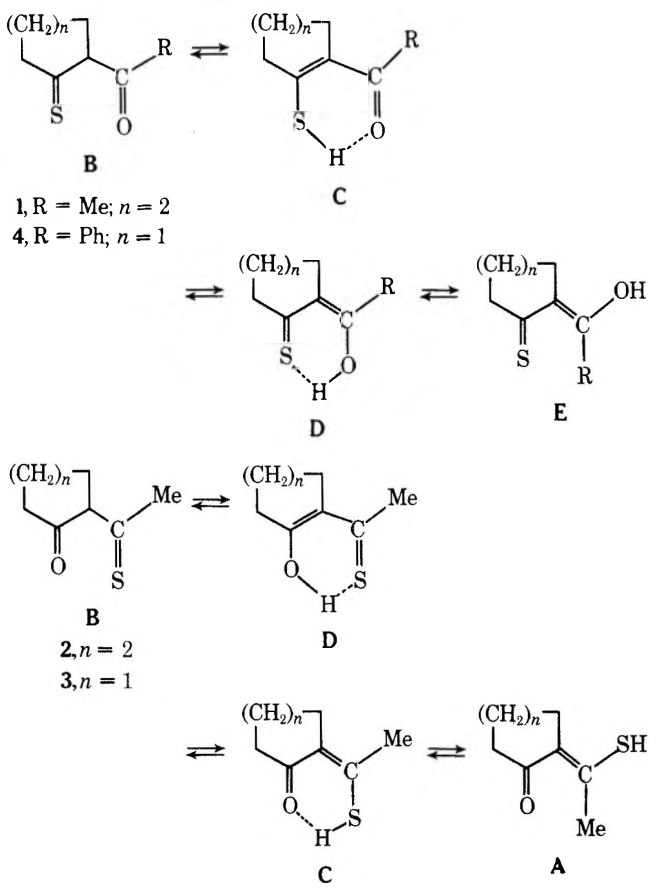


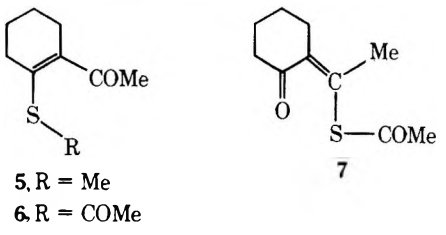
Figure 1. ^1H NMR spectrum of 2-acetylcyclohexanethione (1) in CCl_4.

Scheme I



The β-thioxo ketones 1–4 are unstable compounds. At room temperature and in contact with air, decomposition to tarry substances is significant after a few days. However, they can be stored for months under N_2 in ampules at −20 °C.

Some β-thioxo ketone derivatives were synthesized in order to facilitate interpretation of the spectra of the parent compounds. 1-Acetyl-2-methylthiocyclohexene (5) was obtained by reaction of 1 with NaH and MeI, and in better yield by the ion-pair extraction reaction of 1 with tetrabutylammonium hydrogen sulfate and MeI. Upon treatment with acetic anhydride, the β-thioxo ketones 1 and 2 gave the respective S-acylated products 6 and 7 in high yields.



Structure. The ^1H NMR spectrum of 2-acetylcyclohexanethione (1) (Figure 1) shows the pattern of a single component, just as in the case of thioacetylacetone.[1] If this spectrum is interpreted in terms of the existence of a very fast tautomeric interchange between merely the forms **1C** and **1D**, the observed weighted average chemical shift of the chelate proton (δ 6.63 ppm at infinite dilution[8]) clearly reflects a preponderant contribution of **1C**. For comparison, the mercapto proton signal of 2-ethoxycarbonyl-1-mercaptocyclohexene is found at δ 5.23 ppm,[9] whereas the hydroxyl proton signal of enolic 2-ethoxycarbonylcyclohexanone is found at δ 12.12 ppm,[10] and the chemical shift of the chelated hydroxyl proton of enolic nonaromatic β-diketones in general has a δ value between 13 and 18 ppm[11,12] (δ_{OH} 15.90 ppm for enolic 2-acetylcyclohexanone[12]). The chemical shift of the methyl protons (δ 2.16 ppm) is also in accordance with the predominance of **1C** (compare with the corresponding data for **5** and **6**, Table I), as otherwise a somewhat lower value should have been observed.[1]

The ^1H NMR spectrum of **2** is very similar to that of **1** except for the positions of the chelate proton signal (δ 15.50 ppm at infinite dilution) and the methyl signal (δ 2.47 ppm). According to the above considerations, these shifts clearly indicate predominance of **2D** in the equilibrium system **2C** ⇄ **2D**. The methyl proton shift is considerably higher than that found for the corresponding methyl group of thioacetylacetone (δ 2.37 ppm[1]), although not as high as for a "true" thioacetyl group (δ 2.63–2.73 ppm[8,13]). A preponderant contribution of **2C** would have given rise to a considerably lower methyl proton shift and observable coupling of the methyl protons to the chelate proton[1,8] and probably also the ring protons in the 3 position[8] (compare the NMR data for the *S*-acetyl derivative **7**, Table I).

According to the introductory considerations, tautomeric structures with exocyclic C=C double bonds should be of importance for the five-membered ring compounds **3** and **4**. In the case of **3** the fulfillment of these expectations is very nicely illustrated by its ^1H NMR spectrum (Figure 2). In CCl_4 solution **3** exhibits the chelate proton signal at δ 10.45 ppm, i.e., approximately halfway between the positions typical of chelated enethiolic mercapto protons ($\delta_{SH} \sim 6.0$ ppm for α-substituted β-mercaptocrotonates[8]) and chelated enolic hydroxyl protons (δ_{OH} 13.08 ppm for enolic 2-acetylcyclopentanone[11]), thus demonstrating the existence of a considerable

Table I. ^{1}H NMR Chemical Shifts (δ ppm) and Coupling Constants (Hz, in Parentheses) of 2-Acylcycloalkanethiones, 2-Thioacylcycloalkanones, and Derivatives[a]

Registry no.		Solvent	$\delta_{chelat\text{-}H}$	δ_{Me}	δ_{Ph}	δ_{SR}
	1	CCl_4	6.63[b] s	2.16 s		
		CD_3CN	4.53 t (0.35)	2.18 s		
	2	CCl_4	15.50[b] s	2.47 s		
		CD_3CN	13.48 s	2.43 s		
	3[c]	CCl_4	10.45[b] q (0.95)	2.13 q (0.95)		
	4	CCl_4	14.33[b] s		7.2–7.8 m	
		CD_3CN	11.82 s		7.3–7.8 m	
62460-75-7	5	CCl_4		2.19 s		2.19[d] s
		C_6D_6		1.87[e] s		2.05[d,e] s
62460-76-8	6	CCl_4		2.15 s		2.27[f] s
62460-77-9	7	CS_2		2.09 t (1.5)		2.30[f] s

[a] Aliphatic proton resonances at 2.0–3.0 (flanking methylene protons) and 1.5–2.1 ppm (other ring protons). [b] Chemical shift extrapolated to infinite dilution.[8,9] [c] Equilibrium percentage of trans enethiol form (**3A**) 15% (calculated from integrals). δ_{SH} (**3A**) 3.18 ppm (3.00 ppm at infinite dilution[8]), δ_{Me} (**3A**) 2.24 ppm. [d] R = Me. [e] Assignment tentative. [f] R = COMe.

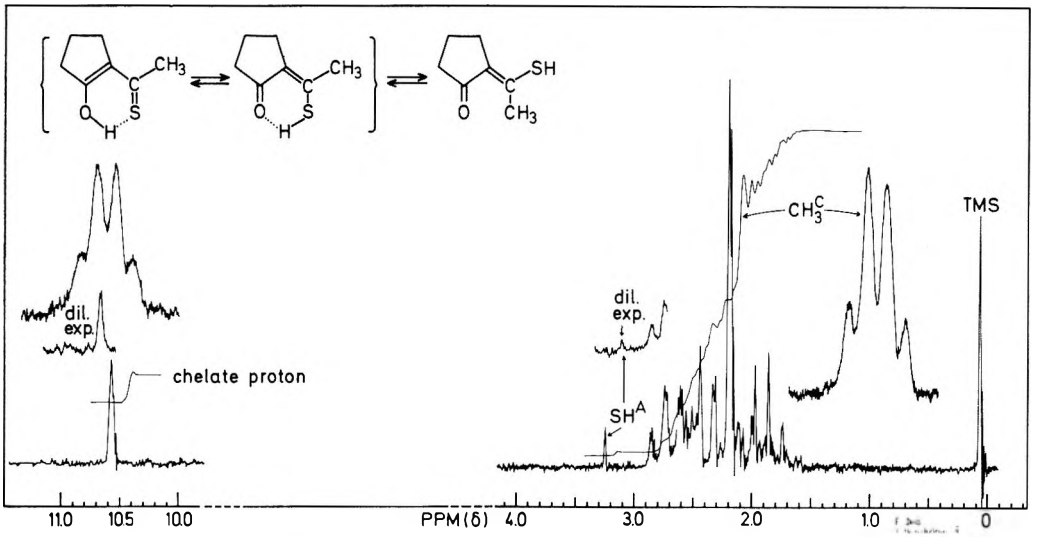


Figure 2. ^{1}H NMR spectrum of 2-thioacetylcyclopentanone (**3**) in CS_2.

equilibrium concentration of **3C**. The importance of the contribution of **3C** is furthermore reflected by the occurrence of well-defined couplings between the chelate proton and the methyl protons and between the methyl protons and the ring protons in the 3 position, the two coupling constants being of approximately the same magnitude. Such couplings are also characteristic of α-alkyl-substituted (*Z*)-β-mercaptocrotonates.[8]

Besides the resonance signals from the rapidly interconverting tautomers **3C** and **3D**, a small peak at δ 3.18 ppm (3.22 ppm in CS_2 solution, see Figure 2), which upon dilution moves to higher field (up to the limiting position of 3.00 ppm at infinite dilution[8]), is notable. This peak can be unambiguously designated as the mercapto proton resonance signal from the trans enethiol tautomer **3A**.[8] According to the integrals, the equilibrium percentages of **3A** are 15 ± 2%. The methyl resonance signal of **3A** is found at δ 2.24 ppm (2.25 ppm in CS_2 solution, see Figure 2).

In the ^{1}H NMR spectrum of **4** (Table I), the chelate proton signal is found at δ 14.33 ppm in accord with a preponderant contribution of the enol tautomer **4D** (the chelate proton signal of enolic 2-benzoylcyclopentanone is found at δ 14.35 ppm in $CDCl_3$[14]). **4D** has the preferred exocyclic C=C double bond framework, which in this case may be further stabilized by the conjugative effect of the phenyl group.

The IR spectra of **1–4** (Table II) are fully consistent with the above interpretation of the ^{1}H NMR spectra. The IR spectra of **1** and **3** show unmistakable S–H, C=O, and C=C stretching vibration bands at wavenumbers expectable[1] for the predominant enethiol tautomers **1C** and **3C**. In addition, the IR spectrum of **3** displays C=O and C=C stretching vibration bands arising from the minor tautomer **3A** (assignments are made by comparison with the IR data for (*E*)-β-mercaptocrotonates[8]). The IR spectra of **2** and **4** show, in accord with the prevalence of the enol tautomer **D** for these compounds, no distinct C=O or S–H stretching vibration bands, whereas in both cases the C=C stretching vibration band is very intense. Furthermore, a band assignable to the stretching vibration of a chelating, conjugated C=S group is found in both spectra (in the IR spectrum of thioacetylacetone[1] the C=S stretching vibration band of the **C** tautomer is at 1125 cm^{-1}). For comparison, IR data for the *S*-methyl and *S*-acetyl derivatives **5–7** are also given in Table II.

Previous investigations of thioacetylacetone and related open-chain α-unsubstituted β-thioxo ketones have shown that the existence of the **C** $\rightleftarrows$ **D** equilibrium can be confirmed nicely by UV spectroscopy and that the position of the equilibrium can be determined, at least semiquantitatively, by UV absorbance measurements.[1,3] The UV spectra of thioacetylacetone in different solvents were found to be characterized by two bands within the regions 291–296 and 354–357 nm, the exact positions depending on the solvent. These bands were assigned to $\pi \rightarrow \pi^*$ transitions in the SC=CC=O chromophore (the enethiol tautomer **C**) and in the OC=CC=S

Table II. Some Characteristic IR Absorption Bands (cm^{-1}) of 2-Acylcycloalkanethiones, 2-Thioacylcycloalkanones, and Derivatives[a]

	ν(S–H)	ν(C=O)	ν(C=C)	ν(C=S)
1	~2540 w	1670 s	1555 s	
2			1545 s	1121[b] m
3	2410 m, br	1670 s	1555 s	
		1702[c] m	1598[c] m	
4			1545 s	1119[d] w
5		1665 s	1536 s	
6		1710 vs	~1625 w, br	
7		1710 vs	1610 m, br	

[a] Measured on CCl_4 solutions. [b] Tentative assignment, made by comparison with the IR spectrum of thioacetylacetone.[1] This band was absent in the IR spectra of **1** and 2-acetylcyclohexanone. [c] Attributed to the trans etheniol form (**3A**). [d] Tentative assignment.[1] A band at 1104 cm^{-1} (m) is an alternative.

chromophore (the enol tautomer **D**), respectively.[1,3] The assignment of the band at lower wavelength is in agreement with UV spectral data for other compounds also containing the SC=CC=O chromophore (α,β-unsaturated β-mercaptoesters,[8] α,β-unsaturated β-mercapto thiolesters,[15] *S*-alkyl derivatives of these,[8,15] the enethiol tautomer of thiodimedone[16]). Unfortunately, comparable UV data for compounds possessing the OC=CC=S moiety are lacking in the literature. Both of the above assignments, however, are consistent with CNDO/2 calculations.[3] From these assignments, the intensities of the two bands in question must reflect directly the equilibrium concentrations of the two tautomers **C** and **D**, if other tautomers (see Scheme I) are nonexistent or present only in negligible concentrations. Assuming approximately equal molar absorption coefficients for the two bands, guiding equilibrium percentages of **C** and **D** may be easily calculated from the equations % **D** = $100A_D/(A_C + A_D)$ and % **C** = $100A_C/(A_C + A_D)$, where A_C and A_D are the measured absorbances. However, a comparison of the UV data of **5** (representative of the pure **C** structure) and **2** (existing in inert solvents to the extent of ~90% in the enol form **D**) reveals that the molar absorption of **D** may be possibly up to twice that of **C**. If so, the equilibrium percentages of **C** and **D** should be calculated according to the equations % **D** = $100A_D/(2A_C + A_D)$ and % **C** = $200A_C/(2A_C + A_D)$.

The UV spectra of the compounds **1–5** are tabulated in Table III, which also contains calculated absorbance ratios (A_D/A_C) and equilibrium percentages of the **C** and **D** tautomers. The percentages listed are averages of those calculated from the above pairs of equations, which are considered to represent cases of extremity. Whereas the *S*-methyl derivative **5** shows only one intense UV absorption, consistent with the existence of only the SC=CC=O chromophore, each of the β-thioxo ketones **1–4** exhibits both of the expected UV absorption bands. It is seen that the absorbance ratios as well as the calculated equilibrium percentages of the **C** and **D** tautomers (in the cases where the less polar solvents C_6H_{12} and CCl_4 were used) go nicely with the estimates made from the ^1H NMR data. The more polar solvents EtOH and MeCN give rise to a general displacement of the **C** ⇄ **D** equilibrium in favor of the enethiol tautomer **C** (Table III). This effect was also observed for thioacetylacetone[1,3] and 1,4-diphenyl-3-thioxo-1-butanone.[1] In order to establish the interpretation of the observed solvent-induced change in the absorbance ratio A_D/A_C as a solvent-promoted equilibrium displacement, ^1H NMR spectra of **1**, **2**, and **4** were also recorded in CD_3CN solution. In accordance with the principle of weighted average signals, a general displacement of the chelate proton signal to higher field (about 2 ppm) was observed (Table I).

Experimental Section

^1H NMR spectra were recorded on a Varian A-60 and/or on a JOEL C-60 HL spectrometer with 20–0.5% solutions. The chemical shifts are expressed as δ values in parts per million downfield from Me_4Si, and are correct to ±0.02 ppm. The chelate proton chemical shifts were found to be constant, unaffected by further dilution, at solute concentrations below 2%. Coupling constants were measured on expanded signals, and are expressed numerically in hertz with an accuracy of ±0.1 Hz. Attainment of tautomeric equilibrium was checked by repetitive NMR measurements during several days on solutions kept in closed tubes at constant temperature (25 °C). All signals were integrated at least five times.

Infrared spectra were recorded for 20–1% CCl_4 solutions on a Perkin-Elmer 457 grating spectrophotometer.

UV spectra were recorded on a Beckman Acta III spectrophotometer. Attainment of equilibrium was checked by repeated measurements on standard solutions.

Boiling and melting points are uncorrected. The yields refer to pure products. The purity was checked by NMR and elemental analyses (carried out by the microanalytical laboratory of the Department of General and Organic Chemistry, H.C. Ørsted Institute, University of Copenhagen).

Known methods were employed for preparation of the starting 2-acylcycloalkanones[17–19] and of ethyl thionoacetate.[20] Cyclohexanone was commercially available. The purity of the starting materials was checked by NMR.

2-Acetylcyclohexanethione (1). A solution of 14.0 g (0.1 mol) of 2-acetylcyclohexanone in 200 mL of MeCN was cooled to −50 °C. A stream of H_2S was passed through the solution for 1.5 h, followed by another stream of dry HCl for 1.5 h (during which the temperature was allowed to rise to −40 °C). Finally, a moderate stream of H_2S was passed through the solution during 3 h while the temperature was kept strictly constant at −40 °C. The reaction mixture was cautiously poured with stirring into a mixture of 300 mL of ice water and 200 mL of light petroleum (or pentane). The aqueous layer was extracted with a further 200 mL of light petroleum (or pentane), and the combined organic layers were washed twice with water until neutral and dried ($CaSO_4$). The solvent was evaporated at reduced pressure at room temperature to leave 10.0–11.4 g of yellow oil,[21] which was immediately distilled[22] twice through a short Vigreux column to give 4.6–6.1 g (30–39%) of pure product as a yellow oil that partly solidified on standing in the refrigerator, bp 76–77 °C (0.1 mm), $n^{25}D$ 1.5750. Anal. Calcd for $C_8H_{12}OS$: C, 61.52; H, 7.75; S, 20.48. Found: C, 61.85; H, 7.80; S, 19.96.

2-Thioacetylcyclohexanone (2). A solution of 39.2 g (0.4 mol) of cyclohexanone in 50 mL of dry ether was added dropwise during 10 min to a stirred suspension of 15.6 g (0.4 mol) of $NaNH_2$ in 300 mL of dry ether at 0 °C. After stirring for 50 min at 0 °C, a solution of 20.8 g (0.2 mol) of ethyl thionoacetate in 50 mL of dry ether was added dropwise during 1 h with stirring at 0 °C. The stirring was continued overnight, during which period the temperature in the reaction flask was allowed to reach room temperature. Ice water (400 mL) was stirred in, and the aqueous layer was isolated and washed with 200 mL of ether. Then 200 mL of ether was added, and 2 N aqueous HCl was added in small portions with vigorous stirring until the aqueous layer had pH about 2. The ethereal layer was separated, the aqueous layer was extracted with a further 200 mL of ether, and the combined ethereal extracts were washed once with water and dried ($CaSO_4$). The solvent was evaporated to leave 24.9 g of practically pure **2**. Distillation[22] through a short Vigreux column gave 15.4 g (49%) of pure **2** as a yellow oil that solidified in the refrigerator, bp 69–70 °C (0.1 mm) [lit.[6] 90–92 °C (0.2 mm)], $n^{25}D$ 1.6172. Anal. Calcd for $C_8H_{12}OS$: C, 61.52; H, 7.75; S, 20.48. Found: C, 61.68; H, 7.88; S, 20.28.

2-Thioacetylcyclopentanone (3). Through a solution of 12.6 g (0.1 mmol) of 2-acetylcyclopentanone in 150 mL of MeCN there was passed successively H_2S (1.5 h at −50 °C), dry HCl (1.5 h at −50 to −40 °C), and H_2S (5 h at −40 °C). The reaction mixture was worked up as described for **1**. The crude product was purified via its lead salt according to a previously described procedure[8] (method D). The final distillation[22] gave 0.65 g (4.5%) of pure **3** as a yellow oil, bp 47 °C (0.1 mm) [lit.[23] bp 80–83 °C (0.5 mm)], $n^{25}D$ 1.5784. Anal. Calcd for $C_7H_{10}OS$: C, 59.14; H, 7.09; S, 22.51. Found: C, 59.41; H, 6.95; S, 22.64.

2-Benzoylcyclopentanethione (4). A solution of 12.2 g (65 mmol) of 2-benzoylcyclopentanone in 200 mL of MeCN was cooled to −50 °C and treated successively with H_2S (1.5 h at −50 °C), dry HCl (1.5 h at −50 °C), and H_2S (8 h, during which the temperature rose to −37 °C). The reaction mixture was poured (caution!) with stirring into a mixture of 400 mL of ice water and 200 mL of chloroform, and the organic layer was washed with water and dried ($CaSO_4$). The solvent

Table III. UV Spectra of 2-Acylcycloalkanethiones, 2-Thioacylcycloalkanones, and S-Methyl Derivatives[a]

	Solvent	Concn, 10^{-5} mol/L	λ_{max} (A)	λ_{max} (C) (A_C)	λ_{max} (D) (A_D)	λ_{max} (A)	A_D/A_C	% D	% C	Registry no. D	Registry no. C
1	C_6H_{12}	6.27		293 (0.341)	372 (0.139)		0.41	23 ± 6	77 ± 6	62460-78-0	62460-82-6
	CCl_4	7.15		296 (0.420)	372 (0.157)		0.37	21.5 ± 5.5	78.5 ± 5.5		
	EtOH	7.08		295 (0.475)	370 (0.085)		0.18	11.5 ± 3.5	88.5 ± 3.5		
	CH_3CN	6.40		293 (0.384)	370 (0.057)		0.15	10 ± 3	90 ± 3		
5	EtOH	13.68		316 (0.873)							
2	C_6H_{12}	6.13	242 (0.103)	290 (0.052)	369 (0.790)	~460 (0.0038)	15.20	91 ± 3	9 ± 3	62460-79-1	62460-83-7
	CCl_4	5.56		290 (0.040)	371 (0.707)	~460 (0.0066)	17.67	92.5 ± 2.5	7.5 ± 2.5		
	EtOH	4.73	242 (0.067)	302 (0.136)	370 (0.504)	~460 (0.0022)	3.71	72 ± 7	28 ± 7		
	CH_3CN	5.69	242 (0.093)	294 (0.164)	370 (0.599)	~460 (0.0030)	3.65	71.5 ± 6.5	28.5 ± 6.5		
3	C_6H_{12}	11.82		302 (0.655)	373 (0.330)		0.65[b] 31.5 ± 7.5[d]	26.5 ± 6.5[c] 68.5 ± 7.5[d]	58.5 ± 6.5[c]	62460-80-4	62460-84-8
	EtOH	11.32		302 (0.788)	368 (0.205)		[e]	16.54 ± 4.5	[e]		
4	C_6H_{12}	9.12		~320 (~0.20)	394 (1.393)		~7.0	83 ± 5	17 ± 5	62460-81-5	62460-85-9
	EtOH	7.84		325 (0.283)	395 (0.684)		2.42	63 ± 8	37 ± 8		

[a] λ is expressed in nm. Absorbances (A) are given in parentheses. [b] A_c was corrected for a contribution by 15% of **3A**. [c] Calculated as coexisting with 15% of **3A**. [d] Relative percentages, referring to the system **3C** ⇄ **3D** only. [e] Not calculable because the equilibrium percentage of **3A** in EtOH is not known.

was evaporated to leave 11.2 g of a red-brown syrup, which was distilled. The fraction collected at 125–130 °C (0.25 mm), a red oil (6.5 g), was further purified via its lead salt according to a previously described procedure[8] (method C). The final distillation[22] gave 1.6 g (12%) of pure **4** as a red oil, bp 122 °C (0.15 mm). Anal. Calcd for $C_{12}H_{12}OS$: C, 70.57; H, 5.92; S, 15.67. Found: C, 70.74; H, 5.96; S, 15.73.

2-Acetyl-1-methylthiocyclohexene (5). A. To a suspension of 0.60 g (25 mmol) of NaH in 75 mL of dry benzene was added dropwise during 30 min, with stirring, a solution of 3.12 g (20 mmol) of **1** in 15 mL of dry benzene. After stirring for a further 2 h a solution of 3.12 g (22 mmol) of MeI in 15 mL of dry benzene was added dropwise during 15 min. The reaction mixture was refluxed for 4 h, allowed to stand overnight, and filtered. Evaporation of the filtrate left an orange oil that solidified in the refrigerator. Recrystallization from a 1:5 mixture of benzene and light petroleum (60–80 °C) gave 0.81 g (24%) of **5** as pale orange crystals, mp 65 °C. Anal. Calcd for $C_9H_{14}OS$: C, 63.51; H, 8.29; S, 18.80. Found: C, 63.86; H, 7.92; S, 18.91.

B. A solution of 2.50 g (16 mmol) of **1** and 2.27 g (16 mmol) of MeI in 40 mL of chloroform was added to 40 mL of an aqueous solution of 1.82 g (32 mmol) of KOH and 5.42 g (16 mmol) of tetrabutylammonium hydrogen sulfate, and the mixture was stirred vigorously for 1.5 h. The organic layer was dried ($CaSO_4$), the solvent was evaporated, and the residue was shaken carefully with 50 mL of ether to separate crystalline tetrabutylammonium iodide. After filtration and evaporation of the ether, the remaining oil solidified in the refrigerator. Recrystallization (n-heptane) gave 1.59 g (72%) of **5**, mp 60–61 °C. The ^1H NMR and IR spectra of the two products were identical.

2-Acetyl-1-acetylthiocyclohexene (6). To a solution of 2.03 g (13 mmol) of **1** in 25 mL of Ac_2O was added a few crystals of anhydrous sodium acetate. The mixture was allowed to stand for 2 days. Ether (50 mL) was added, and the ethereal solution was washed with aqueous potassium carbonate and water and dried ($CaSO_4$). The ether was evaporated and the remaining dark oil distilled to give 2.05 g (80%) of pure **6** as a colorless oil, bp 99–100 °C (0.35 mm), $n^{25}D$ 1.5278. Anal. Calcd for $C_{10}H_{14}O_2S$: C, 60.59; H, 7.12; S, 16.15. Found: C, 60.50; H, 7.15; S, 15.99.

2-(1-Acetylthioethylidene)cyclohexanone (7) was prepared analogously to **6** from 3.28 g (21 mmol) of **2** and 40 mL of Ac_2O: yield 3.40 g (82%); colorless oil; bp 83 °C (0.15 mm); $n^{25}D$ 1.5396. Anal. Calcd for $C_{10}H_{14}O_2S$: C, 60.59; H, 7.12; S, 16.15. Found: C, 60.62; H, 7.22; S, 15.98.

Registry No.—**3A**, 62460-86-0; 2-acetylcyclohexanone, 874-23-7; cyclohexanone, 108-94-1; ethyl thionoacetate, 926-67-0; 2-acetylcyclopentanone, 1670-46-8; 2-benzoylcyclopentanone, 36150-58-0.

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(21) According to ^1H NMR analyses, this oil contained 85–90% of **1**, the remaining 10–15% being mainly residual solvent. Traces of unreacted 2-acetylcyclohexanone and the *gem*-dithiol 2-acetyl-1,1-dimercaptocyclohexane [^1H NMR (CS_2) δ (SH^{free}) 2.79 (s), δ (SH^{chel}) 3.22 (m); cf. ^1H NMR data for 2-ethoxycarbonyl-1,1-dimercaptocyclohexane[9]] were detected in some experiments, but **2** was never observed as a product.
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Thermally Catalyzed and Noncatalyzed [2 + 2] Cycloadditions between Ketene Acetals and Carbonyl Compounds. A Simple Route to 2,2-Dialkoxyoxetanes

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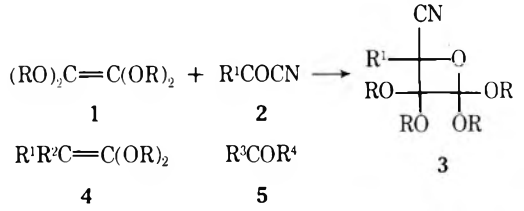
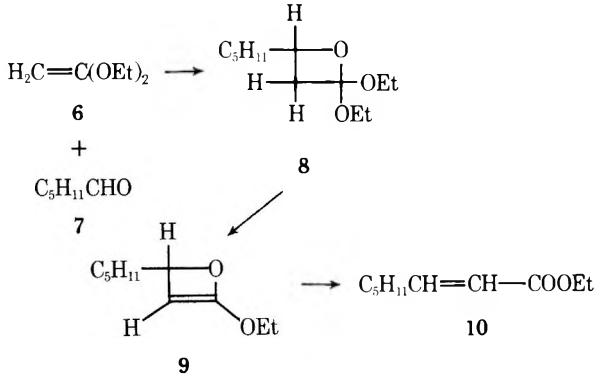
The known thermal cycloaddition between ketene acetals and electron-poor carbonyl compounds can be extended to all sorts of aldehydes and ketones by application of zinc chloride as a catalyst. In general the reactions proceed at room temperature. Only with dialkoxyethene the expected product cannot be isolated owing to thermal instability. Some examples of the reactivity of the 2,2-dimethoxyoxetanes, thus obtained, toward nucleophiles are given.

It is known that oxetanes arise photochemically from many types of olefins and carbonyl compounds.[1] However, the regiospecificity of these reactions, at least for enol ethers and ketene acetals, is low. Irradiation of a mixture of an aldehyde or ketone and a ketene acetal yields a mixture of a 2,2- and a 3,3-dialkoxyoxetane. In general, the 2,2-dialkoxy compound cannot simply be isolated from the reaction mixture, since the 3,3-disubstitution product is usually the main product.[2,3]

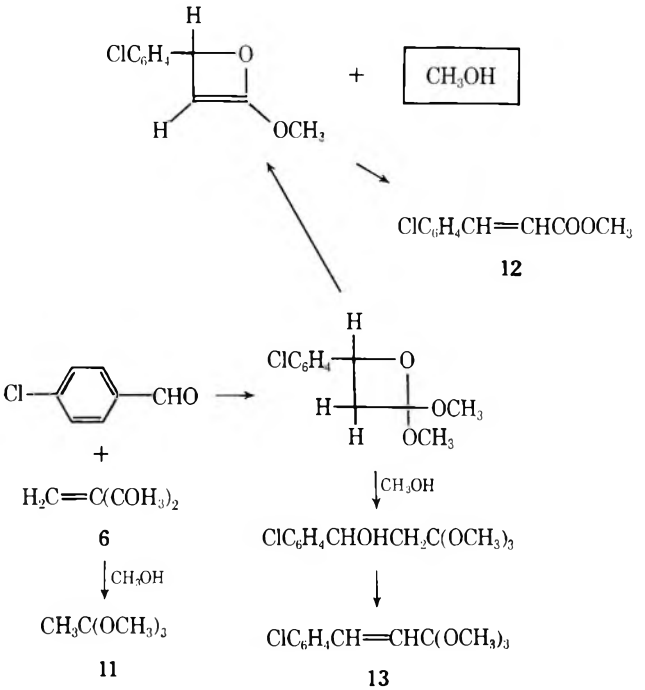
In a recent paper[4] we reported that [2 + 2] cycloadditions between tetraalkoxyethenes (**1**) and sufficiently electron-poor carbonyl compounds (e.g., acyl cyanides **2**) provide a simple method for the preparation of distinct tetraalkoxyoxetanes (**3**). In view of the varied, synthetic applications of ortho esters such oxetanes are potentially useful compounds. Relief of strain in reactions with nucleophiles will enhance the reactivity of their ortho ester function. The usefulness of compounds **3** is, however, limited as a consequence of the additional alkoxy groups on C_3 and the cyano group (or other electron-withdrawing substituent) on C_4. Therefore, we investigated if the oxetane formation via cycloadditions could be extended to less substituted ketene acetals (**4**) and less activated carbonyl compounds (**5**).



In the preparation of 2,2-dialkoxyoxetanes via thermal cycloadditions, instability of the desired product under the reaction conditions has to be considered when hydrogen atoms are present on C_3. McElvain isolated[5] the α,β-unsaturated ester (**10**) from the reaction between 1,1-diethoxyethene (**6**) and hexanal (**7**) at 150 °C, and ascribed the result to elimination of ethanol from an initially formed oxetane (**8**), followed by ring opening of the second intermediate (**9**). We found that **6** reacts at room temperature with more electron-



poor carbonyl compounds (chloral, benzoyl cyanide, *p*-chlorobenzaldehyde). The reaction mixtures were rather complex. The presence of large amounts of methyl orthoacetate (**11**) among the products indicated that even under the mild reaction conditions alcohol had been eliminated at some stage. Careful workup in the experiment with *p*-chlorobenzaldehyde yielded methyl *p*-chlorocinnamate (**12**) (mp 74–76 °C, lit.[6]



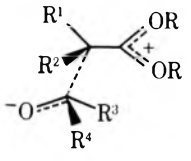
72–73 °C) and the corresponding ortho ester (**13**) (*m/e* 244, 242, M^+ and 213, 211 $M^+ - OCH_3$; NMR δ 7.30, s, 4 H; 6.82 and 5.87, d, AB pattern, J = 15 Hz; 3.22, s, 9 H) which can be explained by the following scheme. Thus it seems that the thermal stability of 2,2-dialkoxyoxetanes having two hydrogen atoms on C_3 is too low for isolation under normal conditions.[7] [It may, however, be possible that with 1,1-dialkoxyethenes oxetanes are not formed at all (see under mechanistic aspects).]

2,2-Dialkoxyoxetanes having only one hydrogen atom on C_3 were obtained from reactions between 1,1-dimethoxypropene and several strongly electrophilic carbonyl compounds at room temperature. The products appeared to be stable up to 80 °C so that they could be purified by distillation. By performance of the reactions in an NMR tube, rough estimates of relative reaction rates could be made by determination of the time of half change ($t_{1/2}$) for the reactants (Table I). The reactions show a moderate solvent effect. Apparently the rate of the cycloadditions strongly depends on the electron-withdrawing ability of the groups at the carbonyl func-

tion. The influence of steric effects is more apparent on variations in the ketene acetal. 1,1-Dimethoxyisobutene is much less reactive toward benzoyl cyanide than 1,1-dimethoxypropene (Table II).

An interesting observation was made with reactions between *p*-chlorobenzaldehyde and 1,1-dimethoxypropene. Whereas freshly distilled aldehyde showed hardly any reaction, older, partly oxidized samples reacted much better, yielding beside polymeric products the expected oxetane. The results were ascribed to acid catalysis since a similar acceleration was found on addition of slight amounts of a proton acid (*p*-toluenesulfonic acid) or a Lewis acid (BF_3, $AlCl_3$, $TiCl_4$, $ZnCl_2$). Best results, viz., high conversion rates at moderate temperatures without serious polymerization of the ketene acetal, were obtained with 0.5–1% $ZnCl_2$. The use of this catalyst gives the preparation of 2,2-dialkoxyoxetanes via thermal cycloadditions a much wider scope. Even simple aldehydes and ketones without electron-withdrawing groups can be converted in this way at room temperature (see Experimental Section, Table III). Unsymmetrical carbonyl compounds yield always a mixture of diastereomeric products in reactions with 1,1-dimethoxypropene.

Mechanistic Aspects. According to a recent frontier orbital treatment of [2 + 2] cycloadditions[9] two limiting geometries, symbolized as $1_s^D + 1_s^A$ and $2_s^D + 1_s^A$, can be considered for the addend approach in reactions between an electron-donating and an electron-accepting compound. The transition state of the respective pathways can be visualized as in the formulas **14** and **15**. The solvent effects [$t_{1/2}$ $(CDCl_3)/t_{1/2}$ (cyclohexane) ca. 0.01] as well as the strong electronic influences of the residues (R_3, R_4) at the carbonyl group are in agreement with such polar transition states. The observed acid catalysis can be ascribed to activation of the carbonyl group by protonation or complexation with a Lewis acid. The complete regiospecificity of cycloadditions with unsymmetrically substituted donor compounds (1,1-dimethoxypropene and -isobutene) points to the $1_s^D + 1_s^A$ approach (via **14**) which leads to a favorable charge separation in these cases. It may be expected that in reactions between donors and acceptors having different R residues ($R^1 \neq R^2$, $R^3 \neq R^4$) via **14** the isomer ratio of the product will not be very sensitive to steric factors. This was found to be true. The cycloadditions between 1,1-dimethoxypropene and several carbonyl compounds gave, in general, isomer ratios between 0.35 and 0.65. Only in one case (biacetyl) a lower value (0.15) was found (Table III). Cycloadditions of tetramethoxyethene via **14** should be expected to be slower than corresponding reactions of 1,1-dimethoxyisobutene as a consequence of the destabilizing effect of the β-methoxy groups (R_1 and R_2) on the positive charge. The reactivity of tetramethoxyethene is, however, much higher (Table II). Probably highly symmetrical donor compounds react via the three-center transition state[10] (**15**) in which the positive charge is delocalized over both sides of the olefin.



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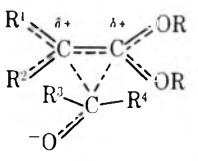

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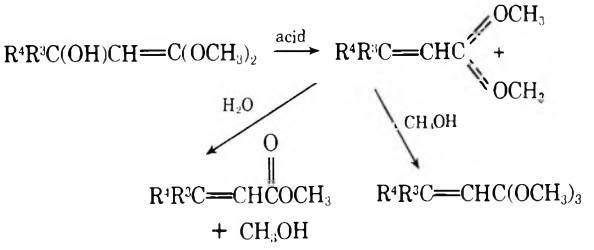
The transition state with the strongest dipolar character (**14**) should be expected for $R^1 = R^2 = H$. In this case proton shift may be faster than ring closure, delivering $R^4R^3C(OH)$-$CH{=}C(OR)_2$. Another explanation for the products of the reaction of 1,1-dimethoxyethene with carbonyl compounds could therefore be:

Table I. $t_{1/2}$ Values for Cycloadditions between 1,1-Dimethoxypropene and Various Carbonyl Compounds (Both Concentrations 0.25 mol L^{-1}) at 25 °C

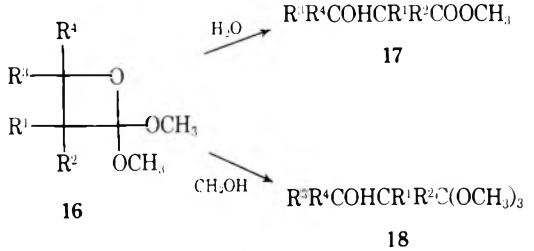
Registry no.	Carbonyl compd	$t_{1/2}$ ($CDCl_3$), min	$t_{1/2}$ (cyclohexane)
75-87-6	CCl_3CHO	<1	50 min
631-57-2	CH_3COCN	~1	
613-90-1	C_6H_5COCN	40	75 h
431-03-8	$CH_3COCOCH_3$	No reaction	
104-88-1	p-ClC_6H_4CHO	No reaction	



We are investigating more systematically the influence of R^1 and R^2 on the character of the transition state in several [2 + 2] cycloadditions and will report on it in another paper.

Reactivity of the Oxetanes. All oxetanes synthesized appeared to be stable at room temperature, even in the presence of 1 mol % $ZnCl_2$. The composition of isomer mixtures obtained from 1,1-dimethoxypropene did not vary under these conditions. In the absence of acids most of the products did not decompose below ca. 80 °C. At higher temperature, the reverse reaction, accompanied by change in the isomer ratio, was observed by following the reactions with NMR. In only one case (the oxetane from chloral and dimethoxypropene) could a pure isomer (probably the trans compound) be obtained in this way. In other cases elimination of alcohol leading to a complex reaction mixture was a serious side reaction on heating oxetanes having hydrogen on C_3.

The oxetanes (**16**) react easily with water and alcohols, giving β-hydroxy esters (**17**) and ortho esters (**18**), respectively.



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18

They may be valuable starting compounds for the preparation of β-hydroxy and β-keto esters and of α,β-unsaturated esters (when R^1 = H). Further applications will be reported in a subsequent paper.

Experimental Section

Since most of the oxetanes are easily hydrolyzed in contact with moisture elemental analyses have only been made for the more stable oxetanes. Therefore, complete purity of all products is not fully guaranteed. From the spectral data, used for structure assignments, it could be concluded, however, that the purity of all preparations is more than 95%.

Infrared spectra were measured with a Perkin-Elmer spectrophotometer, Model 257. Proton magnetic resonance spectra were traced with a Varian T-60 NMR spectrometer, using solutions in deuteriochloroform unless otherwise indicated. Chemical shifts are reported as δ values relative to tetramethylsilane as an internal standard. Mass spectra were obtained with a double focusing Varian Associates SM1-B mass spectrometer.

Table II. $t_{1/2}$ Values for Cycloadditions between Benzoyl Cyanide and Various Ketene Acetals

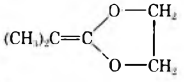
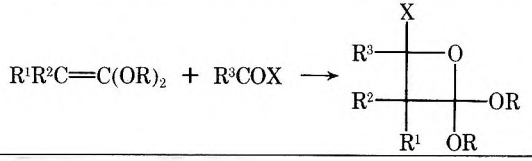
Registry no.	Ketene acetal	Temp, °C	Solvent	Concn	$t_{1/2}$
5634-52-6	$CH_3CH{=}C(OCH_3)_2$	25	$CDCl_3$	Both 0.25 mol L^{-1}	40 min
5634-54-8	$(CH_3)_2C{=}C(OCH_3)_2$	120	None	Acetal in twofold excess	48 h
4351-16-0		25	$CDCl_3$	Both 0.25 mol L^{-1}	200 min[a]
1069-12-1	$(CH_3O)_2C{=}C(OCH_3)_2$	100	None	Acetal in twofold excess	7 h

Table III. Preparation, Yield, Physical Constants, and Spectral Data for Oxetanes from the Reaction



Ketene acetal	Carbonyl compd	Reaction time, h	Yield, %	Isomer ratio[a]	Purification method	Bp, °C (mm)	Mp, °C	IR[b] ν_{C-O}, cm^{-1}	NMR, δ ppm
$CH_3CH{=}C(OCH_3)_2$	C_6H_5CHO[f]	1	75	0.35	*a*	78 (0.2)		952 926	7.20 and 7.25 (s, 5 H), 5.27 and 4.65 (d, 1 H, J = 7 Hz), 2.75 (m, 1 H), 1.20 and 0.60 (d, 3 H, J = 7 Hz) (cis–trans mixture)
	p-$NO_2C_6H_4CHO$[g]	1	85	0.55	*c*		Oil	950–970	8.70 and 7.50 (AB, 4 H), 5.40 and 4.80 (d, 1 H, J = 7 Hz), 2.75 (m, 1 H), 1.25 and 0.62 (d, 3 H, J = 7 Hz) (cis–trans mixture)
	CCl_3CHO	1[c]	75	0.65	*a*	64 (0.5)		975 950	4.16 (d, 1 H, J = 6 Hz), 3.06 (m, 1 H), 1.06 (d, 3 H, J = 7 Hz) (trans isomer)
	C_6H_5COCN	1	80	0.35	*c*		Oil	975 955	7.35 (m, 5 H), 1.45 and 0.75 (d, 3 H, J = 8 Hz) the methine signal is hidden under the methoxy absorptions (cis–trans mixture)
	CH_3COCN	1[c]	75	0.60	*a*	45–50 (0.3)		970 945	2.87 (m, 1 H), 1.62 and 1.53 (s, 3 H), 1.25 and 1.10 (d, 3 H, J = 7 Hz) (cis–trans mixture)
	$CH_3COCOCH_3$	1	70	0.15	*a*	48 (0.5)		952	2.85 (m, 1 H), 2.25 (s, 3 H), 1.40 and 1.30 (s, 3 H), 1.10 and 0.90 (d, 3 H, J = 7 Hz) (cis–trans mixture)
	$(CH_3)_2CHCHO$[h]	1	60		*b*	68 (15)		928 916	2.53 (m, 1 H), 1.73 (m, 1 H), 1.15–0.75 (complex pattern, 9 H). A methine signal is hidden under the methoxy absorptions (cis–trans mixture)
	CH_3COCH_3[i]	2	25[d]		*b*	54 (15)		956	2.58 (q, 1 H), 1.31 (s, 3 H), 1.23 (s, 3 H), 0.96 (d, 3 H, J = 7 Hz)
$(CH_3)_2C{=}C(OCH_3)_2$	$(CH_3)_2CHCHO$	48	70		*a*	78 (15)		995–965 Several absorptions	(in CCl_4) 3.25 (d, 1 H), 1.75 (m, 1 H), 1.16 (s, 3 H), 1.10 (s, 3 H), 0.83 (d, 3 H, J = 9 Hz), 0.72 (d, 3 H, J = 9 Hz)

C_6H_5CHO		4	80	*b*	78 (0.05)		990–950 Several absorptions	(in CCl_4) 7.20 (s, 5 H), 4.83 (s, 1 H), 1.33 (s, 3 H), 0.73 (s, 3 H)
C_6H_5COCN		4	85	*c*		44–46	990–950 Several absorptions	7.37 (s, 5 H), 1.57 (s, 3 H), 0.79 (s, 3 H)
$(CH_3O)_2C{=}O(OCH_3)_2$	$(CH_3)_2CHCHO$	36	65	*a*	52 (0.1)		982	(in CCl_4) 3.60 (d, 1 H, J = 9 Hz), 1.93 (m, 1 H), 0.93 (d, 3 H)
	C_6H_5CHO	2	75	*a*	104 (0.1)		950 960	(in CCl_4) 7.33 (m, 5 H), 4.83 (s, 1 H), 3.43 (s, 6 H), 3.38 (s, 3 H), 3.30 (s, 3 H)
	C_6H_5COCN[e]	1	90	*c*		50	940 990 958	(in CCl_4) 7.35 (m, 5 H), 5.25 (s, 1 H), 3.55 (s, 6 H), 3.45 (s, 3 H), 3.00 (s, 3 H)
	CH_3COCN	2*c*	60	*b*	95 (0.05)		955	3.96 (m, 4 H), 1.57 (s, 3 H), 1.40 (s, 3 H), 1.17 (s, 3 H)
	CCl_3CHO	1*c*	60	*b*	90 (0.2)		950	4.40 (s, 1 H), 4.08 (m, 4 H), 1.42 (s, 6 H)
							925	
	C_6H_5COCN	24	70	*c*		92–95	945 918	7.40 (s, 5 H), 4.13 (m, 4 H), 1.60 (s, 3 H), 0.80 (s, 3 H)
	p-$NO_2C_6H_4CHO$	24	75	*c*		Oil		8.16–7.43 (AB, 4 H), 5.03 (s, 1 H), 4.10 (m, 4 H), 1.45 (s, 3 H), 0.73 (s, 3 H)

[a] Determined from NMR spectra of the reaction mixture after concentration at room temperature. For all compounds having R^3 = aryl the methyl protons (R^1) of the minor product were at higher field. This shielding effect indicates that the larger groups (R^1 and R^3) are in cis position. [b] Oxetanes have C–O stretch vibrations in the range 995–925 cm^{-1}. See ref 1 and 3 and F. Nerdel, D. Frank, H.J. Lengert, and P. Weyerstahl, *Chem. Ber.*, **101**, 1850 (1968). In the table all vibrations in this region are given. [c] No catalyst was used. Therefore, removal of $ZnCl_2$ could be omitted in the isolation procedure. [d] The reaction leads to an equilibrium. Higher yields are obtained when the acetal is used in larger excess. [e] See ref 1. [f] Registry no., 100-52-7. [g] Registry no., 555-16-8. [h] Registry no., 78-84-2. [i] Registry no., 67-64-1.

The preparation of dimethylmethylenedioxolane (lit. in ref 7), 1,1-dimethoxyethene,[11] and tetramethoxyethene[12] was done as described in the literature.

1,1-Dimethoxypropene. 3,3-Dimethoxypropene (0.25 mol) is dissolved in dry ether (50 mL) and the solution is dropped into a solution of potassium amide (0.1 mol) in liquid ammonia at −40 °C. The mixture is left for 2 h at this temperature. Ammonia is then evaporated, and the residue is diluted with dry ether (75 mL). Unreacted potassium amide is filtered off on a glass filter, and carefully destroyed with a 20% solution of *tert*-butyl alcohol in hexane. The filtrate is distilled with a Vigreux column (50 × 1.2 cm), bp 99 °C (lit.[13] 98–102 °C), yield 65%. The corresponding diethyl acetal can be obtained in a similar way, bp 134 °C [lit.[14] 134–137 °C (740 mm)].

1,1-Dimethoxyisobutene. The same procedure is followed with a reaction time of 48 h, bp 108–110 °C (lit.[14] 107–109 °C). The corresponding diethoxy compound has bp 68 °C (55 mm) [lit.[14] 139–140 °C (740 mm)].

General Procedure for the Preparation of 2,2-Dimethoxyoxetanes. A 40% solution of a carbonyl compound in acetonitrile is mixed with 1.1 equiv of a ketene acetal and 0.5–1% $ZnCl_2$. The mixture is left at room temperature for the time indicated in Table III. The solvent and the excess of ketene acetal are then evaporated at reduced pressure (below 40 °C). In order to eliminate the catalyst, pentane and a slight amount of triethylamine are added until the oxetane has been dissolved. Zinc chloride is left undissolved and can be filtered off. The filtrate is evaporated leaving the oxetane.

For further purification sufficiently volatile products are distilled in the presence of a slight amount of potassium *tert*-butanolate either with a Vigreux column (30 × 1 cm) (method a) or in a ball tube (method b). Oxetanes which cannot be distilled are purified by repeated washings with pentane (10 mol per 0.05 mol) at 0 °C (method c). Yields, physical constants and spectral data of the products are given in Table III. In the mass spectrometer the molecular ions of oxetanes undergo fragmentations by loss of dialkyl carbonate and ketene acetal fragments. M^+ peaks are generally weak. Sometimes $M^+ + 1$ peaks were observed.

Anal. Calcd for 2,2-dimethoxy-3,3-dimethyl-4-phenyloxetane, $C_{13}H_{18}O_3$: C, 70.24; H, 8.16; Found: C, 70.16; H, 8.26. Calcd for 2,2,3,3-tetramethoxy-4-phenyloxetane, $C_{13}H_{18}O_5$: C, 61.41; H, 7.14. Found: C, 61.06; H, 7.31.

Methyl Esters of β-Hydroxycarboxylic Acids by Hydrolysis of 2,2-Dimethoxyoxethanes. Two equivalents of water and a pinpoint of *p*-toluenesulfonic acid are added to a 20% solution of an oxetane in acetonitrile. The mixture is left at room temperature for 1 h. Acetonitrile is evaporated, and ether is added to the residue. The ethereal solution is dried over sodium sulfate, the solvent evaporated, and the residual oil distilled. The following esters were obtained in this way.

Methyl 3-hydroxy-2-methyl-3-phenylpropionate, $C_6H_5CHOHCH(CH_3)COOCH_3$: yield 90%; bp 92–98 °C (0.5 mm); *m/e* 194 (M^+), 163 ($M - OCH_3$), 107 [$M - CH(CH_3)COOCH_3$]; NMR: ($CDCl_3$) δ 7.17 (s, 5 H), 4.58 (d, 1 H, J = 9 Hz), 3.58 (s, 3 H), 2.63 (m, 1 H), 1.05 and 0.87 (d, 3 H, J = 8 Hz) (mixture of diastereomers).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.84; H, 7.35.

Methyl 3-hydroxy-2,2-dimethyl-3-phenylpropionate, $C_6H_5CHOHC(CH_3)_2COOCH_3$: yield 80%; bp 96 °C (0.3 mm); mp 69.5–70.5 °C; *m/e* 208 (M^+), 177 ($M - OCH_3$); 107 [$M - C(CH_3)_2COOCH_3$]; NMR ($CDCl_3$) δ 7.16 (s, 5 H), 4.77 (s, 1 H), 3.60 (s, 3 H), 3.20 (s, 1 H), 1.07 (s, 3 H), 1.00 (s, 3 H).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.66; H, 7.74. Found: C, 69.21; H, 7.92.

Registry No.—3,3-Dimethoxypropene, 6044-68-4; (*R**,*R**)-methyl 3-hydroxy-2-methyl-3-phenylpropionate, 14366-89-3; (*R**,*S**)-methyl 3-hydroxy-2-methyl-3-phenylpropionate, 17226-79-8; methyl 3-hydroxy-2,2-dimethyl-3-phenylpropionate, 35022-33-4; *cis*-2,2-dimethoxyl-3-methyl-4-phenyloxetane, 62841-79-6; *trans*-2,2-dimethoxy-3-methyl-4-phenyloxetane, 62841-80-9; *cis*-2,2-dimethoxy-3-methyl-4-*p*-nitrophenyloxetane, 62841-81-0; *trans*-2,2-dimethoxy-3-methyl-4-*p*-nitrophenyloxetane, 62841-82-1; *trans*-2,2-dimethoxy-3-methyl-4-trichloromethyloxetane, 62841-83-2; *cis*-2,2-dimethoxy-3-methyl-4-cyano-4-phenyloxetane, 62841-84-3; *trans*-2,2-dimethoxy-3-methyl-4-cyano-4-phenyloxetane, 62841-85-4; *cis*-2,2-dimethoxy-3,4-dimethyl-4-cyanooxetane, 62841-86-5; *trans*-2,2-dimethoxy-3,4-dimethyl-4-cyanooxetane, 62841-87-6; *cis*-2,2-dimethoxy-3,4-dimethyl-4-acetyloxetane, 62841-88-7; *trans*-2,2-dimethoxy-3,4-dimethyl-4-acetyloxetane, 62841-89-8; *cis*-2,2-dimethoxy-3-methyl-4-isopropyloxetane, 62841-90-1; *trans*-2,2-dimethoxy-3-methyl-4-isopropyloxetane, 62841-91-2;

2,2-dimethoxy-3,4,4-trimethyloxetane, 62841-92-3; 2,2-dimethoxy-3,3-dimethyl-4-isopropyloxetane, 62841-93-4, 2,2-dimethoxy-3,3-dimethyl-4-phenyloxetane, 62841-94-5; 2,2-dimethoxy-3,3-dimethyl-4-cyano-4-phenyloxetane, 62841-95-6; 2,2,3,3-tetramethoxy-4-isopropyloxetane, 62841-96-7; 2,2,3,3-tetramethoxy-4-phenyloxetane, 62841-97-8; 2,2,3,3-tetramethoxy-4-cyano-4-phenyloxetane, 60299-87-8; 2,3,3-trimethyl-2-cyano-1,5,8-trioxaspiro[3.4]octane, 62841-98-9; 3,3-dimethyl-2-trichloromethyl-1,5,8-trioxaspiro[3,4]octane, 62841-99-0; 2-cyano-2-phenyl-3,3-dimethyl-1,5,8-trioxaspiro[3.4]octane, 62842-00-6; 2-*p*-nitrophenyl-3,3-dimethyl-1,5,8-trioxaspiro[3,4]octane, 62842-01-7; 1,1-diethoxypropene, 21504-43-8; 3,3-diethoxypropene, 3054-95-3.

References and Notes

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A Novel Acylative Degradation of Uric Acid. Carbon-13 Nuclear Magnetic Resonance Studies of Uric Acid and Its Degradation Products

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Treatment of uric acid (1) with boiling isobutyric anhydride causes cleavage and rearrangement of the pyrimidine and imidazole rings to give a new heterocyclic derivative, 2-(1-methylethyl)-4-(1-hydroxy-2-methylpropylidene)aminoimidazole-5-carboxylic acid 5,1′-lactone (2). The structures of the lactone and related derivatives have been elucidated by infrared spectroscopy, ^1H and ^{13}C NMR, and mass spectrometry. Experiments with uric acids labeled with carbon-14 at either C-2, C-6, or C-8 confirmed that C-2 and C-8 were eliminated during the cleavage process. Uric acid, its 1,3-$^{15}N_2$ labeled derivative, and a series of degradation products and related model compounds have been studied by ^{13}C NMR spectroscopy, and the carbon-13 chemical shifts and coupling constants correlated with molecular structure.

In the course of a study of uric acid (1) to find volatile derivatives for chemical analysis of 1 in serum by isotope dilution mass spectrometry, we have examined its reactions with a series of aliphatic acylating agents, including acetic, propionic, *n*-butyric, and isobutyric acid anhydrides. Considerable work on the acetylation of uric acid has been described previously, notably conversion of 1 into 8-methylxanthine (3) by prolonged treatment (80 h) of 1 with a boiling mixture of acetic anhydride and pyridine.[1-4] However, there has been little or no work on the reaction of higher boiling, aliphatic acid anhydrides with 1.

Whereas reactions of 1 with boiling propionic or *n*-butyric anhydrides in the presence of pyridine, as observed in this laboratory, generally follow the path described earlier for acetic anhydride (e.g., conversion of 1 to 3),[1-4] treatment of 1 with boiling isobutyric anhydride either alone or in the presence of a tertiary amine (e.g., pyridine) gave surprising results. Reactions of 1 with a variety of oxidants[5] lead to either cleavage of the pyrimidine ring (e.g., with alkaline permanganate) to give allantoin, or degradation of the imidazole ring (e.g., with nitric acid) to produce alloxan, or cleavage of both rings (e.g., with permanganate in acetic acid) to give acyclic oxaluric acid. The structures and carbon-13 nuclear magnetic resonance (^{13}C NMR) data of some of the degradation products of 1 are shown in Table I.

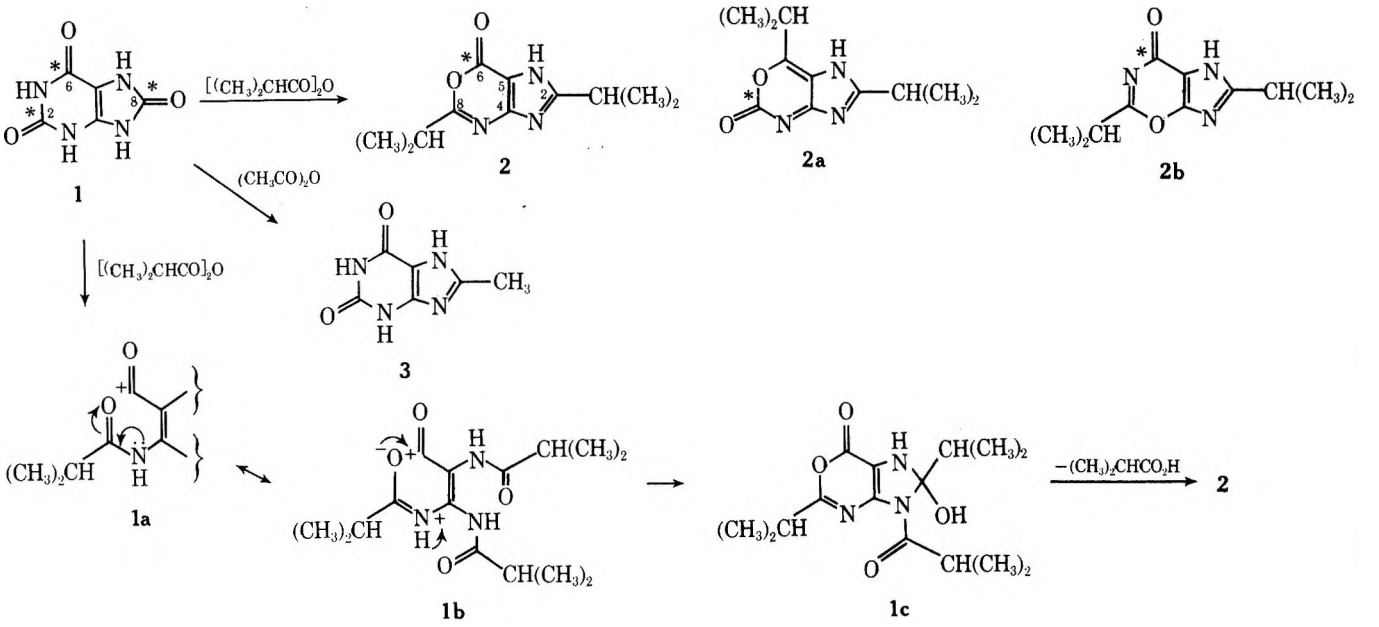
We report here a novel acylative degradation that involves simultaneous cleavage and rearrangement of the pyrimidine and imidazole rings in 1, with the formation of a new heterocyclic ring system. When mixtures of uric acid with isobutyric anhydride or isobutyric anhydride and pyridine were boiled under reflux for 8–24 h and 3–4 h, respectively, concentration followed by trituration of the resulting residues with ethyl acetate yielded 32–36% of a colorless crystalline material, mp 211–212 °C, that has proved to be 2-(1-methylethyl)-4-(1-hydroxy-2-methylpropylidene)aminoimidazole-5-carboxylic acid 5,1′-lactone (2).

Results and Discussion

Spectroscopic Evidence for the Structure of 2. The infrared spectrum of 2 displayed a strong absorption at 1772 cm^{-1} that suggested the possibility of an ester or lactone group derived from an unsaturated alcohol. The ^{13}C NMR spectra of 2 (see Figure 1) and its proton NMR spectra revealed that two, chemically nonequivalent isopropyl groups had been introduced.[6] The presence of a nonacylated NH group in the structure of 2 was indicated by its proton NMR spectra in pyridine-d_5 and dry methyl-d_6 sulfoxide solutions, each of which displayed a broad, one-proton signal at low field that was displaced to higher field on addition of deuterium oxide to the solution. The chemical shift of this signal was found to be highly variable, in agreement with its assignment as an NH proton. The proton-decoupled ^{13}C NMR spectra (Figure 1a and 1b) of 2 display only five carbon resonances other than those of the isopropyl groups, which indicates that two carbon atoms have been eliminated from the reactants.

The apparent molecular ion in the electron impact (EI)

Scheme I



mass spectrum of **2** was found at *m/e* 221. Verification that this ion is indeed the molecular ion was obtained from the chemical ionization (CI) mass spectrum, which showed an M + 1 at *m/e* 222. The EI spectrum of **2** displayed ions at *m/e* 206 ($M^+ - CH_3$), 193 ($M^+ - CO$), 178 [$M^+ - CH(CH_3)_2$], and 43 [$(CH_3)_2CH^+$]. The molecular ion at *m/e* 221 corresponds to the molecular formula $C_{11}H_{15}N_3O_2$ for **2**.

The ultraviolet spectrum of **2** showed absorptions at 231, 239, 247, and 269 nm that are consistent with a conjugated lactone–imidazole ring system.

Degradation of ^{14}C-Labeled Uric Acids. On the basis of the foregoing evidence, the isomeric structures **2, 2a,** and **2b** were considered. Structure **2b** was thought to be less likely, since it is not a lactone. Structures **2** and **2a** could be formed by loss of either C-2 and C-8, or C-6 and C-8, respectively, from uric acid.

When uric-2-^{14}C acid and uric-8-^{14}C acid were treated separately with boiling mixtures of isobutyric anhydride and pyridine, products (**2**) were obtained that contained negligible radioactivity, thus confirming that C-2 and C-8 of uric acid are lost during this reaction. However, the application of these reaction conditions to uric-6-^{14}C acid led to a product that retained 97% of its original specific activity, thereby providing strong evidence in favor of structure **2** (see Scheme I). The loss of C-8 in this reaction (presumably as carbon dioxide) is consistent with the earlier observations[1-4] of acetylative cleavage of the imidazole ring of **1**, and with the scission of both rings of **1** during its alkaline oxidation, which has been confirmed by radiotracer techniques.[7,8]

That one nitrogen atom (N-1) is also eliminated from **1** during its reaction with isobutyric anhydride was confirmed by the gas chromatographic detection of isobutyramide and diisobutyramide in the crude product of the reaction, and by the isolation from it, of crystalline diisobutyramide. These simple amides and also urea diisobutyrate were prepared separately as reference compounds for the chemical and spectroscopic studies. The proton NMR spectrum (Figure 2a) of isobutyramide at 60 MHz displays two overlapping broad singlets at low field that were assigned as chemically nonequivalent ^{14}NH proton signals by comparison with the spectrum (Figure 2b) of the ^{15}N-labeled amide. The latter spectrum shows sharp, overlapping quartets, from which the coupling constants $^2J_{HNH}$ = 2.1 Hz and $^1J_{^{15}NH}$ = 88.9 and 87.4 Hz were readily measured. Thus isobutyramide is a further example of restricted rotation about the amide bond.[9,10]

Chemical Evidence for the Structure of 2. Ammonolysis of the lactone **2** yielded a crystalline amide (**4**) that also displayed the signals of two chemically nonequivalent isopropyl groups in its proton and ^{13}C NMR spectra (Scheme II). The

Scheme II

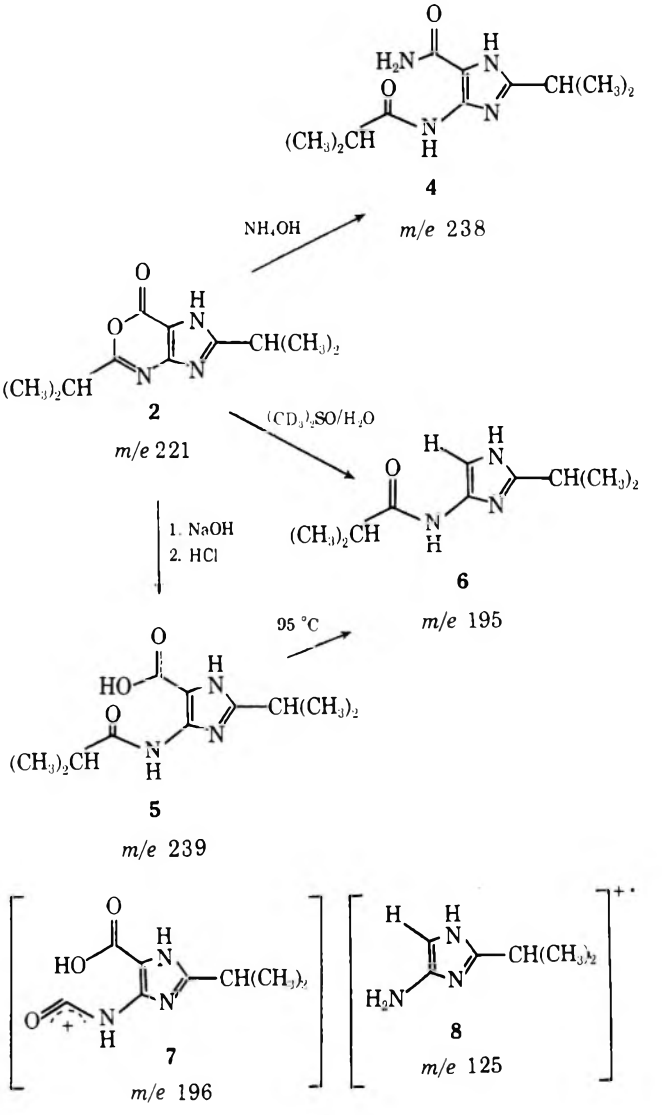
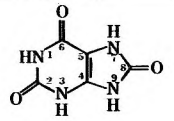
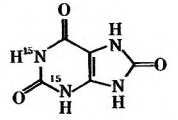
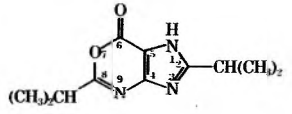
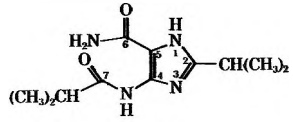
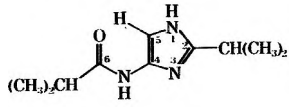
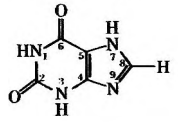
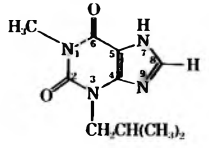
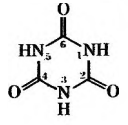
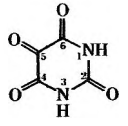
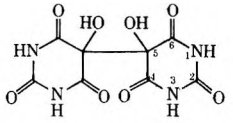
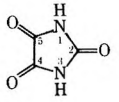
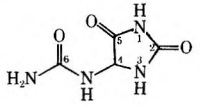
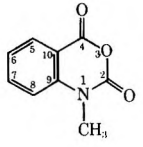
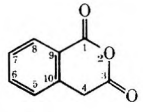


Table I. ^{13}C Chemical Shifts[a] of Uric Acid, Related Derivatives, and Other Model Compounds

Compd (registry no.)		C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	Others		
Uric acid (1) (69-93-2)			150.1		136.6	97.1	153.4		152.2					
Uric-1,3-$^{15}N_2$ acid[b] (62948-75-8)			150.1 t[c]		136.7 d	97.1[d]	153.3 d		152.3					
Lactone (2) (62948-76-9)			159.4[d]		152.7[d]	112.8[d]	153.8		169.8			$(CH_3)_2$	19.7	21.0
												CH	28.5	33.4
			159.5[e]		152.8	112.7	153.7		169.9			$(CH_3)_2$	19.6	20.9
												CH	28.6	33.5
			161.4[f]		154.1	113.3	155.1		171.8			$(CH_3)_2$	20.1	21.4
												CH	30.0	35.1
Amide (4) (62948-77-0)			161.6[d]		147.6[d]	112.2[d]	152.5	167.3				$(CH_3)_2$	20.1	21.3
												CH	27.8	33.3
Imidazole derivative[e,g] (6) (62948-78-1)			149.1		136.5	102.8	173.9					$(CH_3)_2$	19.5	21.6
												CH	27.8	34.1
Xanthine[h] (69-89-6)			151.3		148.8	106.7	155.5		140.4					
3-(2-Methylpropyl)-1-methylxanthine[i] (28822-58-4)			151.3		148.1	106.5	154.6		140.4			$(CH_3)_2$	19.9	
												CH_3N	27.0	
												CH_2	50.1	
												CH	27.8	
Cyanuric acid (504-19-8)			149.9		149.9		149.9							
Alloxan[j] (50-71-5)			149.8		156.3	168.8	156.3							

Alloxantin (76-24-4)			150.3		167.3	78.6	167.3					
Parabanic acid (120-89-8)			154.6		159.7	159.7						
Allantoin (97-59-6)			156.7		62.3	173.4	157.4					
1-Methylisatoic anhydride (10328-92-4)			147.6		158.9	129.3	123.6	137.2	114.7	142.1	111.3	CH_3 31.6
Homophthalic anhydride (703-59-3)		161.6		165.6	34.1	127.7[k]	135.0	127.6[k]	129.4	121.4	136.4	

[a] In ppm from internal tetramethylsilane, for solutions in methyl-d_6 sulfoxide. [b] ^{13}C–^{15}N coupling constants $J_{1,2} = J_{2,3} = J_{3,4} = 18.3$, $J_{1,5} = 8.5$, and $J_{1,6} = 11.0$ Hz. [c] Multiplicities of ^{13}C signals are indicated by d (doublet) or t (triplet). [d] Broad signal. [e] At 80 °C. [f] In methanol-d_4. [g] ^{13}C–H coupling constants $J_{4,H\text{-}6} = 7.3$ (tentative), $J_{5,H\text{-}5} = 190.4$, $J_{5,NCCH} = 3.7$ Hz. The assignment of the spacing in the C-4 doublet observed in the absence of proton decoupling as a coupling of C-4 with H-5 is tentative because of possible alternative assignments of this spacing as a coupling of C-4 with a methine proton of one of the 1-methylethyl groups. [h] ^{13}C–H coupling constants $J_{4,H\text{-}8} = 9.8$, $J_{5,H\text{-}8} = 4.9$, and $J_{8,H\text{-}8} = 211.2$ Hz. [i] ^{13}C–H coupling constants $J_{4,H\text{-}8} = 13.4$, $J_{5,H\text{-}8} = 4.9$, and $J_{8,H\text{-}8} = 211.2$ Hz, measured from the N-deuterated derivative 3-(2,2-dimethylethyl)-1-methylxanthine-7(9)-*d*. [j] Data taken from a spectrum of a mixture of alloxan and its hydrate. [k] Assignments interchangeable.

Table II. ^{13}C Chemical Shifts[a] of Carbonyl Derivatives

Compd		Registry no.	C=O	$(CH_3)_2$	CH
Urea	$(NH_2)_2CO$	57-13-6	160.5		
Urea diisobutyrate	$[(CH_3)_2CHCONH]_2CO$	62948-79-2	177.4, 149.9 (CHCONH)(NHCONH)	18.8	34.5
Isobutyramide	$(CH_3)_2CHCONH_2$	563-83-7	179.0	19.5	33.9
Diisobutyramide	$[(CH_3)_2CHCO]_2NH$	3668-74-4	177.4	18.8	34.5
Isobutyric anhydride	$[(CH_3)_2CHCO]_2O$	97-72-3	172.8	18.3	35.1

[a] In ppm from internal tetramethylsilane, for solutions in methyl-d_6 sulfoxide.

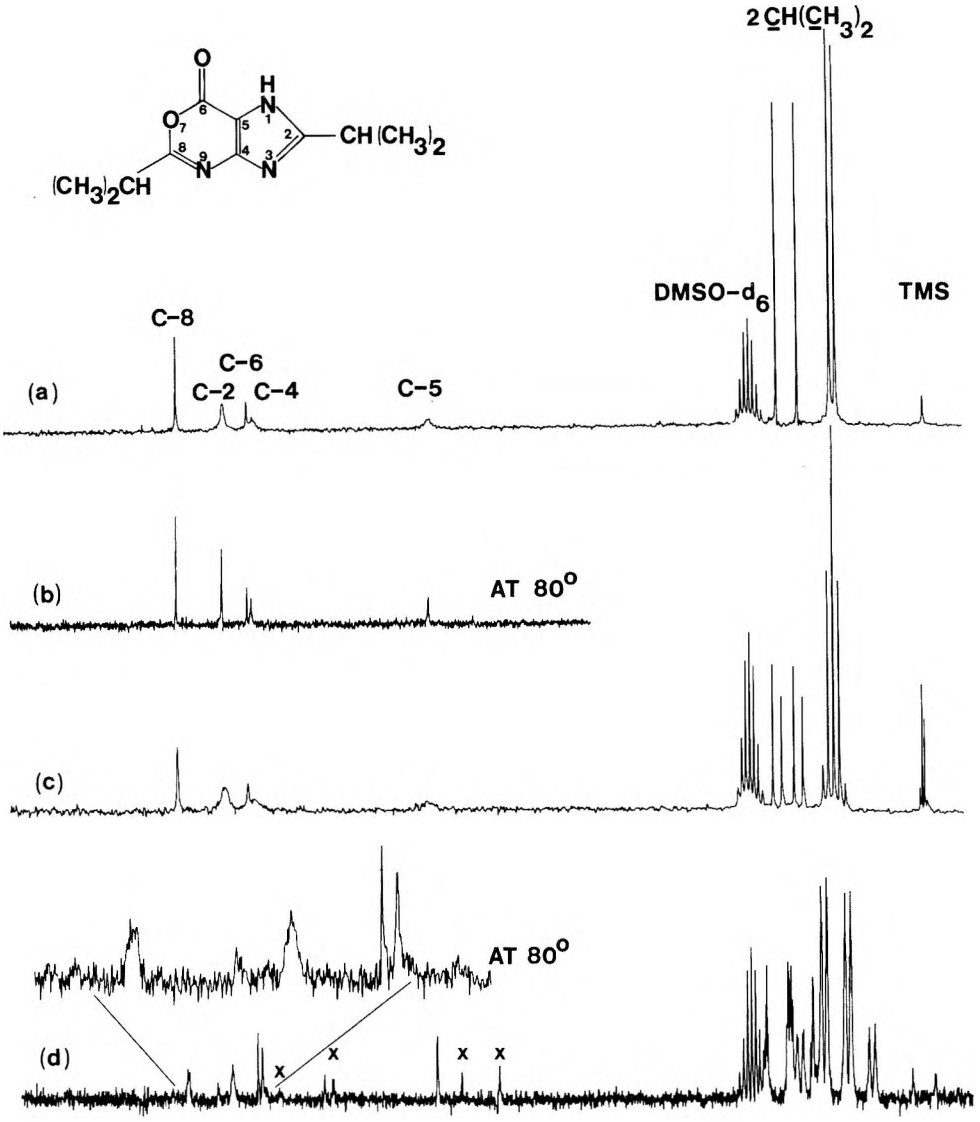


Figure 1. ^{13}C NMR spectra of 2-(1-methylethyl)-4-(1-hydroxy-2-methylpropylidene)aminoimidazole-5-carboxylic acid 5,1′-lactone (**2**) in methyl-d_6 sulfoxide at 22.6 MHz; (a) proton decoupled at 30 °C; (b) proton decoupled at 80 °C; (c) off-resonance, proton decoupled at 30 °C; and (d) proton coupled at 80 °C. The latter spectrum was obtained from a solution that contained 10% v/v of water, and it displays the signals (×) of a minor proportion of the imidazole derivative **6**.

retention of these signals and of five other carbon signals at low field in the ^{13}C NMR spectrum of **4** indicated that the reaction of **2** with ammonia achieved merely opening of the lactone ring, without further degradation. The proton NMR spectrum of **4** also showed two broad NH resonances of differing intensity. The EI mass spectrum of **4** showed a molecular ion at *m/e* 238 (confirmed by chemical ionization). Pertinent fragment ions were observed at *m/e* 223 ($M^+ - CH_3$), 205 ($M^+ - CH_3 - H_2O$), 177 ($M^+ - CH_3 - H_2O - CO$), 167, 151, 125, and 110. The presence of an amide group in **4** was confirmed by the observation of a band at 1650 cm^{-1} in its infrared spectrum. The facile opening of the lactone ring of **2** by ammonium hydroxide resembles the hydrolyses of structurally related 1,3-benzoxazinone derivatives in the presence of nucleophilic reagents.[11]

Hydrolysis of **2** with sodium hydroxide yielded a syrupy acid **5**, which displayed a molecular ion at *m/e* 239 in its EI mass spectrum, and also a characteristic fragment ion at *m/e* 196 that was assigned to the carbonium ion **7**. A fragment ion at *m/e* 125 was assigned to the imidazole moiety **8**. On heating at 95 °C, the acid **5** was readily decarboxylated to an imidazole derivative **6** that was characterized by its molecular ion at *m/e* 195.

A slow conversion of the lactone **2** into the imidazole derivative **6** was monitored by ^{13}C NMR spectroscopy of **2** under gentle hydrolytic conditions (see Figure 3). Compound **6** was distinguished by a wide quartet in its proton-coupled ^{13}C NMR spectrum (Figure 3b) at mid-field. The larger spacing (190.4 Hz) in this quartet was assigned as the coupling between C-5 of the imidazole ring and its directly attached proton (H-5). A comparably large value (211.2 Hz) was measured for the coupling of H-8 with C-8 in the imidazole rings of xanthine and its 3-(2-methylpropyl)-1-methyl derivative (Table I). The values $J_{2,H\text{-}2} = 208$ Hz and $J_{4,H\text{-}4}$ ($J_{5,H\text{-}5}$) = 199 Hz have been measured previously for imidazole.[12] Presumably, the slow conversion of **2** into **6** in hot, aqueous methyl sulfoxide proceeds by an initial, aqueous hydrolysis of lactone **2** to the acid **5**, which then decarboxylates to give the imidazole derivative **6**. Lactone **2** was also readily hydrolyzed (with strong effervescence) by concentrated hydrochloric acid either on brief warming or at room temperature. However, careful processing of this reaction mixture yielded a product that was somewhat sensitive to air and light, but which showed a predominant ion in its mass spectrum at *m/e* 125 (**8**).

On the basis of the foregoing chemical and spectroscopic evidence, the product isolated from the reaction of uric acid with boiling isobutyric anhydride is assigned structure **2**. The mechanism of formation of this structure may be rationalized

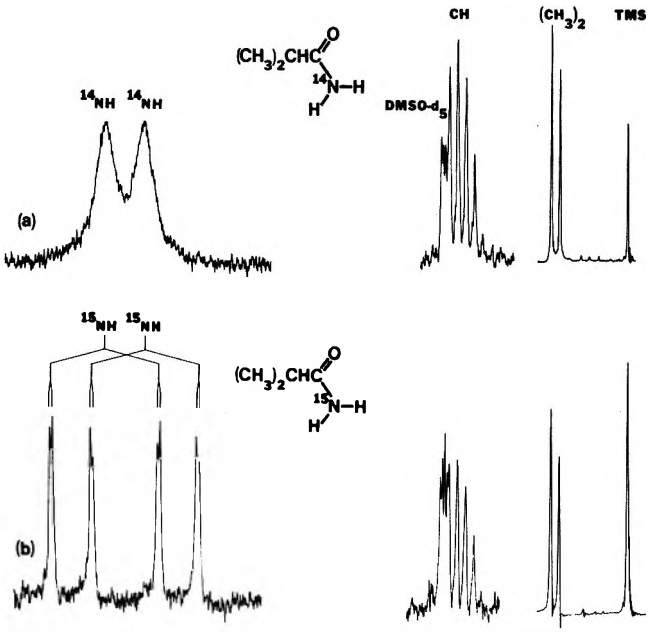


Figure 2. Proton NMR spectra of solutions in methyl-d_6 sulfoxide at 60 MHz; (a) isobutyramide; (b) isobutyramide-^{15}N.

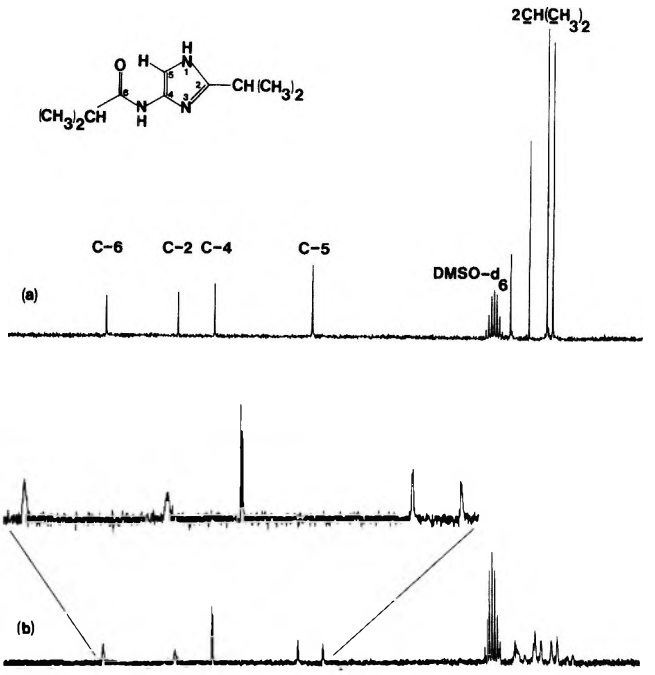


Figure 3. ^{13}C NMR spectra of 2-(1-methylethyl)-4-(2-methyl-1-oxo-propyl)aminoimidazole (**6**) in 5:1 v/v methyl-d_6 sulfoxide–water at 22.6 MHz; (a) proton decoupled at 80 °C; (b) proton coupled at 30 °C.

in terms of cleavage of the five- and six-membered rings of **2** by acyl exchange to give a resonance stabilized, *N,N',N''*-triisobutyryl intermediate (**1a** ↔ **1b**), which undergoes ring closure to the intermediate **1c**, which then forms **2** by elimination of isobutyric acid.

^{13}C NMR Studies of Uric Acid and Its Degradation Products. A suitable starting point for assignments of the ^{13}C NMR spectra of uric acid and its derivatives was the known assignment for purine, which has been confirmed by deuteration.[13] In many heterocyclic derivatives of the purine type, C-5 is characteristically shielded and resonates at considerably higher field than does C-4.[14,15] Thus, for uric acid, the ^{13}C resonance at highest field (97.1 ppm) was assigned to C-5. Additional evidence for assignments was obtained from the ^{13}C spectrum of uric-*1,3*-$^{15}N_2$ acid, which displayed only one resonance that was not split by coupling with ^{15}N. This resonance (152.3 ppm) was assigned to C-8, which is relatively remote from the ^{15}N nuclei at the 1 and 3 positions. The remaining four ^{13}C resonances of 1-*1,3*-$^{15}N_2$ were split by coupling with ^{15}N and the moderately large spacings (11.0–18.3 Hz) observed were assigned as couplings of ^{15}N nuclei with directly bonded, sp^2-hybridized carbons. The magnitudes of these coupling constants are similar to the values $J_{^{15}N^{13}C=O}$ = 13.4 and 14.6 Hz measured previously for[16] methyl 5-deoxy-2,3-*O*-isopropylidene-5-phthalimido-β-D-ribofurano-side-*5*-^{15}N and[16,17] 6-deoxy-1,2:3,5-di-*O*-isopropylidene-6-phthalimido-α-D-glucofuranose-*6*-^{15}N, respectively, and to the value $J_{^{15}N^{13}C=O}$ = 18.3 Hz found[18] for dixanthylurea-$^{15}N_2$. Because C-2 of 1-*1,3*-$^{15}N_2$ might be expected to be coupled equally to each of its directly bonded ^{15}N nuclei, the triplet (spacings $J_{1,2} = J_{2,3}$ = 18.3 Hz) at 150.1 ppm was assigned to C-2. Doublets at 153.3 ppm ($J_{1,6}$ = 11.0 Hz) and 136.7 ppm ($J_{3,4}$ 18.3 Hz) were assigned to C-6 and C-4, respectively, on the basis of the chemical shifts expected for these amide carbonyl carbon and olefinic carbon nuclei (see Tables I and II).

The assignment of C-8 of xanthine and its 3-(2-methylpropyl)-1-methyl derivative was indicated by the observation of wide doublets ($J_{8,H\text{-}8}$ = 211.2 Hz) in the proton-coupled ^{13}C spectra of these compounds. C-4 and C-5 were each characterized by narrow doublets due to coupling (4.9–13.4 Hz) of these nuclei with H-8. The C-2 resonance was assigned on the basis of the similarity of its ^{13}C chemical shift (151.3 ppm) to that (149.9 ppm) of cyanuric acid (Table I). By elimination, the ^{13}C resonance at lowest field was assigned to C-6, as was also the case for uric acid. Made in this way, the ^{13}C assignments for xanthine and its 3-(2-methylpropyl)-1-methyl derivative (see Table I) agree with those published previously for xanthosine.[14]

The ^{13}C assignments for lactone **2**, amide **4**, and imidazole derivative **6** were based partially on comparisons with the data shown in Tables I and II for uric acid, its degradation products, and various related model compounds, including 1-methylisatoic and homophthalic anhydrides, which each contain an oxycarbonyl function attached to an aromatic ring. Where possible, the assignments were confirmed by the use of proton-coupled spectra and off-resonance proton decoupling techniques. In the proton-decoupled ^{13}C NMR spectrum (Figure 1a) of lactone **2** obtained at ambient probe temperature (30 °C), three of the five carbon resonances at low field are broad. This observation and the fact that the three broad resonances are sharper at 80 °C (Figure 1b) and in the spectrum of **2** in methanol-d_4 measured at 30 °C suggest the presence of a proton exchange process or tautomeric equilibrium,[19-22] which would, indeed, be expected of structure **2**. For example, the NH proton could reside at either nitrogen atom in the imidazole ring of **2**, or at its carbonyl oxygen atom. The annular prototropy of the N-7 and N-9 atoms in purine[20] and N-1 and N-2 atoms in pyrazole[22] may be compared. The assignment of the aliphatic carbon resonances of **2** at high field (Figure 1a) was confirmed by the partially decoupled spectrum (Figure 1c) which contains two overlapping quartets due to nonequivalent pairs of methyl groups and two doublets that represent nonequivalent methine protons. The proton coupled spectrum (Figure 1d) of **2** obtained at 80 °C displays two complex multiplets at lowest field that were assigned to C-2 and C-8 on the basis that only the carbon nuclei bearing the isopropyl groups are near enough to the methyl protons to be significantly spin-coupled to them. The resonance at lowest field was assigned as that of C-8, since this nucleus is attached to an electronegative oxygen atom. In the group of five quaternary carbon resonances of **2**, the resonance at highest field was assigned to C-5 and that at next lowest field to C-4, in

agreement with the assignments for uric acid. The chemical shift of the remaining resonance at 153.8 ppm (C-6) is quite similar to that (158.9 ppm) of C-4 of 1-methylisatoic anhydride and to that (161.6 ppm) of C-1 of homophthalic anhydride (see Table I). The broadening of the C-2, C-4, and C-5 signals at ambient temperature is consistent with a tautomeric equilibrium involving the imidazole nitrogen atoms (compare purine[20]), since proton exchange between these sites would be expected to have the most influence on the chemical shifts of the carbon nuclei that are directly bonded to the imidazole nitrogen atoms.

By comparison with the ^{13}C chemical shifts (177.4 ppm) of the carbonyl carbon nuclei of the isobutyryl groups in diisobutyramide and urea diisobutyrate (see Table II), the sharp resonance at lowest field (167.3 ppm) in the ^{13}C NMR spectrum of the amide **4** was assigned to the carbonyl carbon nucleus (C-7) of the isobutyramido group. The quaternary carbon resonance at highest field (112.2 ppm) was assigned to C-5, and the resonance at next lowest field (147.6 ppm) to C-4, by analogy with **1** and **2**. Since the chemical shift of C-2 would be expected to be relatively unchanged by conversion of **2** into **4**, the resonance of **4** at 161.6 ppm was assigned to C-2. The chemical shift of the remaining quaternary carbon resonance at 152.5 ppm (C-6) is comparable with the shifts (153.4 and 155.5 ppm) of C-6 in uric acid and in xanthine, respectively. At 80 °C, narrowing of the C-2, C-4, and C-5 resonances of **4** (in methyl-d_6 sulfoxide) was observed, which again suggested the presence of an exchange process involving the NH proton of the imidazole moiety.[19-22]

For the imidazole derivative **6**, the assignment of the ^{13}C signal at 102.8 ppm to C-5 was confirmed by the observation of a large coupling (190.4 Hz) of this nucleus with H-5 in the proton coupled spectrum of **6** (Figure 3b). This spectrum showed a doublet at next lowest field (136.5 ppm) that was assigned to C-4 by analogy with compounds **1**, **2**, and **4**. The spacing (7.3 Hz) in this doublet was assigned tentatively as a coupling of C-4 with H-5.[12] The proton-coupled ^{13}C spectrum of **6** also displayed two narrow complex multiplets (at 149.1 and 173.9 ppm) that were assigned on the basis of their complexity to the nuclei (C-2 and C-6), which are bonded to isopropyl groups. The resonance of **6** at lowest field (173.9 ppm) was assigned to C-6 by comparison with the chemical shifts of carbonyl carbon nuclei in urea diisobutyrate, isobutyramide, and diisobutyramide (Table II).

Replacement of the 5-carboxamide substituent of amide **4** by a hydrogen atom evidently causes significant redistribution of the charge densities in the imidazole ring, so that for derivatives **4** and **6**, the chemical shifts of C-2 are substantially different (see Table I).

The ^{13}C NMR spectra of alloxan, alloxantin, parabanic acid, and allantoin (see Table I) were assigned by comparison with each other, and by correlation with the spectra of cyanuric acid (Table I) and the simple amides (Table II). For alloxantin and allantoin, the ^{13}C resonance at highest field is in each case assigned to the nucleus of an sp^3-hybridized carbon atom (C-5 and C-4, respectively). The chemical shifts of C-2 in parabanic acid and allantoin are similar to that of C-8 in uric acid, as would be expected.

The ^{13}C spectra of 1-methylisatoic and homophthalic anhydrides were assigned by use of proton-coupled spectra and from the substituent effects expected on the basis of previous studies of aromatic compounds.[23]

The ^{13}C chemical shifts and coupling constants shown in Table I provide basic data for further elucidation of the chemistry of uric acid and other purines.

Experimental Section[24]

Melting points are uncorrected and were determined in open capillaries in a silicone oil bath apparatus. Infrared spectra were recorded by use of Perkin-Elmer spectrophotometers, Models 137 and 257 (grating), and ultraviolet spectra with a Cary spectrophotometer, Model 14. Mass spectra were obtained with a Hewlett-Packard instrument, Model 5930A, by use of the direct insertion probe and Model 5933A data system. Methane was employed for chemical ionization spectra. Proton NMR spectra were measured either with a Varian A-60 spectrometer, or in the pulse Fourier transform mode at 90 MHz by means of a Bruker spectrometer, Model HFX-11, equipped with a Model BSV-2 pulse amplifier and Nicolet Model BNC-12 data system. ^{13}C NMR spectra were obtained at 22.6 MHz.

Qualitative and quantitative analyses of reaction products were performed by TLC on layers (0.25- and 2-mm thick) of silica gel that included a fluorescent indicator (Brinkman Silica Gel GF 254, or HF 254 and 366). The plates were developed with 1:1 v/v ethyl acetate–hexane for lactone **2**, 2:3 v/v ethyl acetate–methanol for amide **3**, and 1:4 v/v methanol–ethyl acetate for amine salts (e.g., products from hydrolysis of **2** with concentrated hydrochloric acid). GLC analyses were performed with a Hewlett-Packard gas chromatograph, Model 5750, equipped with a dual flame ionization detector, a glass column (10 ft. × 0.25 in.) of 2% OV-101 on Chromosorb WHP, and temperature programming (190–250 °C). Microanalyses were performed by Schwarzkopf Laboratories, Woodside, N.Y. 11377.

2-(1-Methylethyl)-4-(1-hydroxy-2-methylpropylidene)aminoimidazole-5-carboxylic Acid 5,1′-Lactone (2). Procedure A. A mixture of uric acid (2 g), isobutyric anhydride (180 mL), and pyridine (20 mL) was boiled under reflux for 4 h to give an orange or slightly brown solution. The mixture was filtered (if necessary) and concentrated under vacuum and then under nitrogen flush with some methanol present to a syrupy residue that was dissolved in chloroform (or methanol) and left overnight in the hood to induce slow crystallation. The crude product was triturated with cold ethyl acetate and thereby isolated in several crops: first crop (~450 mg) after 24 h, and second crop (300 mg) after 48 h; total yield 850–950 mg (32–36%). Careful recrystallization from 1:1 v/v ethyl acetate–cyclohexane gave microcrystalline **2**: mp 211–212 °C; UV λ_{max} (MeOH) 231 nm (sh, ϵ 8.66×10^3), 239 (9.71×10^3), 247 (8.48×10^3), 269 (6.88×10^3); IR ν_{max} (Nujol) 3120 w (NH), 1772 s (lactone C=O), 1609 m, 1590 m, and 1540 m cm^{-1} (C=C and C=N); proton NMR (C_5D_5N, 60 MHz) δ 11.30 or 12.5 (br, 1, NH), 3.29 (sp, 1, J = 7 Hz, CH), 2.91 (sp, 1, J = 7 Hz, CH), 1.46 [d, 6, J = 7 Hz, $C(CH_3)_2$], 1.27 [d, 6, J = 7 Hz, $C(CH_3)_2$].

Anal. Calcd for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99. Found: C, 60.12; H, 6.77; N, 18.96.

Procedure B. A mixture of uric acid (2 g) and isobutyric anhydride (180 mL) was boiled under reflux for 8 h. The reaction mixture was filtered and concentrated (with some methanol present, nitrogen flush) to a syrup that crystallized on standing overnight. Compound **2** was recovered in several crops; yield 800 mg (30.5%); the product was identical with that obtained by procedure A.

Diisobutyramide, mp 174–175 °C, crystallized from the mother liquors of **2**, which showed TLC R_f values of 0.32 (lactone **2**), 0.42 (diisobutyramide), and 0.14, 0.50, 0.57, 0.65, and 0.71 (unknown), and GLC retention times (min, ±3%) of 5.63 (diisobutyramide), 14.88 (lactone **2**), and 3.78, 5.19, 11.65, 12.13, 12.60, 12.91, 14.64, 15.15, 16.25, 17.01, and 24.41 (unknown).

Experiments with ^{14}C-Labeled Uric Acids. Commercially available ^{14}C-labeled uric acids were used and their radiochemical purity was checked by paper chromatography in *tert*-butyl alcohol–2-butanone–water–ammonium hydroxide (4:3:2:1 v/v) and in 1-butanol–acetic acid–water (2:1:1 v/v); chromatograms were scanned with a radiochromatogram scanner. Purity was also checked by addition of a known activity of ^{14}C-labeled uric acid to unlabeled uric acid, followed by dissolution of the mixture in lithium carbonate solution, crystallization by acidification, and determination of specific activity. The uric-2-^{14}C acid and uric-6-^{14}C acid were determined by these criteria to be of suitable purity, but the uric-8-^{14}C acid was found to be impure, and, therefore, was recrystallized to constant specific activity. All samples were radioassayed by counting with a liquid scintillation counter.

Uric-2-^{14}C Acid. A mixture of uric-2-^{14}C acid (27.125 mg at 0.0386 μCi/mg, 1.047 μCi total), isobutyric anhydride (15 mL), and pyridine (1 mL) was boiled under reflux for 4 h. The mixture was then concentrated (N_2 flush), and the residue was subjected to TLC on silica gel GF 254 (8 × 8 × 0.025 cm) by development with 1:1 v/v ethyl acetate–hexane. The band corresponding to lactone **2** was scraped off, extracted with methanol, and its radioactivity determined. The main band contained only 0.003 μCi, indicating that C-2 is lost during formation of lactone **2**.

Uric-8-^{14}C Acid. Uric-8-^{14}C acid (25.343 mg at 0.0170 μCi/mg, 0.431 μCi total) was heated with isobutyric anhydride–pyridine for

4 h. Preparative TLC gave a lactone band that contained only 0.006 μCi, indicating that C-8 is lost when **2** is formed.

Uric-6-^{14}C Acid. Uric-6-^{14}C acid (937 mg at 0.0419 μCi/mg) was converted to lactone **2**, which was recrystallized to a constant activity of 0.0314 μCi/mg. The theoretical specific activity of the lactone if all radiolabel at position 6 is retained is 0.0318 μCi/mg.

Verification of Specifically Labeled Uric Acids by Oxidation to Allantoin. Uric-6-^{14}C acid (100 mg at 0.009 15 μCi/mg) was oxidized to allantoin with potassium permanganate. All of the radioactivity of the uric-6-^{14}C acid would be lost if it were labeled only at position 6. The specific activity of the allantoin found was 7.8×10^{-6} μCi/mg; the theoretical specific activity if all radioactivity were retained would be 9.7×10^{-3} μCi/mg.

Uric-2-^{14}C acid (201.5 mg at 0.0411 μCi/mg) was oxidized to allantoin. The radioactivity should be completely retained if the label is at position 2. The theoretical specific activity of the allantoin was 0.0437 μCi/mg; the activity found was 0.0378 μCi/mg (86% of theoretical).

2-(1-Methylethyl)-4-(2-methyl-1-oxo-propyl)aminoimidazole-5-carboxamide (4). A suspension of lactone **2** (200 mg) in concentrated ammonium hydroxide (2 mL) was carefully stirred at 40 °C (not above!) until dissolution was complete (3–4 min). The pale yellow solution was concentrated in a vacuum desiccator over concentrated sulfuric acid, phosphorus pentoxide, and sodium hydroxide for 72 h. The greenish syrup was dissolved in methanol (3 mL), and the solution was filtered through a layer of carbon (the use of an excess of decolorizing carbon imparts a red color). The clear filtrate was stirred and diluted with ethyl acetate to incipient turbidity. Amide **4** was isolated in several crops: total yield, 100–105 mg (47–49%); mp 185–186 °C (crystallized from 1:2 v/v pyridine–ethyl acetate); UV λ_{max} (MeOH) 213 nm (ϵ 10.6×10^3), 233 (9.3×10^3), 277.5 (14.6×10^3); IR ν_{max} (Nujol) 3190 m (NH), 1650 m (amide C=O), 1590 s (amide CNH) cm^{-1}; proton NMR (C_5D_5N, 90 MHz) δ 9.83 (br, 1, NH), 6.28 (br, 7, NH, NH_2, and H_2O), 3.21 (sp, 1, J = 7 Hz, CH), 2.74 (sp, 1, J = 7 Hz, CH), 1.37 [d, 6, J = 7 Hz, $C(CH_3)_2$], 1.28 [d, 6, J = 7 Hz, $C(CH_3)_2$].

Anal. Calcd for $C_{11}H_{18}N_4O_2$: C, 55.44; H, 7.61; N, 23.51. Found: C, 55.72; H, 7.59; N, 23.79.

2-(1-Methylethyl)-4-(2-methyl-1-oxo-propyl)aminoimidazole-5-carboxylic Acid (5). A suspension of lactone **2** (150 mg) in water (15 mL) was stirred and titrated with 0.2 mol/L sodium hydroxide to phenolphthalein. Dissolution of **2** was complete after 8 min, and the alkaline solution was kept for 20 h at room temperature. After neutralization (hydrochloric acid), the solution was extracted with 9:1 v/v ethyl acetate–dichloromethane (four 30-mL portions), and the combined extracts were dried (Na_2SO_4) and concentrated to a syrupy residue (45 mg). TLC indicated the presence of one major component, and two minor components. The EI mass spectrum showed m/e 239 (M^+) and fragment ions at m/e 196 ($M^+ - 43$), 178 (m/e 196 $- H_2O$), and 125 (imidazole derivative). On heating at 95 °C for 30 min, this material was partially decarboxylated to **6**. The EI mass spectrum of the product displayed characteristic peaks at m/e 196 and 195, indicating the presence of unchanged **5** and the imidazole derivative **6**, respectively.

Hydrolysis and Decarboxylation of 2 to 6 Monitored by ^{13}C NMR Spectroscopy. A solution of **2** (0.14 g) in 10:1 v/v methyl-d_6 sulfoxide–water (0.33 mL) was maintained at 80 °C in the NMR probe and was analyzed periodically over a period of 30 days by ^{13}C NMR spectroscopy, under either proton-coupled, proton-decoupled, or off-resonance proton-decoupled conditions. ^{13}C spectra taken after 2–4 days displayed four resonances in the isopropyl region in addition to those of **2** and four resonances at lower field in addition to the five resonances of **2** at low field. After 5 days, more water (0.03 mL) was added to the solution. In a spectrum taken after 6 days, the corresponding carbon resonances of **2** and **6** were of approximately equal intensity, except for the C-5 signal of **6** which showed substantial enhancement of intensity due to the Overhauser effect of an attached proton. After 30 days at 80 °C, the nine ^{13}C resonances of **2** had disappeared from the spectrum, and only the eight ^{13}C resonances of **6** remained (see Figure 3): proton NMR [$(CD_3)_2SO$, 60 MHz] δ 10.05 (s, 2, NH), 7.12 (s, 1, C=CH), 2.78 (m, 2, J = 7 Hz, CH), 1.26 [d, 6, J = 7 Hz, $C(CH_3)_2$], 1.11 [d, 6, J = 7 Hz, $C(CH_3)_2$].

Acid Hydrolysis of Lactone 2. Treatment of **2** (0.1 g) with concentrated hydrochloric acid (1 mL) at 60 °C for 5 min, followed by neutralization ($NaHCO_3$), extraction (9:1 v/v EtOAc–CH_2Cl_2), and concentration gave a syrupy residue. This was chromatographed in subdued light on a layer of silica gel HF 254 + 366 in 3:7 v/v MeOH–EtOAc. The mass spectrum of the fraction with $R_f \sim 0.47$ resembled that of the imidazole derivative **8** (m/e 125). In a separate experiment, lactone **2** (0.15 g) was stirred with concentrated hydrochloric acid (3 mL) at room temperature for 30 min. The clear solution was then concentrated (vacuum desiccator, KOH, 72 h) and the solid residue was extracted with warm pyridine. The mass spectrum of the *pyridine insoluble* fraction [about 50%, mp > 320 (d) from MeOH–Et_2O] showed a fragment ion at m/e 126 which was assigned to the cation of amine **8**. Mass spectrometry of the *pyridine soluble* fraction indicated that it contained starting material (m/e 221) and the hydrochloride of amine **8** (m/e 126).

Isobutyramide-^{15}N. Ammonium-^{15}N hydroxide was generated by mixing an ice-cold solution of ammonium-^{15}N chloride (0.166 g) in water (5 mL) with 1.0 mol/L sodium hydroxide; isobutyric anhydride (1 mL) was then added and the mixture stirred in a closed vessel at room temperature for 1 h, and then at 85 °C for 30 min. The solution was cooled and extracted with ethyl acetate, and the extracts dried (Na_2SO_4) and concentrated to give isobutyramide-^{15}N (40 mg): mp 128–129 °C; IR ν_{max} (KBr) 1625 s cm^{-1} (C=O); proton NMR [$(CD_3)_2SO$, 60 MHz] δ 7.20 (q, 1, $^2J_{HNH}$ = 2.1 Hz, $^1J_{^{15}NH}$ = 88.9 Hz, NH), 6.65 (q, 1, $^2J_{HNH}$ = 2.1 Hz, $^1J_{^{15}NH}$ = 87.4 Hz, NH), 2.34 (sp, 1, J = 7 Hz, CH), 0.99 [(d, 6, J = 7 Hz, $C(CH_3)_2$]; MS (EI) m/e 88 (M^+). Nonlabeled isobutyramide was prepared by boiling a mixture of ammonium carbonate and isobutyric anhydride under reflux for 30 min, followed by concentration (N_2 flush) and recrystallization from ethyl acetate. The isobutyramide had: mp 128–129 °C; proton NMR [$(CD_3)_2SO$, 60 MHz] δ 7.20 (br, 1, NH), 6.67 (br, 1, NH), 2.34 (sp, 1, J = 7 Hz, CH), 0.99 [d, 6, J = 7 Hz, $C(CH_3)_2$]; MS (EI) m/e 87 (M^+).

Diisobutyramide. Treatment of either urea, biuret, cyanuric acid, or isobutyramide with an excess of boiling, refluxing isobutyric anhydride, followed by concentration and crystallization from hot water yielded diisobutyramide: mp 174–175 °C; IR ν_{max} (Nujol) 1720 cm^{-1} (C=O); proton NMR ($CDCl_3$, 60 MHz) δ 8.94 (br, 1, NH), 3.06 (sp, 2, J = 7 Hz, CH), 1.18 [d, 12, J = 7 Hz, $C(CH_3)_2$]; MS (EI) m/e 157 (M^+).

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Registry No.—**5**, 62973-61-9; ammonium-^{15}N hydroxide, 62948-80-5; isobutyramide-^{15}N, 62962-45-2; ammonium carbonate, 10361-29-2.

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(6) For convenience in tabulation and description of the ^{13}C chemical shifts, compounds **2**, **4**, **5**, and **6** are all described herein as imidazole derivatives, as indicated in Table I. Compound **2** may also be named systematically as 2,5-bis(1-methylethyl)imidazo[4,5-*d*][1,3]oxazine-7(1*H*)-one. This name was kindly determined by Dr. R. S. Tipson (personal communication), by consultation with the Chemical Abstracts Service.
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Conformational Analysis of Prostaglandins F_1 Based on Proton Nuclear Magnetic Resonance Spectral Data

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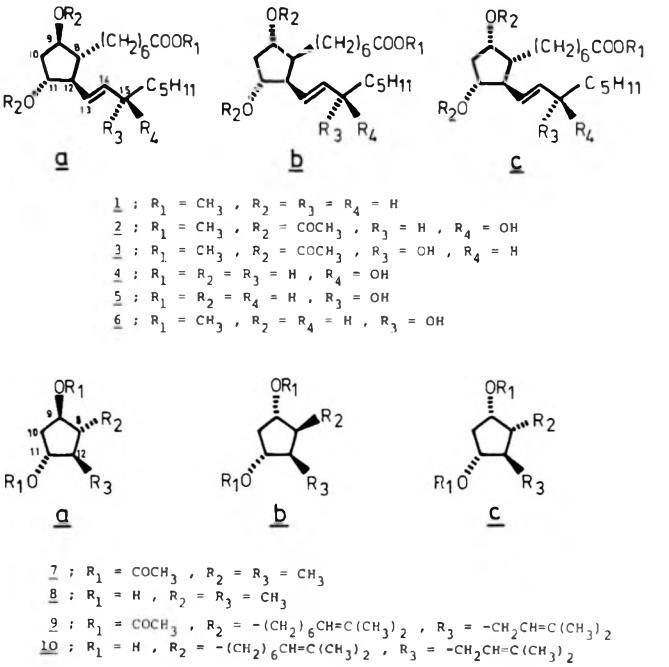
The ^1H NMR spectral parameters of prostaglandin $F_{1\alpha}$ (**5c**), prostaglandin $F_{1\beta}$ (**5a**), 8-*epi*-prostaglandin $F_{1\alpha}$ (**5b**), and derivatives are discussed. Evidence is presented for the occurrence of a restricted number of conformations in the three series. The solvent-dependent variation of the ^1H NMR spectral parameters of prostaglandin $F_{1\alpha}$ is interpreted on the basis of intramolecular hydrogen bonding between the 9- and 11-hydroxyl groups.

Studies of the conformational behavior of prostaglandins are important since it has been shown that there exist strict stereostructural requirements for certain characteristic actions[2a] and for substrate suitability with prostaglandin-metabolizing enzymes.[2b] The restraints applied to the prostaglandin molecule to fix a preexisting receptor site[2c,d] as a stable conformational isomer, or conformer, are so far little understood. Especially x-ray analysis[3] and theoretical calculations[4] have brought some knowledge about the conformation of prostaglandin $F_{1\beta}$ and of prostaglandins of the E series. The results of these studies are generally interpreted on the basis of a conformation (designated "hairpin" [5]) in which the two side chains are closely aligned. In these studies abstraction is made of the molecular environment, as no solvent effects are taken into account. In a series of refined experiments using different techniques Andersen[6] has investigated the occurrence of the "hairpin" conformation in solvated prostaglandins. While a lot of work is done in understanding the relation of the side chains, little attention has been paid to the conformational behavior of the five-membered ring in this molecule.[7] Accurate ^1H NMR spectral data of prostaglandins are scarcely found in the literature (see, however, ref 8). These data should be suited for the study of the conformation of the cyclopentane part of the prostaglandin molecule. We will discuss the ^1H NMR spectral data of the prostaglandins $F_{1\alpha}$, $F_{1\beta}$, and 8-epi-$F_{1\alpha}$ in chloroform-d_1 and methanol-d_4, and we will present evidence for the occurrence of a restricted number of conformations. Hydrogen bonding in aprotic medium, between the 9- and 11-hydroxyl groups of prostaglandin $F_{1\alpha}$ will be proven. The latter fact may be of crucial importance in understanding the ability of prostaglandins to pass through discrete conformational states as the environment changes.

Results and Discussion

In Tables I–III the relevant ^1H NMR spectral parameters are found for products with three different configurations, **a** (as found in prostaglandin $F_{1\beta}$), **b** (as found in 8-epiprostaglandin $F_{1\alpha}$), and **c** (as found in prostaglandin $F_{1\alpha}$; Scheme I). Whereas products **1–6** are prostaglandins,[9] compounds **7–10** are used as references.[10] Comparison of the ^1H NMR spectral parameters of a large number of differently functionalized 1,4-dihydroxy- (and diacetoxy-) 2,3-dialkylcyclopentanes[11] indicates comparable pseudorotational itinerary energetics

Scheme I



for products with the same configuration. We will therefore assume throughout the discussion that the conformational behavior of prostaglandins is similar to that of the model compounds **7** and **8** as far as the cyclopentane is concerned. Although only sums of vicinal coupling constants are available to substantiate this assumption in the case of prostaglandins with **a** and **b** configurations, individual coupling constants will be used for prostaglandins with the "natural" **c** configuration.

One can expect that the conformational behavior of products with the **a** configuration will be dictated by the requirement of the two trans alkyl side chains to be diequatorial[12] on the base of torsional strain. Calculations[13] of the potential energy of the ten twist and the ten envelope conformations encountered during the itinerary of pseudorotation[14,15] of **7a** show that the C_2 conformation with the methyl groups in the most puckered part of the molecule ($^8_{12}T$; Scheme II) is the minimal-energy form. This conformation is, however, only

Scheme II. Conformations for 1,4-Dihydroxy- (or diacetoxy-) 2,3-dialkylcyclopentanes

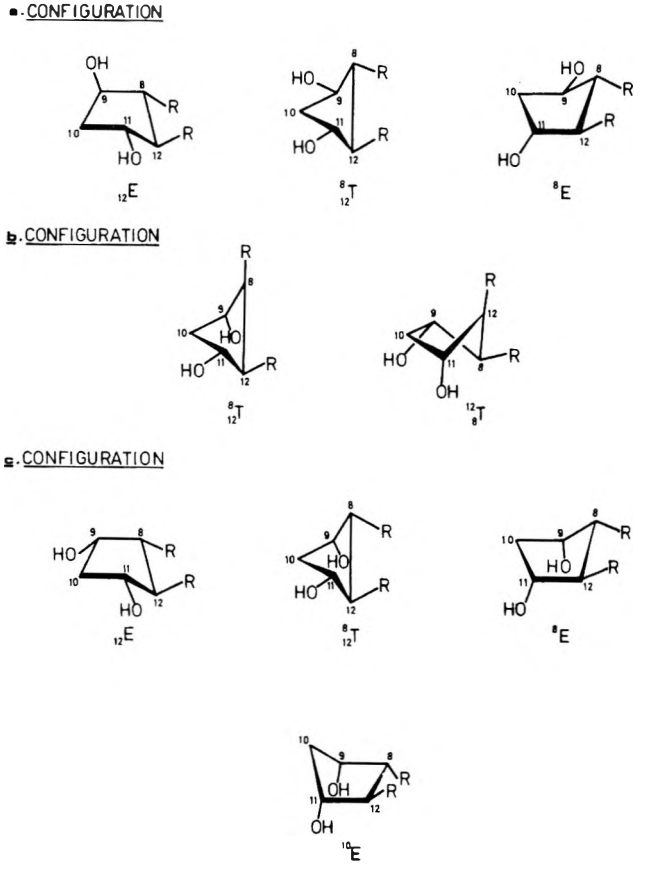


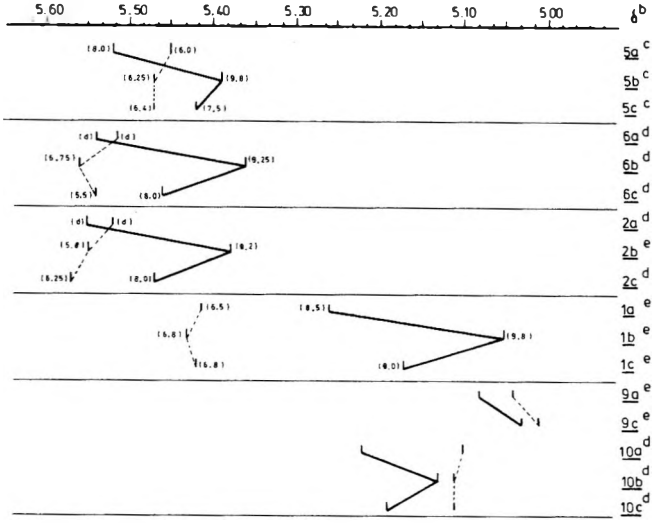
Table I. ^{1}H NMR Spectral Parameters of *a* Series (Prostaglandin $F_{1\beta}$ Analogues)[a]

Product Solvent	1a[h] CCl_4	2a[i] $CDCl_3$	4a[j] CD_3OD	5a[k] CD_3OD	6a[l] $CDCl_3$	7a[m] CCl_4
δH-10[b,f]	*c*	2.00	1.85	1.90	1.99	1.97
δH-10′[b,f]	1.76	2.00	1.85	1.80	1.95	1.97
δH-9[g]	3.88	4.97	3.95	3.95	4.07	4.67
δH-11[g]	3.83	4.89	3.88	3.87	3.98	4.67
δH-8	*c*	*c*	*c*	*c*	*c*	1.49
δH-12	*c*	2.18	*c*	1.90	1.95	1.49
Σ[e]*J* 10[f]	*d*	*d*	*d*	14.0	11	14.2
Σ*J* 10′[f]	15.0	*d*	*d*	14.0	*d*	14.2
Σ*J* 9[g]	22.0	23.5	23.0	21.6	*d*	21.8
Σ*J* 11[g]	17.0	17.5	17.0	18.5	18	21.8

[a] Obtained at 300 MHz at room temperature; chemical shifts are given in parts per million (δ scale) relative to Me_4Si as internal standard; coupling constants are given in hertz. [b] H-10 cis with OH-9 or Ac-9; H-10′ trans with OH-9 or Ac-9. [c] Could not be located. [d] Could not be measured. [e] Sum of vicinal coupling constants given in hertz. [f,g] The values superscripted by *f* or *g* have not been unambiguously assigned and can be pairwise permuted; e.g., in **1a** δH-9 can be either 3.88 or 3.83, but then the tied value of Σ*J* 9 must also be exchanged with Σ*J* 11. [h] Registry no., 61557-24-2. [i] Registry no., 61557-35-5. [j] Registry no., 62860-86-0. [k] Registry no., 10164-73-5. [l] Registry no., 21562-49-2. [m] Registry no., 62860-87-1.

slightly more stable than the two nearest envelope conformations ^8E and $_{12}E$. Restricted pseudorotation, designated pseudolibration by Altona,[15e] may occur around the minimal-energy form. Important coupling constants of **7a** are $^3J_{8,12}$ = 10.4 and $^3J_{8,9} = {}^3J_{11,12}$ = 7.6 Hz.[10a] The former value clearly locates the maximum pucker of the ring in the C_8–C_{12} bond; the latter relatively small coupling constant can be interpreted

Scheme III. Chemical Shift Values for Olefinic Hydrogen Atoms[a]



[a] For products 1, 2, 5, and 6, the straight lines correspond to the chemical shift values of H-13 (values in parentheses are for $^3J_{12,13}$) and the dotted lines to the corresponding values of H-14 (values in parentheses are for $^3J_{14,15}$); $^3J_{13,14}$ are comprised between 15.0 and 15.5 Hz; straight lines for H-2′ of the 3-methyl-2-butenyl side chain, dotted lines for H-7′ of the 8-methyl-7-nonenyl side chain (products 9 and 10). [b] Chemical shifts are given in parts per million relative to Me_4Si as internal standard. [c] Methanol-d_4 solution. [d] Chloroform-d_1 solution. [e] Carbon tetrachloride solution.

as well by a single $^8_{12}T$ form as by a rapidly interconverting pair of ^8E and $_{12}E$ conformations, or a combination of both possibilities. Anyhow, in the simple model compound **7a** calculation and experiment point in the same direction. We assume that in the prostaglandins **1a**–**6a** the maximum pucker will also be in the C_8–C_{12} bond. The value of ΣJ_{11} is here systematically somewhat smaller, that of ΣJ_9 somewhat larger than the unique value found in **7a**. This is precisely what would be expected for the predominant occurrence of one *E* form. The ring conformation observed by Abrahamsson[3a] for the tri-*p*-bromobenzoylated prostaglandin $F_{1\beta}$ methyl ester is also an envelope conformation with C_{12} at the flap position. While it is satisfactory to find the same basic conformation in the solid state and in solution, we are not able to assign H-9 and H-11 unambiguously and hence cannot tell which atom, C_8 or C_{12}, occupies the flap position preferentially. It has been suggested[7a] on the basis of ^{13}C NMR data that there exists in solution a hydrogen bond between the 9-hydroxyl group and the 5,6 double bond and between the 11-hydroxyl group and the 13,14 double bond in prostaglandin $F_{2\beta}$, among other prostaglandins. The possible occurrence of a weak hydrogen bond between a hydroxyl function and a π-electron cloud is a well-known phenomenon;[16] it has been shown[17] that this results in a downfield shift (e.g., 0.1 ppm) of the vinylic hydrogen atoms. Our data, however, do not support the existence of such a hydrogen bond in the prostaglandins **5a** and **6a** since the chemical shifts of the olefinic hydrogen atoms 13 and 14 in prostaglandin $F_{1\beta}$ methyl ester (**6a**) and the corresponding diacetoxy derivative **2a** are nearly identical (Scheme III).

Analogous calculations[13] of the potential energy during pseudorotation for **7b** indicate the presence of two distinct minima of equal energy in the potential energy curve, coinciding with the two twist conformations $^8_{12}T$ and $^{12}_8T$ (Scheme II). Comparison of the values for the sum of coupling constants of the hydrogen atoms 9 and 11 obtained for the dimethyl derivative **7b** and the prostaglandins (e.g., **5b**) indicates that in the latter products one twist conformation should be more

Table II. ^{1}H NMR Spectral Parameters of *b* Series (8-Epiprostaglandin $F_{1\alpha}$ Analogues)[a]

Product Solvent	1b[g] CCl_4	2b[h] CCl_4	3b[i] CCl_4	4b[j] CD_3OD	5b[k] CD_3OD	6b[l] $CDCl_3$	7b[m] CCl_4
δH-10[b]	1.55	*c*	*c*	*c*	*c*	*c*	1.50
δH-10′[b]	2.32	2.68	2.68	2.47	2.46	2.41	2.66
δH-9	3.80	4.78	4.77	3.84	3.81	3.9	4.68
δH-11[f]	3.85	4.81	4.82	3.92	3.90	4.0	4.68
δH-8	1.97	2.12	2.11	2.04	*c*	*c*	2.17
δH-12	2.59	2.73	2.72	2.67	2.62	2.73	2.17
Σ[e]*J* 10	8	*d*	*d*	*d*	*d*	*d*	8.0
Σ*J* 10′	14	14.5	16	*d*	15	14.5	15.4
Σ*J* 9	19	*d*	19	*d*	21	*d*	16.2
Σ*J* 11	12	*d*	14	*d*	14	*d*	16.2

[a] Obtained at 300 MHz at room temperature; chemical shifts are given in parts per million (δ scale) relative to Me_4Si as internal standard; coupling constants are given in hertz. [b] H-10 cis with OH-9 or Ac-9; H-10′ trans with OH-9 or Ac-9. [c] Could not be located. [d] Could not be measured. [e] Sum of vicinal coupling constants given in hertz. [f] The assignment of the H-9 and H-11 resonances is based on the downfield β effect of the C13–C14 double bond. [g] Registry no., 61507-23-1. [h] Registry no., 61557-37-7. [i] Registry no., 61557-36-6. [j] Registry no., 61557-40-2. [k] Registry no., 26771-96-0. [l] Registry no., 21562-59-4. [m] Registry no., 53099-13-1.

Table III. ^{1}H NMR Spectral Parameters of *c* Series (Prostaglandin $F_{1\alpha}$ Analogues)[a]

Product Solvent	1c[h] CCl_4	2c[i] $CDCl_3$ (CCL_4)	3c[j] $CDCl_3$ (CCl_4)	5c[k] CD_3OD	6c[l] $CDCl_3$	7c[m] CCl_4	8c[n] CCl_4
δH-10[b]	1.70	*c*	*c*	1.57	1.77	1.53	1.66
δH-10′[b]	2.00	2.55	2.50	2.36	2.16	2.51	2.02
δH-9	4.06	5.15	5.13	4.10	4.19	5.03	3.92
δH-11	3.80	4.87	4.90	3.81	3.95	4.57	3.67
δH-8	*c*	*c*	*c*	*c*	*c*	1.52	1.29
δH-12	*c*	2.55	2.50	2.21	2.27	1.79	1.59
J 10,10′	−14.5	*d* (−15.5)	*d* (−15.5)	−14.5	−15.0	−15.7	−14.8
J 9,10	*d*	*d* (*d*)	*d* (*d*)	2.0	1.0	1.8	1.3
J 10,11	*d*	*d* (*d*)	*d* (*d*)	5.5	2.5	5.0	2.7
J 9,10′	*d*	5.5[f] (6.0[g])	*d* (5.5[f])	6.2	5	6.2	4.7
J 10′,11	*d*	8.5[f] (9.5[g])	*d* (9.0[f])	8.75	7.5	8.8	7.4
J 8,9	*d*	*d* (*d*)	*d* (*d*)	6	*d*	4.9	3.8
J 11,12	*d*	*d* (7.75)	*d* (8.75)	7	*d*	7.8	4.7
J 8,12	*d*	*d* (12.0)	*d* (12.0)	11	*d*	11.8	10.4
Σ[e]*J* 10	5.0	*d* (*d*)	*d* (*d*)	5.0	3.5	6.8	4.0
Σ*J* 10′	*d*	*d* (15.5)	*d* (14.5)	15.0	12.5	15.0	12
Σ*J* 9	9.5	11 (11)	11 (10)	14.0	12.0	12.9	10
Σ*J* 11	14.5	*d* (22.5)	20 (22)	22.0	16.0	21.6	16

[a] Obtained at 300 MHz at room temperature; chemical shifts are given in parts per million (δ scale) relative to Me_4Si as internal standard; coupling constants are given in hertz. [b] H-10 cis with OH-9 or Ac-9; H-10′ trans with OH-9 or Ac-9. [c] Could not be located. [d] Could not be measured. [e] Sum of coupling constants given in hertz. [f,g] Values superscripted by *f* or *g* can be pairwise permuted. [h] Registry no., 61557-25-3. [i] Registry no., 62860-88-2. [j] Registry no., 62860-89-3. [k] Registry no., 745-62-0. [l] Registry no., 13227-94-6. [m] Registry no., 62860-90-6. [n] Registry no., 62928-69-2.

stabilized than the other one. Indeed Table II indicates a somewhat smaller value for the sum of coupling constants of hydrogen atom 11 and a larger value for hydrogen atom 9 in the prostaglandins (**1b–6b**), compared to product **7b**; this suggests a more axial position of H-9—and a more equatorial position of H-11—thus designating $^{12}_{8}T$ as the preferred conformation. The location of the alkyl group (C_7 of the acid side chain) in the equatorial position and the alkenyl group (C_{13}) in the axial position is in accordance with the large $^3J_{12,13}$ value and with a x-ray study.[18] A hydrogen bridge is geometrically not possible between the axial alkenyl side chain and the roughly antiperiplanar OH-11.

Since the values for the sums of coupling constants of respectively H-9 and H-11 in the diacetoxy derivatives with **c** configuration (**2c, 3c, 7c**; Table III) are nearly equal, we believe that these products have the same conformation or conformations. Again, the $J_{8,12}$ of **7c** discloses the most puckered part of the ring. This leaves only three possibilities, $^{8}_{12}T$, $_{12}E$, and ^{8}E, but in view of the magnitude of $J_{11,12}$ and $J_{8,9}$ only the envelope conformation with C_8 at the flap has to be

retained. As mentioned above, this conclusion based on **7c** would also be valid for the diacetoxy prostaglandins. However, the diols in this series (**1c, 6c, 8c**) show a much smaller sum of coupling constants for H-11 and, but to a lesser extent, for H-9. These data are easily rationalized by accepting the existence of an intramolecular hydrogen bond between the cis 1,3-hydroxyl groups. This hydrogen bond demands an ^{10}E conformation, resulting in a smaller value for ΣJ_{11}. The occurrence of this hydrogen bond is independently proven by IR spectroscopy for **8c** and **6c** (methyl ester of prostaglandin $F_{1\alpha}$) for which respectively hydrogen bonded hydroxylic absorptions at 73 and 60 cm^{-1} lower frequencies (CCl_4) are observed. The similarity in conformational behavior of products **6c** and **8c** is further displayed by four individual coupling constants comparable in magnitude. The ^1H NMR spectrum of prostaglandin $F_{1\alpha}$ itself could only be recorded in methanol-d_4 solvent; this solvent, however, interacts with the hydroxyl groups and destroys the intramolecular hydrogen bond. A great similarity is indeed observed between the individual coupling constant values of **5c** and **7c.** It has already been suggested that the side chain alignment in prostaglandins is more favorable in aqueous media than in less polar solvents;[6a] this is in complete agreement with our observations. No intramolecular hydrogen bond in prostaglandin $F_{1\alpha}$ (**5c**) in a polar solvent (methanol-d_4) is observed and the minimal-energy conformation ^8E has the two side chains in the most puckered part of the molecule, with a torsional angle around 73°, thus allowing alignment of the side chains. However, considering prostaglandin $F_{1\alpha}$ methyl ester (**6c**) in an apolar solvent (chloroform-d_1) one has to consider also conformation ^{10}E on the basis of intramolecular hydrogen bonding; the very large torsional angle (around 120°) clearly does not allow side chain alignment in this envelope conformation. It cannot a priori be predicted if the conformation of the five-membered ring actually induces the alignment of the side chains in prostaglandins in a certain medium or if the reverse situation is correct. Considering the magnitude of the different energy values, which have to be accounted for, we advise the latter possibility.[19]

Practical information can be learned from the ^1H NMR data of the olefinic hydrogen atoms of the 13,14 double bond. Theoretical calculations have shown that the most favorable position of the 13,14 double bond is an eclipsed one with H-12 and H-15;[4a] this is in accordance with the absence of a homoallylic coupling between hydrogen atoms 12 and 15 in products **5** and **6.** The chemical shift values for the hydrogen atoms located on the 13,14 double bond of 15(R)-prostaglandins (e.g., **2** and **4**) are situated at lower field compared to the values of the corresponding 15(S) products.[20] A remarkable regularity is observed when considering the chemical shift values of H-13 as a function of the configuration: the magnitude of the δ value increases when considering consecutively the **b, c,** and **a** configuration. The influence of the steric position of the vicinal alkyl side chain and the hydroxyl (or acetoxy) groups on the chemical shift of an H-1′ atom of a side chain has already been observed.[21] As already mentioned, our results do not concord with the occurrence of an intramolecular hydrogen bond between the 11-hydroxyl group and the 13,14 double bond. However, we have evidence that a hydrogen bond between the OH-9 group and the 5,6 double bond in prostaglandins of the 2 series could exist in an apolar solvent.[7a] Products **9** and **10** have two side chains containing a trisubstituted double bond in the 2′ position (for the 3-methyl-2-butenyl side chain) and in the 7′ position (for the 8-methyl-7-nonenyl side chain);[10b] the presence of the 7′ double bond is very convenient since the H-7′ is far removed from the cyclopentane, thus allowing the chemical shift of this hydrogen atom to serve as an internal standard value. Considering the diacetoxy derivatives **9a** and **9c** we may conclude that the steric position of the substituents on the five-membered ring does not influence the shift value of the vinylic proton in the 2′ position. The corresponding diols (**10**), however, exhibit a fairly large downfield effect—relative to the shift value of H-7′—for this hydrogen atom dependent on the configuration (Scheme III); thus, we assume that in **10a** and **10c** (in chloroform-d_1 solution) an intramolecular hydrogen bond occurs between the 11-OH group and the double bond in the 2′ position of the ring.

Careful analysis of the magnitude of the ^1H NMR spectral data of prostaglandins allows easy configurational assignment within the set of the three configurations **a, b,** and **c.** A tentative assignment of the most stabilized conformations of prostaglandins with **a, b,** or **c** configuration can be performed on the basis of ^1H NMR spectral data. It has been proven that those conformations for prostaglandin $F_{1\alpha}$ (**5c** and **6c**) are strongly influenced by the molecular environment. Our results suggest that prostaglandins are able to pass through discrete conformational states as the environment changes. This could bring some light about the still unresolved problem of the mode of action of prostaglandins in the cell membrane.

Experimental Section

The ^1H NMR spectra were recorded in CCl_4, $CHCl_3$-d_1, or CH_3OH-d_4 and the δ values were measured with Me_4Si as internal standard on a Varian HR-300 MHz spectrometer. Double irradiations experiments were done on this apparatus equipped with a Varian SC 8525-2 decoupler unit. IR spectra for the determination of intramolecular hydrogen bonding were recorded on a Perkin-Elmer 337 apparatus in CCl_4 solution. Concentration was 5×10^{-3} mol L^{-1}.

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Registry No.—**9a,** 62842-22-2; **9c,** 62860-91-7; **10a,** 62860-92-8; **10b,** 62860-93-9; **10c,** 62860-94-0.

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(12) The "axial-equatorial" terminology used in cyclohexane has been retained, although in cyclopentanes the dihedral angles will not generally equal those in cyclohexane. If ψ is the dihedral angle between cis vicinal bonds, and if there is no angular deformation, then $\psi_{ea} = \psi$; $\psi_{aa} = 120° + \psi_{ea}$; $\psi_{ee} = 120° - \psi_{ea}$. Considering the most puckered part of the molecule we used $\psi = 48.1°$ for the twist conformation and $\psi = 46.1°$ for the envelope conformation.[15d]
(13) These calculations will be discussed in detail elsewhere. The method used was derived from the work of Ouannes[15d] and Altona.[15e] The shape of the potential barrier restricting pseudorotation was calculated from torsional barriers only; nonbonded interactions and dipole–dipole interactions were not calculated but were considered during the study of Dreiding models. The method consists basically in calculating the torsional strain around each carbon–carbon bond of the ring from the rotational barrier of known acyclic compounds and summation of these values for each of the 20 basic conformations met along the itinerary of pseudorotation.
(14) Although the concept of pseudorotation was first introduced[15f] in relation with the conformation of unsubstituted cyclopentane, we will use the same term in the discussion of the conformational behavior of 2,3-dialkyl-1,4-cyclopentanediols.
(15) (a) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morisson, "Conformational Analysis", Wiley, New York, N.Y., 1965; (b) C. Altona, H. R. Buys, and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, **85**, 973 (1966); (c) D. Korver, *ibid.*, **88**, 1070 (1969); (d) C. Ouannes and J. Jacques, *Bull. Soc. Chim. Fr.*, 3603 (1965); (e) ref 15b; C. Altona, H. R. Buys, H. J. Hageman, and E. Havinga, *Tetrahedron*, **23**, 2265 (1967); (f) J. E. Kilpatrick, K. S. Pitzer, and R. Spitzer, *J. Am. Chem. Soc.*, **69**, 2483 (1947); (g) C. Altona and M. Sundaralingam, *ibid.*, **94**, 8205 (1972).
(16) See, e.g., P. v. R. Schleyer, D. S. Trifan, and R. Bacskai, *J. Am. Chem. Soc.*, **80**, 6691 (1958); M. Oke and H. Iwamura, *Bull. Chem. Soc. Jpn.*, **32**, 306 (1959).
(17) F. De Pessemier, Ph.D. Thesis, Gent, Belgium, 1976.
(18) G. Germain, J. P. De Clercq, and M. Van Meerssche, *Bull. Soc. Chim. Belg.*, **85**, 557 (1976).
(19) The ^{10}E form is a high-energy conformation, whereas an approximate value for the hydrogen bond is 1.5 kcal/mol. Thus the stabilization of the hairpin conformation (4.9 kcal/mol)[5] would normally be the leading factor in the determination of the composition of the conformational equilibrium for prostaglandin $F_{1\alpha}$ methyl ester in an apolar solvent. Since this is not the case (at least not exclusively) we assume that the nature of the solvent will in great part determine if the aligned conformation is indeed a preferred one.
(20) So far, the difference between prostaglandins with 15(*R*) or 15(*S*) configuration has been made only on the base of their TLC behavior; e.g., J. Ide and K. Sakai, *Tetrahedron Lett.*, 1367 (1976).
(21) The chemical shift values of the methyl groups in 2,3-dimethyl-1,4-diacetoxycyclopentane (**7**) are greatly influenced by the considered configuration: M. Samson, Ph.D. Thesis, Ghent, Belgium, 1976.

Synthesis of Deoxyribooligonucleotides by Means of Cyclic Enediol Pyrophosphates

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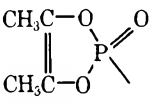
A new method of synthesis of deoxyribooligonucleotides by means of di(1,2-dimethylethenylene) pyrophosphate is described. Reaction of 5′-*O*-*p*-methoxytritylthymidine with the pyrophosphate in dichloromethane (triethylamine as proton acceptor) gives a cyclic enediol phosphate derivative, which is allowed to couple in dimethylformamide (triethylamine as catalyst) with unprotected thymidine to yield the 1-methylacetonyl ester of (5′-*O*-*p*-methoxytrityl)thymidylyl-(3′ → 5′)-thymidine. This protected dinucleotide triester is converted first into the deprotected triester by trifluoroacetic acid in dichloromethane solution, and then into $TpT^{-}(C_2H_5)_3NH^{+}$ by triethylamine in aqueous acetonitrile. The protected dinucleotide triester is converted into the protected tri- and tetranucleotide triesters by repetition of the reaction with pyrophosphate and the coupling with thymidine. The tetranucleotide, $TpTpTpT^{3-}[(C_2H_5)_3NH^{+}]_3$, is obtained after removal of the *p*-methoxytrityl 5′-OH protecting group, and the 1-methylacetonyl phosphate blocking group, from the protected triester. The di- and tetranucleotides are isolated as hydrated triethylammonium salts after DEAE-cellulose chromatography.

One of the strategies employed in the nonenzymatic synthesis of deoxyribooligonucleotides involves the establishment of the 3′ → 5′ internucleotide bond as a phosphotriester, $(R^{I}O)(R^{II}O)(BLO)PO$, where BL represents the phosphate blocking group, which must eventually be removed to produce the desired phosphodiester, $(R^{I}O)(R^{II}O)P(O)OH$. This approach, introduced by Todd[2] and explored initially by Letsinger,[3] by Reese,[4] and by Cramer and Eckstein,[5] has been used by many investigators,[6-14] sometimes in conjunction with a search for new reagents to convert the two nucleosides into the triester intermediate. Intensive research effort during the past four years[15-28] discloses a continuing interest in deoxyribooligonucleotide syntheses, in spite of the solution by Khorana and his co-workers[29] of the problem of constructing genes by a combination of nonenzymatic and enzymatic techniques.[30]

The synthesis of ribooligonucleotides is also receiving much attention, in particular by Ikehara, Ohtsuka, and their coworkers, who have developed methods to produce segments suitable for conversion into larger units with amino acid acceptor activity.[31-34] The construction of tRNA's by a combination of nonenzymatic and enzymatic procedures seems possible based on these results.

Work in this Laboratory[35-39] has focused on the development of phosphorylating reagents capable of being applied



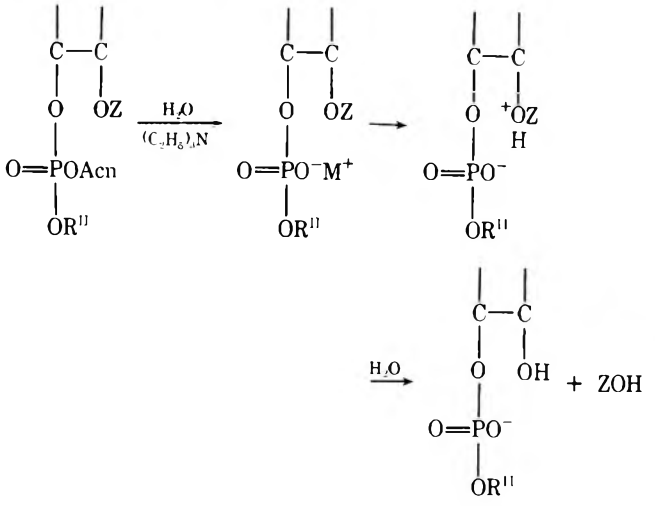
by standard procedures to the synthesis of complex phosphodiesters, such as the phospholipids of biological membranes,[40] and both types of oligonucleotides. Previous papers have described the preparation of several derivatives of the 1,2-dimethylethenylenedioxyphosphoryl group, abbreviated X=P(O)–, which are useful for this purpose.[35-37] The conversion of the alcohols $R^{I}OH$ and $R^{II}OH$ into the phosphodiester can be achieved as "three-, two-, or one-flask" syntheses, according to the number of intermediates isolated and purified:

$$R^{I}OH + X{=}P(O)Y + B \rightarrow X{=}P(O)OR^{I} + Y^{-}BH^{+} \quad (1)$$

$$R^{II}OH + X{=}P(O)OR^{I} \rightarrow (R^{I}O)R^{II}O)P(O)OCH(CH_3)COCH_3 \quad (2)$$

$$(R^{I}O)(R^{II}O)P(O)OCH(CH_3)COCH_3 + H_2O \rightarrow (R^{I}O)(R^{II}O)P(O)OH + HOCH(CH_3)COCH_3 \quad (3)$$

An attractive feature of this approach is the interdependence of the techniques used to remove the 1-methylacetonyl group (Acn) and the various alcohol-protecting groups in complex molecules.[41,42] A *tert*-butyldimethylsilyl group[43-45] (Z) on an alcohol adjacent to the phosphotriester function is relatively stable in mildly acidic and basic conditions. The Acn



group is easily removed in basic medium, and the silyl group in the phosphodiester becomes extremely acid labile, probably due to a high local acid concentration.[42]

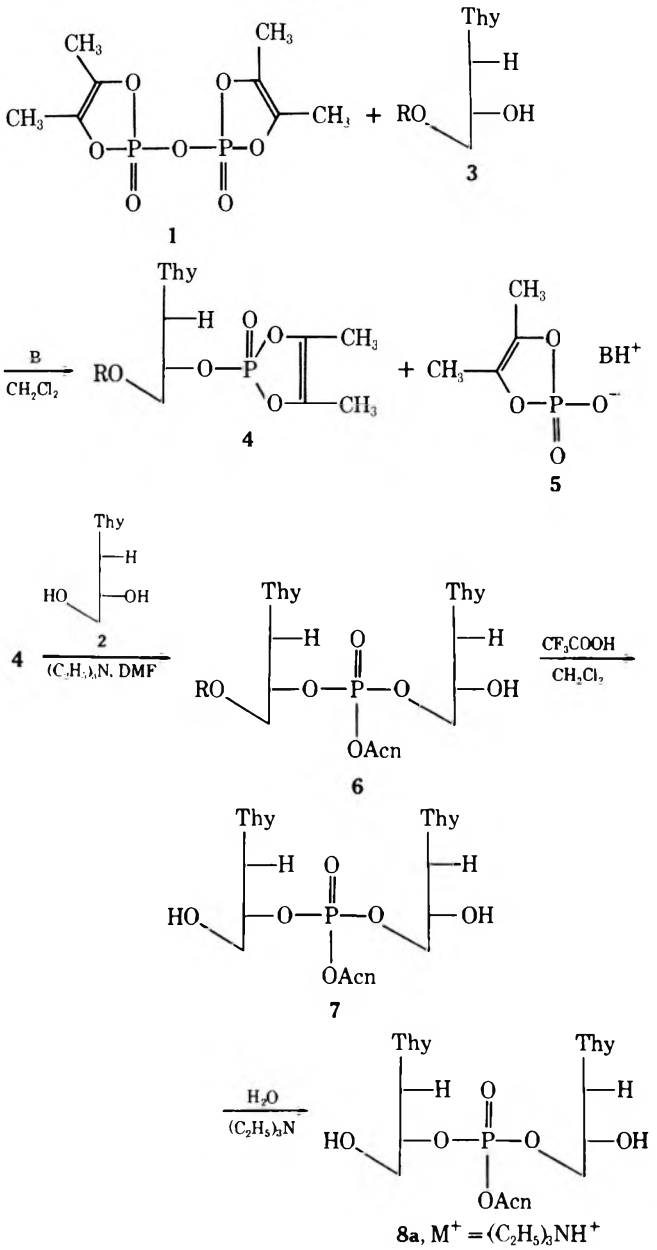
The neighboring group effect which operates in β-silyloxyethyl α-methylacetonyl phosphates can be exploited, in conjunction with other acid-labile alcohol-protecting groups, e.g., *p*-methoxytrityl,[46] in ribooligonucleotide synthesis. The present paper deals with one aspect of this general problem, namely, the application of the pyrophosphate, **1**, to the synthesis of di- and tetranucleotides from thymidine,[47] *using the p-methoxytrityl group to protect the C(5′)–OH function of only the first nucleoside of the chain.* The emphasis of the work is on isolation of the oligonucleotides in the form of their triethylammonium salts. The replacement of this cation by monovalent and divalent metal ions utilizing techniques similar to those that have been developed in the field of cardiolipins[40] would provide specimens needed for basic research on oligonucleotide–cation associations.[48]

Results

Stepwise Deoxyribooligonucleotide Synthesis. Thymidine (**2**) is converted into its dinucleotide, TpT, by means of the pyrophosphate **1**, according to the procedure outlined in Scheme I. The dinucleotide is isolated as the triethylammonium triaquo salt, **8a**·3H$_2$O. The first step of the synthesis is a displacement at the cyclic phosphorus atom by the 5′-protected nucleoside **3** with ring retention, which yields the cyclic phosphate **4** and the salt **5**. The reaction is carried out in dichloromethane solution in the presence of triethylamine as proton acceptor. The solvent is evaporated and replaced by dimethylformamide for the second step, which is a displacement at the cyclic phosphorus atom by the C(5′)–OH of *unprotected* thymidine (**2**), this time with ring opening. Triethylamine is an effective catalyst in this phosphorylation.[37] The protected dinucleotide triester is isolated as its monohydrate, **6**·H$_2$O, in 82% yield based on **3**, after silica gel chromatography; see Table I.

The third step of the synthesis is the removal of the *p*-

Scheme I[a]



[a] R = (*p*-CH$_3$OC$_6$H$_4$)(C$_6$H$_5$)$_2$C; Acn = –CH(CH$_3$)COCH$_3$; B = (C$_2$H$_5$)$_3$N.

methoxytrityl protective group by means of trifluoroacetic acid in dichloromethane solution.[49] The dinucleotide triester is isolated as its monohydrate, **7**·H$_2$O, in 90% yield based on **6**·H$_2$O, after silica gel chromatography.

The final step is the removal of the 1-methylacetonyl blocking group from the triester, **7**·H$_2$O, and is carried out for 2.5 h at 0 °C in a mixture of water and acetonitrile in the presence of 2 molar equiv of triethylamine. The crude product from this step contains 85–90% of TpT as its triethylammonium triaquo salt, **8a**·3H$_2$O, according to the analytical criteria described in the Experimental Section.[50] The pure salt, **8a**·3H$_2$O, is isolated in 85% of the theoretical yield based on **7**·H$_2$O, after chromatography on DEAE–cellulose.[51]

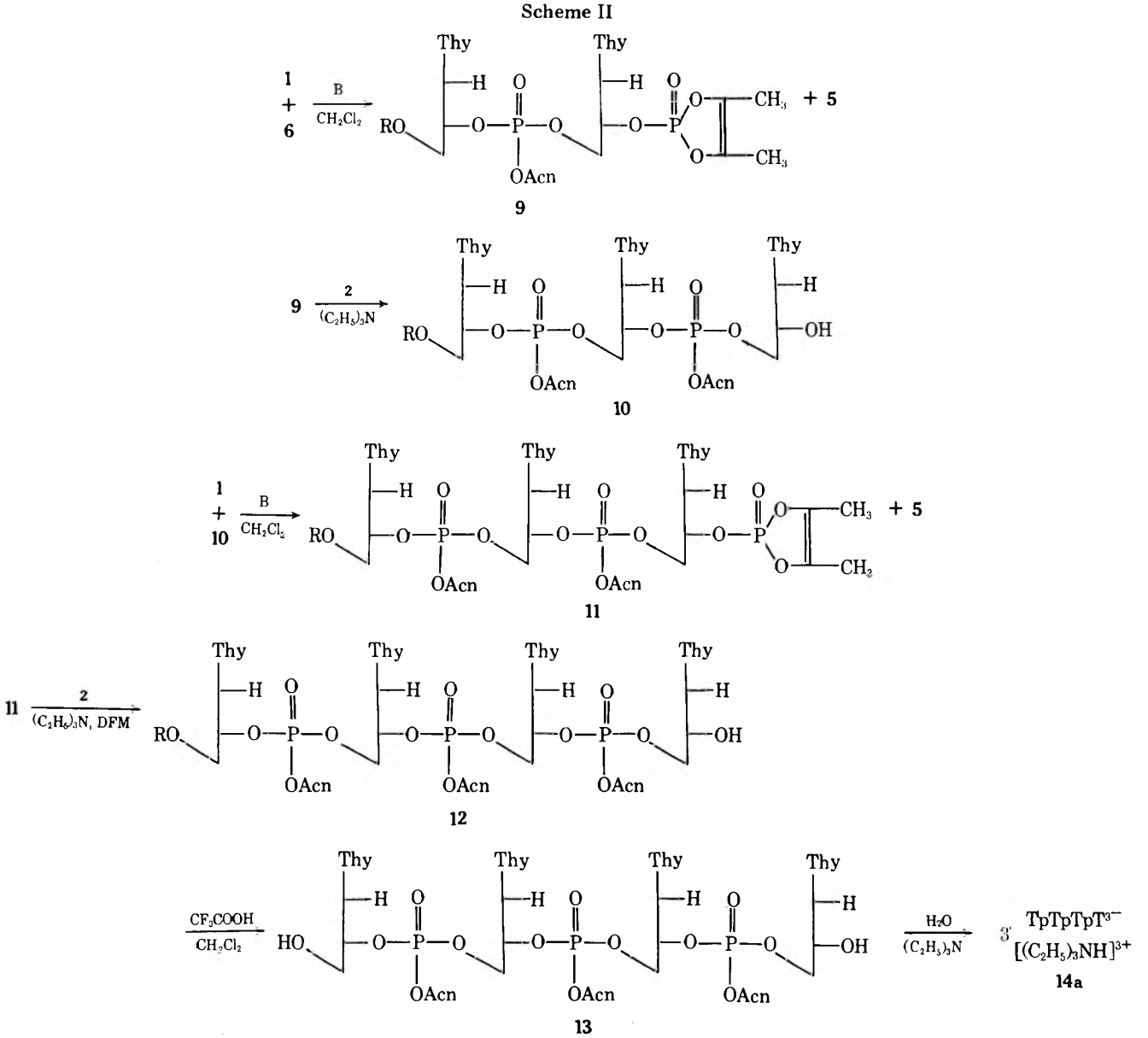
The conversion of thymidine into its tetranucleotide, isolated as the tris(triethylammonium) heptaaquo salt, **14a**·7H$_2$O, is shown in Scheme II. Reaction of the pyrophosphate **1** with the 5′-protected dinucleotide triester **6**, which has been rendered anhydrous by evaporation of a pyridine solution, generates the new cyclic phosphate **9**. The latter is allowed to couple with more thymidine to give the protected trinucleotide triester **10**·2H$_2$O, isolated in 61% yield based on dinucleotide

Table I. Properties of Synthetic Thymidine Oligonucleotides and Their Derivatives [R = $(p\text{-}CH_3OC_6H_4)(C_6H_5)_2C$; Acn = $-CH(CH_3)COCH_3$]

Registry no.	Compd no.	Compd	Mp, °C	R_f in TLC[a,b]
62930-00-1	**4**	5′-OR-T-3′-Cyclophosphate	92–100	...
62930-01-2	**6**·H_2O	5′-OR-Tp(Acn)T·H_2O	120–125	0.24 (I,B); 0.80 (I,C); 0.44 (II,D)
62962-23-6	**7**·H_2O	Tp(Acn)T·H_2O	105–114	0.42 (I,A); 0.08 (I,B); 0.63 (I,C); 0.13 (II,D)
62930-02-3	**8a**·$3H_2O$	$TpT^-(C_2H_5)_3NH^+ \cdot 3H_2O$	68–76	0.15 (I,C); 0.33 (III,F)[c,d]
62930-03-4	**10**·$2H_2O$	5′-OR-Tp(Acn)Tp(Acn)T·$2H_2O$	126–132	0.57 (I,A); 0.06 (I,B); 0.31 (II,D)
62930-04-5	**12**·$3H_2O$	5-OR-Tp(Acn)Tp(Acn)Tp(Acn)T·$3H_2O$	130–140	0.29 (I,A); 0.21 (II,D)
62930-05-6	**13**·$2H_2O$	Tp(Acn)Tp(Acn)Tp(Acn)T·$2H_2O$	90–100	0.16 (I,A); 0.21 (II,E)
62930-06-7	**14a**·$7H_2O$	$TpTpTpT^{3-}[(C_2H_5)_3NH^+]_3 \cdot 7H_2O$	140–149	0.06 (III,F)[e]
62930-07-8	**21a**·H_2O	$5'\text{-OR-TpT}^-(C_2H_5)_3NH^+ \cdot H_2O$	131–139	0.31 (I,C); 0.13 (II,G)
62930-08-9	**17**·H_2O	$(5'\text{-OR-T-}3')_2p(Acn) \cdot H_2O$	125–130	0.50 (I,B)

[a] I = silica gel plates, Eastman Kodak Co., Cat. No. 13179 (polyvinyl alcohol binder). II = silica gel plates, 60 F-254 (0.25-mm thickness), Merck Cat. No. 5760. III = Whatmann 3 MM paper. Solvents: A = THF; B = $c\text{-}C_6H_{12}/CH_3COCH_3/C_5H_5N$, 3/1/1; C = $i\text{-}C_4H_9OH/C_5H_5N/H_2O$, 7/2/1; D = CH_2Cl_2/CH_3OH, 9/1; E = CH_2Cl_2/CH_3OH, 5.7/1; F = $i\text{-}C_3H_7OH/H_2O$/conc NH_4OH, 7/2/1; G = CH_2Cl_2/CH_3OH, 3/1 v/v UV detection. Samples containing the *p*-methoxytrityl group are also detectable after spraying with 70% aqueous $HClO_4$ (2.5 mL) in acetone (50 mL). All phosphates are detectable after spraying with Hanes reagent [C. W. Stanley, *J. Chromatog.*, **16**, 467 (1964)]. [b] Reference R_f: T, 0.74 (I, C), 0.20 (II, D), 0.59 (III, F); 5′-OR-T (**3**), 0.63 (I, B), 0.58 (II, D); Tp, 0.01 (III, F); TpTpTp, 0.13 (III, F). Tentative Tp(Acn) or p(Acn)T (**21** or **22**), 0.40 (III, F). [c] Authentic TpT: R_f, 0.31 (III, F). [d] Paper electrophoresis: *Rm*, 0.30 (pH 7.2), 0.89 (pH 1.9) for **8a**; 0.30 (pH 7.2), 0.89 (pH 1.9) for authentic TpT. Reference: T**p**, 1.00. Savant flat head for 1 h, in phosphate buffer (pH 7.2), Gilson Model D electrophorator for 1.5 h, in acetic–formic acid buffer (pH 1.9), both at 2000 V, ref 50. [e] Paper electrophoresis: *Rm*, 0.80 (pH 7.2), 1.35 (pH 1.9) for **14a** vs. T**p** = 1.00. Other reference *Rm* values: trinucleotide TpTpT, 0.56 (pH 7.6), 1.18 (pH 1.9). Tentative Tp(Acn) or p(Acn)T, 0.45 (pH 7.2), 1.11 (pH 1.9); ref 50.

Scheme II



$6{\cdot}H_2O$, after silica gel chromatography. Repetition of the phosphorylation and the coupling steps yields the protected tetranucleotide triester $12{\cdot}3H_2O$ via the cyclic phosphate **11**. The triester $12{\cdot}3H_2O$ is obtained in 49% yield based on trinucleotide $10{\cdot}2H_2O$. The removal of the *p*-methoxytrityl group from $12{\cdot}3H_2O$ is carried out also with trifluoroacetic acid and affords the tetranucleotide triester $13{\cdot}2H_2O$ in 82% yield after silica gel chromatography. The final hydrolysis of the 1-methylacetonyl group is carried out as in the synthesis of the dinucleotide. The crude product obtained in this step contains 80–85% of TpTpTpT as the tris(triethylammonium) heptaaquo salt, $\mathbf{14a}{\cdot}7H_2O$ (See Experimental Section[50]). Pure $\mathbf{14a}{\cdot}7H_2O$ is isolated in 75% of the theoretical yield based on $13{\cdot}2H_2O$, after chromatography over DEAE–cellulose.

The purified dinucleotide **8a** and tetranucleotide **14a** were completely degraded by snake venom and spleen phosphodiesterases, and the theoretical pT/T and Tp/T ratios were observed, within the limits of accuracy of these assays, using paper electrophoresis and chromatography as analytical tools.

The pyrophosphate reagent **1** is employed in stoichiometric amounts in the conversion of protected thymidine **3** into the protected dinucleotide triester **6**; however, in subsequent steps, an excess of pyrophosphate corresponding to about 25 mol % for each additional thymidine unit is required to achieve the reported yields of protected tri- and tetranucleotide triesters **10** and **12**. This requirement may be related to increasing difficulty in removing the last traces of water from the larger oligonucleotides. In the purification of the protected triesters **6**, **10**, and **12** by silica gel chromatography, the most efficient eluting solvent is a mixture of dichloromethane and methanol. This solvent is satisfactory for both column and preparative LC techniques, in the case of dinucleotide **6**. However, only PLC is recommended for the purification of the tri- and tetranucleotides **10** and **12** using this solvent, since the more protracted column chromatography results in a significant decrease in the yields of the pure triesters. Mixtures of ethyl acetate and tetrahydrofuran can also be used as the eluting solvent in silica gel column chromatography in all cases, although the efficiency of the separation is lower than in the corresponding CH_2Cl_2/CH_3OH procedure.

By-Products of the Synthesis. The cyclic pyrophosphate **1** is a powerful phosphorylating reagent, and its reactions with compounds which have one unprotected hydroxyl group, **3**, **6** and **10**, are rapid and quantitative. Not surprisingly, the pyrophosphate **1** is also very sensitive to water.

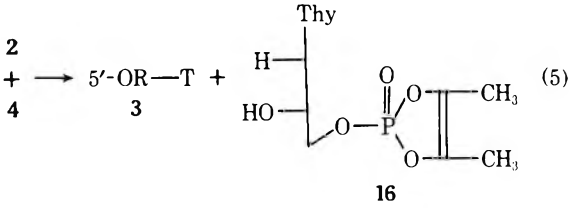
The triethylamine salt of 1,2-dimethylethenylene phosphate does not interfere in the phosphorylation steps required to establish the 3′ → 5′ internucleotide bond. The cyclic *anion*, unlike the corresponding acid and esters (hydrogen or alkyl 1,2-dimethylethenylene phosphates) is not a phosphorylating reagent. The salt is easily removed during the final purification of the triesters.

The cyclic phosphotriesters **4**, **9** and **11** are effective phosphorylating reagents toward alcohols, although they are much less reactive than the pyrophosphate **1**. Consequently, there is no appreciable competition between the cyclic phosphates and the pyrophosphate for the alcohol in the first step of the synthesis. We have shown that the phosphorylation of alcohols by alkyl 1,2-dimethylethenylene phosphates in aprotic solvents is effectively catalyzed by imidazole and by triethylamine.[34] Furthermore, triethylamine is quite effective in increasing the selectivity of the cyclic phosphates for primary alcohol functions in the presence of unprotected secondary alcohol groups in polyols.[34] The attack of the C(3′)–OH group of thymidine (**2**) on the cyclic phosphate **4**, in a displacement at phosphorus with ring opening, would produce the unnatural isomer **15** with the 3′ → 3′ internucleotide bond, according to the equation:

$$\mathbf{2} + \mathbf{4} \rightarrow \underset{\mathbf{15}}{\text{5′-OR-T-3′p(Acn)-3′-T}} \qquad (4)$$

Isomer **15** is probably responsible for a spot observed in the TLC plates of the crude reaction product, with an R_f value somewhat higher than that of the 3′ → 5′ structure **6**. It is estimated that approximately 2% of the unnatural isomer **15** is formed in the synthesis of the dinucleotide; the by-product **15** is removed in the purification of the triester by silica gel chromatography. We have not detected spots in the TLC plates of the crude reaction products of the tri- and tetranucleotide syntheses[52] that could reasonably be attributed to structures containing the 3′ → 3′ bond resulting from lack of selectivity in the coupling step. It is noteworthy that, without triethylamine as catalyst in the coupling reaction, a significant amount of the unnatural isomers are produced.

A second potential source of by-products in the syntheses is the occurrence of transesterification during the reaction of alcohols with alkyl 1,2-dimethylethenylene phosphates. The transesterification reaction is a displacement at the cyclic phosphorus with ring retention, and we have shown that the triethylamine catalysis of this type of phosphorylation is accompanied by a significant decrease in the extent of transesterification.[34] In the dinucleotide synthesis, transesterification regenerates 5′-OR-T (**3**) and produces a new cyclic phosphate



(5)

16

16, as indicated in eq 5. 5′-OR-T (**3**) is detectable in the TLC plates of the crude reaction product, to an extent estimated as 1–2%. The second by-product **16** could be partly responsible for the spot observed at the origin in the plates. The corresponding transesterification by-products in the synthesis of tri- and tetranucleotides are, respectively, the di- and the trinucleotides **6** and **10**; these by-products are generated in approximately 5% yields in the syntheses. In all cases, these by-products are easily removed by silica gel chromatography.

The transesterification reaction can, in principle, introduce two additional by-products, namely, the symmetrical phosphotriesters, as illustrated in eq 6 and 7, for the dinucleotide case.

$$\mathbf{3} + \mathbf{4} \longrightarrow \underset{\mathbf{17}}{\text{(5′-OR—T3′)}_2\text{p(Acn)}} \qquad (6)$$

$$\mathbf{2} + \mathbf{16} \longrightarrow \underset{\mathbf{18}}{\text{(T-5′)}_2\text{p(Acn)}} \qquad (7)$$

Neither of these by-products have been detected.[52] For comparison purposes, compound **17** was independently synthesized from 2 molar equiv of 5′-OR-T (**3**) and the pyrophosphate **1**.

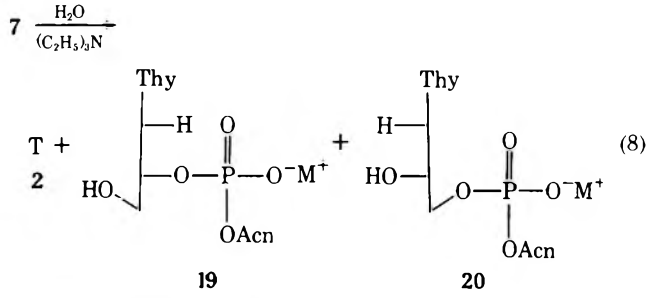
Removal of the *p*-methoxytrityl group from the protected oligonucleotides **6** and **12** is reasonably efficient using trifluoroacetic acid in dichloromethane solution at 0 °C; this method proved to be superior to that involving 75–80% glacial acetic acid as reagent.

The rate of basic hydrolysis of the 1-methylacetonyl group[41] from the oligonucleotide phosphotriesters **7** and **13** is significantly higher than that of simpler dialkyl 1-methylacetonyl phosphates.[37] The hydrolysis is sensitive to temperature and solvent composition. At 0 °C and in water/acetonitrile 1/2

Table II. Main ^{1}H NMR Signals[a] of Synthetic Thymidine Oligonucleotides and Their Derivatives

Assignments[b]	T(2)[i]	5′-OR-T (3)[i]		Cyclophosphate,[c,d] 4		R·Acn·T$_2$ (6·H$_2$O[e])	Acn·T$_2$ (7·H$_2$O[f])	TpT$^-$M$^+$ (8a·3H$_2$O[g])	TpTpTp-T^3-3M$^+$ (14a·7H$_2$O[g])	5′-OR-Tp-T$^-$M$^+$ (21a·H$_2$O[g])	(5′-OR-T-3′)$_2$-p(Acn) (17·H$_2$O)
	C_5D_5N	C_5D_5N	$CDCl_3$	C_5D_5N	$CDCl_3$	C_5D_5N	C_5D_5N	C_5D_5N	C_5D_5N	C_5D_5N	C_5D_5N
C(5)–CH_3	8.10	8.27	8.60	8.43	8.57	8.30 (1) 7.90 (2)	8.20 (1) 7.90 (2)	8.08 (1) 7.70 (2)	8.10 (1) 7.76 (2, 3, 4)	8.30 (1) 7.84 (2)	8.30
C(2′)–H_2	7.32	7.40	7.64	7.17	7.40	7.37 7.07	7.40 7.27	7.30	7.30	7.33	7.15
C(5′)–H_2	5.76	6.40	6.65	6.40	6.48	6.32 (1) 5.31 (2)	5.85 (1) 5.40 (2)	5.70 (1) 5.40 (2)	5.72 (1) 5.40 (2, 3, 4)	6.25 (1) 4.44 (2)	6.41
C(4′)–H	5.56	5.55	6.00	5.45	5.67	5.33	5.40	5.40	5.40	5.44	5.44
C(3′)–H	4.96	5.10	5.50	4.54	4.70	5.18 (2) 4.25 (1)	4.90 (2) 4.30 (1)	4.90 (2) 4.40 (1)	4.90 (4) 4.40 (1, 2, 3)	5.00 (2) 4.44 (1)	4.35
CH_3O		6.37	6.30	6.33	6.20	6.30				6.25	6.37
Acn–CH_3[h]						8.50	8.48				8.54
Acn–CH_3CO						7.76	7.74				7.80

[a] In ppm vs. Me_4Si = 10. Numbers in parentheses refer to nucleoside sequence, 1, 2, . . . n + 1, in a chain of n phosphates and n + 1 nucleosides from left to right. Signals of possible diastereomers of triesters are not resolvable. [b] C(1′)–H is at $\tau \sim 3.0$, C(6)–H at somewhat lower field. Exchangeable and aromatic ^{1}H omitted. [c] $CH_3C = CCH_3$: τ 8.28 (C_5D_5N), 8.10 ($CDCl_3$); ^{31}P δ −11.6 ppm vs. H_3PO_4 = 0 ($CDCl_3$). [d] Spectral changes for **6** → **9** and **10** → **11**, are analogous to those for **3** → **4**. [e] Spectra of **6**, **10**, and **12** are similar. [f] δ ^{31}P −3.7 (C_5D_5N) vs. H_3PO_4 = 0. Spectra of **7** and **13** are similar. [g] $(C_2H_5)_3NH^+$, τ 8.67 (quartet), 6.90 (triplet); J = 6 Hz. [h] Doublet, J = 7 Hz. The methine ^{1}H of Acn gives a multiplet at ~5.2–5.4. [i] Registry no.: **2**, 50-89-5; **3**, 42926-80-7.



19 20 (8)

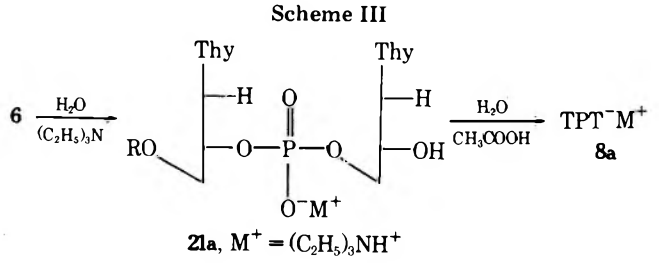
mixtures, the hydrolysis in the presence of triethylamine produces <2–3% phosphodiesters **19** and **20**, resulting from internucleotide bond cleavage (eq 8). This type of by-product is easily removed by chromatography.

Other Chain Building Sequences. Additional synthetic flexibility is provided by a reversal of the sequence of deprotection and deblocking steps, as illustrated in Scheme III. The 1-methylacetonyl group is removed from the protected dinucleotide triester **6** to give the protected diester, isolated as its triethylammonium aquo salt, **21a**·H_2O, after silica gel chromatography. The protected salt **21a** is a useful intermediate for the preparation of metal ion dinucleotide salts, and of other phosphotriesters. The removal of the *p*-methoxytrityl group from **21a** yields the salt of TpT, **8a**·3H_2O. A comparison of the relative deprotection rates of the phosphodiester **21a** and the phosphotriester **6** was carried out in 75% acetic acid; the deprotection of the diester is significantly faster.

State of Hydration and X-Ray Powder Photographs of Solid Deoxyribooligonucleotides. In the solid state, the oligonucleotides are quite hydroscopic. Reproducible results in the elemental analyses of the triesters **6, 7, 10, 12, 13,** and **17** and of the 5′-O-protected diester salt **21a** are obtained when the material which is isolated after silica gel chromatography is dissolved in tetrahydrofuran and the solution is added to moist diethyl ether. These substances are obtained as free-flowing powders which retain certain stoichiometric amounts of water after drying for 24 h at 25 °C and 0.1 mm. X-ray powder photographs reveal that the hydrated triesters **6, 7, 12,** and **13** are noncrystalline solids.

The triethylammonium salts of the oligonucleotides **8a** and **14a** are also obtained as free-flowing noncrystalline hydrates when their aqueous solutions are freeze-dried, and kept several hours at 25 °C and 0.1 mm.

Scheme III



21a, $M^+ = (C_2H_5)_3NH^+$

^{1}H NMR Spectra of Oligonucleotides in Pyridine-d_5. The cyclic phosphates **4, 9,** and **11** are characterized by the relatively large downfield shift of the C(3′)-H signal of the respective precursors, **3, 6,** and **10,** as a result of the phosphorylation of the alcohol, C(3′)–OH, and by the sharp signal of the two CH_3 groups on the 1,3,2-dioxaphospholene ring; Table II. The relatively large negative value of the ^{31}P NMR signal, −11 ppm vs. H_3PO_4 = 0, is also typical of the cyclic phosphates.

The spectrum of the protected dinucleotide triester **6** clearly shows the C(5)–CH_3 groups of T-1 and T-2, the latter being at lower magnetic field, possibly as a result of relative deshielding by the phosphoryl group (Table II). The signals from C(3′)–H of T-1 and C(5′)–H_2 of T-2 of **6** move downfield relative to those of protected and unprotected T, respectively, and relative to the signals from C(3′)–H and C(5′)–H_2 of T-2 and T-1 in **6.** These observations confirm the establishment of the 3′ → 5′ internucleotide bond in **6.** The spectra of the protected tri- and tetranucleotide triesters **10** and **12** are very similar to each other and to that of **6,** except that the signal(s) due to the C(5)–CH_3 of the internal nucleosides of the chain are shifted ca. 3 Hz toward high field from that of the terminal T, or T-(n + 1), with n = number of phosphates. The signals of the two internal C(5)–CH_3 of **12** overlap, at 60 MHz.

The isomer 5′-OR-T-3′-p(Acn)-3′-T (**15**) is characterized by signals at τ 8.20 and 5.85, associated with C(5)–CH_3 andC(5′)–H_2, respectively, of T-2 in the molecule of **15.** These two signals are very close to those of the corresponding groups in thymidine, reflecting the similarities in the magnetic environment of the respective protons.

In the salts **8a** and **14a** the C(5)–CH_3 signals of T-1 and T-(n + 1) are widely separated, but those of the internal nucleosides of **14a** are no longer resolvable at 60 MHz, and overlap with the signal of T-(n + 1). In crude samples of the

salts, a very weak signal at ca. τ 7.65 is indicative of 1-methylacetonyl containing by-products, e.g., **19** or **20**.

Discussion

The novel sequence for deoxyribooligonucleotide synthesis described in this paper has several noteworthy features: (1) The protected triesters are produced in essentially a "one-flask" reaction, since the cyclic phosphate intermediates prepared from the pyrophosphate and triethylamine are not isolated. This procedure is simpler than that which uses nicotinamide as proton acceptor.[1b] (2) The first P–O bond [at C(3′)–OH] is formed in a rapid and quantitative reaction. (3) The second P–O bond [at C(5′)–OH] is established on an unprotected nucleoside. The strategy of establishing the internucleotide bond with unprotected nucleosides has already been utilized by several groups.[6a,12a,27,28] (4) The 1-methylacetonyl (or 3-oxo-2-butyl) blocking group is not affected by the conditions required to deprotect the C(5′)–OH function, and conversely, the blocking group can be removed without affecting the 5′ protection. (5) Less than 2% of 3′ → 5′ internucleotide bond cleavage occurs in the phosphorus-deblocking step. (6) No internucleotide bond isomerization is detected in the deblocking step; venom and spleen phosphodiesterases completely degrade the synthetic oligonucleotides, before and after the DEAE–cellulose chromatography.

Experimental Section

Reactions involving derivatives of the 1,2-dimethylethenylenedioxyphosphoryl group must be carried out under strictly anhydrous conditions. The DMF was refluxed with P_2O_5, distilled in vacuum, shaken with Na_2CO_3, and redistilled under vacuum and stored over 4A molecular sieves until used. CH_2Cl_2 was distilled from P_2O_5 then from $CaCO_3$ and stored over molecular sieves. The triethylamine was dried over Na, distilled, and stored over molecular sieves. Thymidine was dehydrated by repeated evaporations from dry pyridine. Except as noted, all evaporations were carried out at ca. 30 °C and 20 mm (rotoevaporator), followed by 0.1 mm.

Elemental analyses of all compounds (except 4) in Table I were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Values obtained for C, H, N, P, and H_2O (Karl Fischer method) agree with the calculated figures: C, ±0.7; H, ±0.5; N, ±0.3; P, ±0.1; H_2O, ±0.5% [all phosphotriesters were dried for 24 h at 25 °C (0.1 mm) prior to analysis]. The triethylammonium salts were dried as indicated, prior to analysis.

Purifications of oligonucleotide triesters **6, 7, 10, 12,** and **13** in a scale of 1 g or less were carried out on 20 × 20 cm precoated silica gel plates (2 mm-thick, PLC 60 F-254, Merck Cat. No. 5766). The triesters were applied to the plates in CH_2Cl_2 solution (0.3 g/plate), eluted as indicated, and extracted from the adsorbent by means of THF. Large-scale (>1 g) purification of the protected *dinucleotide* triester **6** was performed by column chromatography on silica gel 60 (70–230 mesh; Merck Cat. No. 7734) or silica gel H (short-column chromatography[53]) as indicated. All solvent compositions are v/v.

Di(1,2-dimethylethenylene) Pyrophosphate (Acetoin Enediol Cyclophosphate, 1). The pyrophosphate 1 was prepared as described.[32] The samples utilized exhibited one sharp signal at τ 8.02 (Me_4Si = 10) in their ^1H NMR spectra (60 mg of 1 in 0.5 mL of $CDCl_3$), and were assumed to contain at least 98% pure **1**.

5′-*O*-*p*-Methoxytritylthymidine (3). The procedure in the literature[46] was modified as follows to provide **3** of suitable quality for reaction with the pyrophosphate **1**.

A pyridine solution (100 mL) of T (**2**, 10.08 g) and *p*-methoxytrityl chloride (12.94 g) was stirred at 20 °C for 20 h. The solution was evaporated, the residue dissolved in chloroform (400 mL), and the solution extracted with water (two 400-mL portions, two 200-mL portions), dried (Na_2SO_4), and evaporated. The residue was redissolved in chloroform, and the solution was evaporated (three 25-mL portions). The foamy residue (22 g) was dissolved in CH_2Cl_2 (20 mL) and applied to a silica gel column (445 g, packed in CH_2Cl_2). Elution with 2 L of 49/1 and 1 L of 24/1 CH_2Cl_2/CH_3OH removed impurities. The product appeared in 500 mL of 24/1 CH_2Cl_2/CH_3OH; the solvent was evaporated and the residue was kept 1 h at 0.1 mm. The foamy residue was dissolved in anhydrous benzene (150 mL) and added to cyclohexane (200 mL); crystallization (6 h at 25 °C; 2 h at 0 °C) afforded 18.7 g (87% yield) of 5′-OR-T (**3**), mp 119–120 ° (after drying at 25 °C, 0.5 mm).

Protected Dinucleotide Triester 6. 5′-*O*-*p*-Methoxytritylthymidine (**3**) was dried by evaporation from pyridine (four 25-mL portions) followed by drying at 25 °C (0.1 mm), prior to reaction. A solution of **3** (5.14 g, 10 mmol) in dichloromethane (20 mL) was added, dropwise, to a stirred dichloromethane solution (10 mL) of the pyrophosphate **1** (2.82 g, 10 mmol) containing triethylamine (1.53 mL, 10 mol % in excess of 1 molar equiv) at 0 °C. After 5 h at 0 °C, the mixture was evaporated to yield the crude cyclic phosphate **4**, which was kept 5 min at 25 °C (0.1 mm). A solution of this material in DMF (10 mL) was added, *with protection against moisture*, to a stirred mixture of anhydrous thymidine (**2**, 2.42 g, 10 mmol), triethylamine (1.80 mL, 20 mmol), and DMF (10 mL), at 0 °C. The solution was stirred for 2 h at 0 °C, and was kept 12 h at 0 °C and 2 h at 25 °C. The solution was evaporated at 25 °C, first at 30 mm and then at 0.1 mm to remove all the DMF. The residue was dissolved in dichloromethane and the solution was poured into ice (ca. 200 g). The layers were separated and the aqueous solution was thoroughly extracted with dichloromethane. The combined organic solution was dried (Na_2SO_4) and evaporated at 25 °C (30 mm followed by 0.1 mm, overnight) to yield the crude triester **6**·H_2O (8.63 g). This material was applied (as a CH_2Cl_2 solution) to silica gel PLC plates (0.3 g/plate); two elutions with CH_2Cl_2/CH_3OH 9/1, followed by extraction of the substance from the silica by THF and evaporation of the solvent, afforded the pure triester **6**·H_2O. Purification of larger quantities was also performed by column chromatography, using the same elution solvent, or with ethyl acetate/THF 1/1. The pure triester **6**·H_2O was isolated in 82% of the theoretical yield based on 5′-OR-T (**3**). To obtain a free-flowing powder suitable for elemental analysis, a THF solution of the triester was added to stirred diethyl ether (1/10); the sample was dried several hours at 25 °C (0.1 mm).

Dinucleotide Triester 7. Approximately 20 molar equiv of trifluoroacetic acid[49] was added to a 0.002 M CH_2Cl_2 solution of the protected dinucleotide triester **6**·H_2O at 0 °C. After 20 min at 0 °C, pyridine was added to neutralize the acid, and the solution was evaporated. The crude product was purified by silica gel H (short-column chromatography[53]) using CH_2Cl_2/CH_3OH 9/1. Pure **7**·H_2O was obtained as a free-flowing powder in 90% yield based on **6**·H_2O upon addition of a THF solution to diethyl ether (1/10).

Removal of the *p*-methoxytrityl group from **6**·H_2O was also carried out in 75% acetic acid (0.1 M solution at 20 °C for 5 h). Pure **7**·H_2O was isolated in 65% yield after chromatography (ethyl acetate/THF 1/1 and 1/2 successively).

Thymidylyl-(3′ → 5′)-thymidine (8). Triethylamine (2 molar equiv, as a 0.2 M aqueous solution) was added, over a 15-min period, to a stirred 0.02 M solution of the dinucleotide triester **7**·H_2O in water/acetonitrile (1/5) at 0 °C. After 2.5 h at 0 °C, the solution was diluted with water (1/1) and was evaporated. The crude product was redissolved in water and was again evaporated [three 2-mL portions of H_2O, 25 °C (0.1 mm)]. The residue was dissolved in 2 mL of water and was freeze-dried to yield crude **8a** as a free-flowing powder (after 2 h at 25 °C and 0.1 mm). This crude material was submitted to elemental, NMR spectrometrical, and chromatographic analyses.

The crude dinucleotide was chromatographed over DEAE-Sephadex A-25 (bicarbonate form; equilibrated with 0.1 M NH_4HCO_3, pH 8.5; 1 × 20 cm column). The salt was applied in the minimum volume of buffer; the gradient to 0.25 M NH_4HCO_3 (pH 8.5) was started at fraction 6, ended at fraction 34, and followed by straight 0.25 M buffer. Fractions were ca. 7.5 mL, flow rate 60 mL/h; Isco UA-2 UV analyzer was used. OD 267 were determined on a Beckman D.U. spectrometer with a Gelford attachment. Three components accounted for 90% of the crude dinucleotide: T (2%), Tp(Acn) and/or p(Acn)T (2%), and TpT (96%), eluted successively. The expected nucleotide/nucleoside ratios were obtained in the snake venom and spleen phosphodiesterase digestions[50] of TpT.

Large-Scale Purification of the Triethylammonium Salt of TpT (8a). BioRad Cellex-D, normal capacity DEAE–cellulose was converted into the bicarbonate form by repeated washings with 0.5 M aqueous triethylammonium bicarbonate, followed by deionized water. (A stock 0.5 M triethylammonium bicarbonate solution was made by passing a solution of 0.5 mol of $NaHCO_3$ in 500 mL of deionized water through a Dowex cation-exchange resin in its triethylammonium form and washing the resin with an additional 500 mL of water.)

A solution of the crude triethylammonium salt of the oligonucleotide **8a** in water (ca. 0.2 g in 4 mL) was applied to a column of the DEAE–cellulose (bicarbonate) resin (2.5 × 20 cm). Elution was performed with the gradient which resulted from 1.5 L of deionized water in the mixing vessel and 1.5 L of 0.25 M triethylammonium bicarbonate in the reservoir; 180 17-mL fractions were automatically collected at 9-min intervals. The fractions were monitored by TLC (UV

detection). The combined fractions containing the oligonucleotide were evaporated at 30 °C (20 mm), the residue was dissolved in water (10 mL) and reevaporated, and the residue was dissolved in water (10 mL) and passed through a column of Dowex AG 50W-X8 cation exchange resin (50 g) in its triethylammonium form. The column was washed with water (100 mL) and the combined solution and washing were evaporated. The residue was taken up in 2 mL of H_2O and freeze-dried to give the pure salt **8a**·$3H_2O$ as free-flowing powder. This substance was shown to be homogeneous by TLC and by paper chromatography and electrophoresis. The results of the phosphodiesterase digestions of the oligonucleotide salt were in agreement with its structure.

Protected Trinucleotide Triester 10. The chromatographed protected dinucleotide triester **6**·H_2O (0.575 g, 0.63 mmol) was dehydrated by repeated evaporations from pyridine (five 5-mL portions), followed by drying at 25 °C (0.2 mm). A solution of **6** and triethylamine (80 mg, 0.80 mmol) in dichloromethane (1.0 mL) was immediately added to a stirred dichloromethane solution (0.5 mL) of the pyrophosphate **1** (0.223 g, 0.80 mmol) at 0 °C. An additional 0.2 mL of dichloromethane was used to transfer the material, and the final concentration of the solution was 0.3–0.4 M; this solution was stirred for 5 h at 0 °C and evaporated at 0 °C in vacuum. The residue was suspended in DMF (0.4 mL) at 0 °C and treated with a mixture of anhydrous thymidine (0.153 g, 0.63 mmol) and triethylamine (2 molar equiv) in DMF (1.0 mL). The resulting solution was kept for 12 h at 0 °C and for 2 h at 25 °C. The solvent and the amine were evaporated at 25 °C (0.1 mm; ca. 6 h). The residue was dissolved in dichloromethane and the solution was applied to two 20 × 20 cm PLC plates. The plates were successively eluted with CH_2Cl_2/CH_3OH 9/1 (twice) and 5.6/1 (once). Extraction of the substance from the silica by THF, evaporation of the solution, and drying at 25 °C (0.1 mm; ca. 12 h) afforded the pure triester **10**·$2H_2O$ in 61% of the theoretical yield based on dinucleotide **6**. A free-flowing powder suitable for elemental analysis was obtained by addition of a THF solution of the triester to stirred diethyl ether (1/10), filtration of the precipitate, and drying at 25 °C (0.1 mm).

Protected Tetranucleotide Triester 12. The chromatographed protected trinucleotide triester **10**·$2H_2O$ (0.286 g, 0.22 mmol) was dehydrated and submitted to the same sequence of reactions which transformed the dinucleotide **6**·H_2O into the trinucleotide **10**·$2H_2O$. The following amounts of reagents were employed: triethylamine (0.31 mmol) and dichloromethane (0.5 mL), pyrophosphate **1** (0.093 g, 0.31 mmol) and dichloromethane (0.3 mL) in the first step; thymidine (0.060 g, 0.23 mmol), triethylamine (2 molar equiv), and DMF (0.8 mL) in the second step. The experimental conditions were virtually identical with those described in the synthesis of the lower homologue. The crude tetranucleotide, in CH_2Cl_2 solution, was applied to one 20 × 20 cm PLC plate. The plate was successively eluted with CH_2Cl_2/CH_3OH 9/1 (twice) and 5.6/1 (twice). The pure triester **12**·$3H_2O$ was isolated in 49% of the theoretical yield based on trinucleotide **10**. A free-flowing powder suitable for elemental analysis was prepared as in the case of the lower homologue.

Tetranucleotide Triester 13. The deprotection of **12**·$3H_2O$ was carried out with trifluoroacetic acid as described for the lower homologue. The pure tetranucleotide triester **13**·$2H_2O$ was isolated in 82% yield based on **12**·$3H_2O$, after PLC, with CH_2Cl_2/CH_3OH 3/1 (twice) as the eluting solvent. The analytical sample was prepared by addition of a THF solution of the triester to stirred diethyl ether (1/10).

Removal of the *p*-methoxytrityl group from **12**·$3H_2O$ by 80% acetic acid (0.1 M, 3 h at 20 °C) gave **13**·$2H_2O$ in 71% yield, after chromatography.

TpTpTpT[47] (14). Triethylamine (6 molar equiv, as a 0.2 M aqueous solution) was added, over a 15-min period, to a stirred 0.02 M solution of the tetranucleotide triester **13**·$2H_2O$ in water/acetonitrile (1/5) at 0 °C. After 2.5 h at 0 °C, the solution was worked up as described in the synthesis of TpT (**8a**).

The crude tetranucleotide was chromatographed over DEAE–Sephadex A-25 as described in the case of the lower homologue. Six components accounted for 90% of the crude tetranucleotide: T (1%), Tp(Acn) and/or p(Acn)T (3%), TpT (5%), TpTpT (6%), TpTp(Acn) and/or p(Acn)TpT (6%), and TpTpTpT (79%) eluted successively. Characterization of the pure substances was by paper chromatography and electrophoresis (Table I); the identification of 1-methylacetonyl phosphodiesters is tentative. The expected nucleotide/nucleoside ratios were obtained in the snake venom and spleen phosphodiesterase digestions[50] of the TpTpTpT.

Large-Scale Purification of the Triethylammonium Salt of TpTpTpT (14a). The purification of a 0.2-g sample of **14a** was carried out as in the case of the dinucleotide **8a**. The purified tetranucleotide **14a**·$7H_2O$ was shown to be homogeneous by TLC and by paper chromatography and electrophoresis. The results of the phosphodiester digestions of the salt were in agreement with its structure.

Isolation of Protected Nucleoside Cyclic Phosphate 4 and Protected Dinucleotide Triester Cyclic Phosphate 9. A solution of the respective alcohol, **3** or **6** (1 molar equiv), in CH_2Cl_2 was added dropwise to a stirred solution of the pyrophosphate **1** (1.25 molar equiv) in CH_2Cl_2 containing suspended nicotinamide (1.50 molar equiv) at 0 °C. The final volume of the solution was ca. 0.3 M in alcohol **3** or **6**, and most of the nicotinamide salt of 1,2-dimethylethenylene phosphate formed in the reaction remained in suspension. The mixture was stirred for 4–5 h at 0 °C, and was filtered through a medium-porosity sintered glass funnel under a blanket of N_2 or Ar. The insoluble salt was washed with a few milliliters of CH_2Cl_2 and the solution was evaporated to yield the moisture-sensitive cyclic phosphates **4** and **9** as solid foams. This material contained traces of the nicotinamide salt. The ^1H NMR spectra of the cyclic phosphates are summarized in Table II.

(5′-*O*-*p*-Methoxytrityl)thymidylyl-(3′ → 5′)-thymidine (21). A solution of the purified triester **6**·H_2O (2.65 g, 3 mmol) in a mixture of water (20 mL), acetonitrile, (10 mL), and triethylamine (6 mmol) was stirred at 20 °C for 1 h; TLC indicated completion of the reaction. The solution was evaporated to a 2-mL volume and freeze-dried to a powder (2.54 g). Part of this material (1.0 g) was dissolved in THF (2 mL) and placed on a column of silica gel. Ethyl acetate (50 mL) and THF (50 mL) eluents contained no material. THF/methanol 9/1 (80 mL) and 4/1 (40 mL) eluted a mixture of 5′-OR-TpT$^-$ M^+ (**21a**) and what could be 5′-OR-Tp(Acn)$^-$ M^+, according to their relative TLC mobilities. THF/methanol 4/1 (400 mL) eluted pure **21a** (0.88 g, after evaporation). The salt **21a** was dissolved in water (20 mL) and passed through a column of Dowex AG 50W-X8 cation exchange resin in the $(C_2H_5)_3NH^+$ form. The eluent and the aqueous wash (30 mL) were combined, evaporated to 1 mL, and freeze-dried (0.9 g of **21a**·H_2O, 85% recovery in the purification step). This material was dissolved in THF (7 mL) and the solution was added dropwise with vigorous stirring to 75 mL of diethyl ether. The solid which separated was filtered and dried (50 °C, 0.1 mm, 12 h) to give free-flowing 5′-*O*-*p*-methoxytritylthymidylyl-(3′ → 5′)-thymidine triethylammonium monoaquo salt (**21a**·H_2O).

Removal of the *p*-Methoxytrityl Group from the Protected Dinucleotide Phosphodiester 21. A solution of the salt **21a**·H_2O (0.31 g) in 80% acetic acid (3 mL) was stirred at 20 °C for 3 h. The solution was diluted with water (10 mL) and evaporated. The residue was treated with water (10 mL), the mixture was reevaporated, and the residue was again treated with water (10 mL) and filtered to remove tritanol. The aqueous solution was evaporated to a 2-ml volume and freeze-dried to yield 0.23 g of TpT$^-$$(C_2H_5)_3NH^+$·$3H_2O$ (**8a**·$3H_2O$) characterized by TLC.

1′-Methylacetonyl Bis[(5′-*O*-*p*-methoxytrityl)thymidylyl-3′] Phosphate (17). (a) A solution containing 5′-OR-T (**3**, 1.02 g, 2 mmol) and the pyrophosphate **1** (0.25 g, 1 mmol) in pyridine (1 mL) was stirred at 20 °C for 48 h. The solution was evaporated and the residue was stirred with water (30 mL) and filtered. The solid was washed with water, dried (25 °C, 0.1 mm, 24 h), and dissolved in THF. The solution was filtered and the filtrate added to diethyl ether. The solid was filtered and dried (30 °C, 0.1 mm, 48 h) to give **17** in ca. 75% yield.

(b) The same material was made by reaction of 5′-OR-T (**3**) with the cyclic phosphate **4**.

Registry No.—**1**, 55894-94-5; **9**, 62930-09-0; **11**, 62930-10-3; **15**, 62930-11-4; *p*-Methoxytrityl chloride, 14470-28-1.

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Boron Compounds. 45.[1] 6-Deoxy-*O*-acyl-α-L-mannofuranoses via *O*-Ethylboranediyl Derivatives

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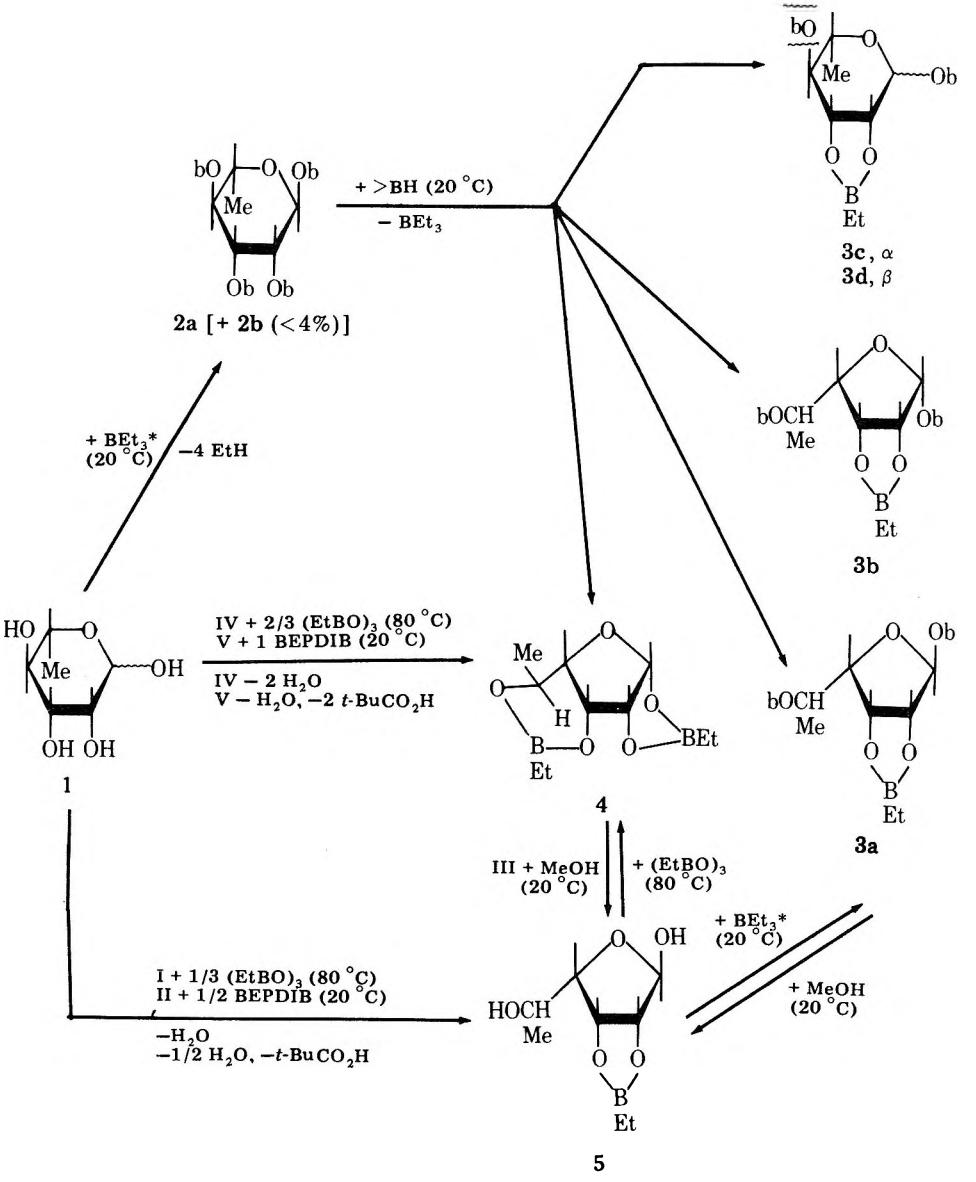
The O-diethylborylation of 6-deoxy-L-mannopyranose (L-rhamnose) (1) yields 6-deoxy-1,2,3,4-tetrakis-*O*-diethylboryl-α-L-mannopyranose (**2a**), which in the presence of >BH gives a mixture of four isomers **3a–d** and 6-deoxy-1,2:3,5-bis-*O*-ethylboranediyl-β-L-mannofuranose (**4**). Ethylboroxine or bis(ethylpivaloyloxy)diboroxane (BEPDIB) and **1** give over 90% yields of **4** or 6-deoxy-2,3-*O*-ethylboranediyl-α-L-mannofuranose (**5**), depending on the molar ratio used. A reversible trans-O-ethylboranediylation between **4** and **5** occurs on heating **5** or on heating a mixture of **1** and **4** in pyridine. The O-acetylation of **5** gives the 1,5-di-*O*-acetyl derivative **6**, which on deborylation and subsequent O-acylations lead to the boron-free derivatives **7** and **8a** or **8b**, respectively. Ethylboroxine and 6-deoxy-2,3-*O*-isopropylidene-L-mannofuranose (**9**) react to give the 1,5-ethylboranediyl derivative **10** in high yield. The hydride numbers (HZ) of 1 H_2O, **3a**, **4**, **5**, **7**, **8a**, and **9** were determined using propyldiborane(6).

Previous investigations[2–5] on the structures and properties of *O*-ethylboranediyl derivatives of some polyhydroxy compounds have shown that they are sometimes attractive alternatives to conventionally protected compounds for regioselective transformations to the O derivatives. The ease of introduction and removal of the *O*-ethylboranediyl protective group has been illustrated with xylitol,[2] D-mannitol,[3] dulcitol,[4] and several methyl glycosides.[5] In our previous publication with some methyl glycosides as model compounds, no ring isomerization could occur. The present study on the *O*-ethylboranediyl derivatives of 6-deoxy-L-mannopyranose (L-rhamnose) (1) shows that facile pyranose/furanose isomerizations and anomerizations can occur with the *O*-ethylboranediyl derivatives of the free monosaccharides.

Results and Discussion

A. The Indirect O-Ethylboranediylation of 1. The O-diethylborylation of the crystalline 6-deoxy-α-L-mannopyranose monohydrate[6] (1·H_2O) with activated triethylborane[7] at room temperature gives 6-deoxy-1,2,3,4-tetrakis-*O*-

Scheme I



b = BEt_2

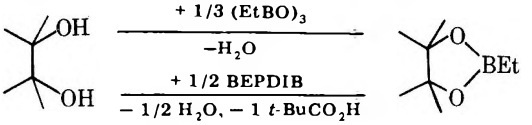
BEt_3* = activated triethylborane

diethylboryl-α-L-mannopyranose (**2a**) in 94% yield. Small amounts (<4%) of the corresponding β isomer (**2b**) can be detected by ^1H NMR measurements (see part E). No per-*O*-diethylborylated 6-deoxy-L-mannofuranoses are formed.

Addition of ethyldiborane(6)[8] to **2a** at room temperature causes the elimination of ca. 1 mol of triethylborane from this compound. However, a mixture of five isomers is obtained on distillation. 6-Deoxy-1,5-bis-*O*-diethylboryl-2,3-*O*-ethylboranediyl-α-L-mannofuranose (**3a**) is the major component (~60%). The other four isomers, which are obtained in equal ratios, include the β-rhamnofuranose derivative **3b**, the α,β-rhamnopyranoses **3c** and **3d**, and 6-deoxy-1,2:3,5-bis-*O*-ethylboranediyl-β-L-mannofuranose (**4**)[16a,b] (see Scheme I). The distilled mixture is obtained in about 70% yield. A residue remains after distillation, which must consist essentially of compounds with intermolecular *O*-ethylboranediyl groups.

The introduction of *O*-ethylboranediyl groups into several methyl glycosides[5] and polyalcohols[2-4] by per-O-diethylborylation and subsequent thermal or >BH-catalyzed triethylborane eliminations is, therefore, a useful alternative route; however, this indirect procedure is not suitable for free monosaccharides as mixtures of anomers and ring isomers are formed. A further disadvantage is that reduction of the carbonyl group can take place at temperature above 80 °C.

B. The Direct Routes to the *O*-Ethylboranediyl Derivatives of 1. The *O*-ethylboranediyl derivatives of monosaccharides are best prepared by direct routes from the free



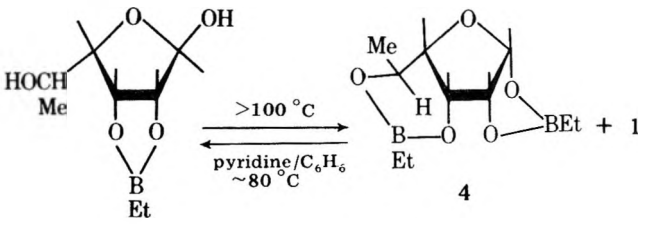
sugars with reagents such as ethylboroxine or bis(ethylpivaloyloxy)diboroxane (BEPDIB).[3-5] Water is formed on reaction of ethyl boroxine with polyhydroxy compounds, whereas pivalic acid and water are formed when BEPDIB is used (see Scheme I).

The presence of water no doubt facilitates anomerization and ring isomerization and hence pure products are generally not obtained. We have found that in certain cases water elimination can occur to give unsaturated derivatives on reaction with ethylboroxine.[17] This observation was not made with BEPDIB. The latter reagent is, however, not as readily accessible as ethylboroxine. The choice of the best reagent,

therefore, depends on the particular substrate.

6-Deoxy-2,3-O-ethylboranediyl-α-L-mannofuranose (**5**) can be prepared in three ways (see Scheme I). The reaction of anhydrous **1** with ethylboroxine in the molar ratio 1:0.33 gives **5** in 95% yield (route I). **5** is also obtained in 98% yield by reaction of 0.5 mol of bis(ethylpivaloyloxy)diboroxane (BEPDIB) with 1 mol of **1** at room temperature (route II).[16a,b] Route III involves treatment of **4** with methanol at room temperature. Partial deboronation and an intramolecular transesterification occur to give **5** in 99% yield.[16a,b]

The viscous liquid **5** disproportionates during vacuum distillation to give **4** and **1**, which is obtained as residue. Heating **1** and **4** to 80 °C in the presence of pyridine as solvent



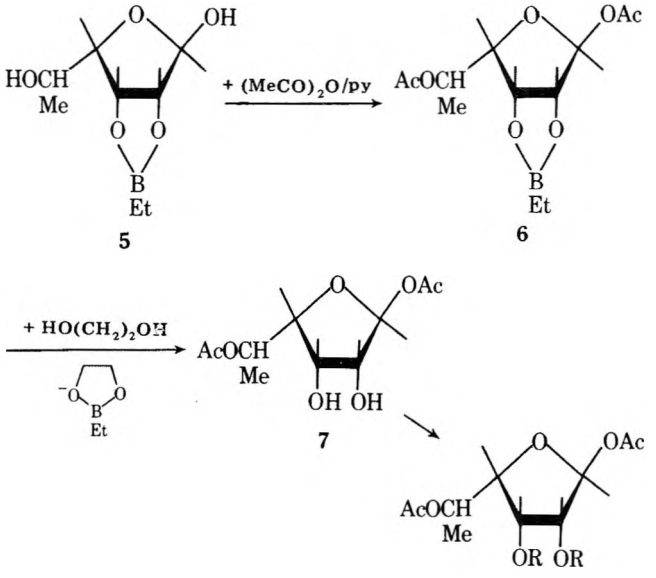
gives **5** in 98% yield. In contrast, the 6-deoxy-2,3-O-isopropylidene-α-L-mannofuranose (**9**)[9,10] can be vacuum distilled without any disproportionation[10] occurring.

5 reacts with activated triethylborane[7,11] at room temperature to give **3a**. This colorless liquid with bp 92–95 °C (10^{-3} Torr) can be selectively de-O-diethylborylated by addition of methanol at room temperature. **5** is obtained in 98% yield.

Isomerically pure **4** can be isolated as vacuum distillable liquid using the three routes IV–VI (see Scheme I). Reaction of **1** with ethylboroxine in the molar ratio 1:≥0.67 (route IV) gives **4** in 92% yield, and in 96% yield by reaction of **1** with BEPDIB in the molar ratio 1:≥1 (route V). It may also be prepared in 92% yield by reaction of **5** with ethylboroxine (route VI).

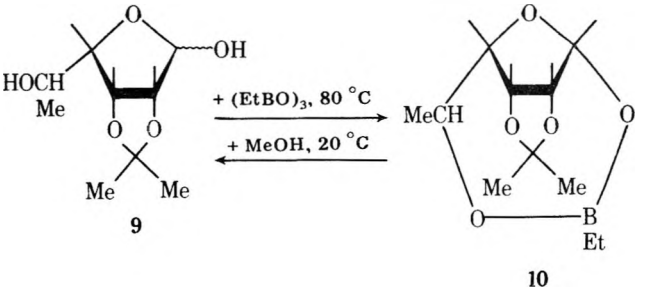
C. Regioselective O-Acylation of 1. O-Acetylation of **5** by normal simple procedure gives the vacuum distillable 6-deoxy-1,5-di-O-acetyl-2,3-O-ethylboranediyl-α-L-mannofuranose (**6**) in 93% yield (see Scheme II).[16a,b] The total deboronation of **6** requires several treatments with hot ethane-1,2-diol. Crystalline 6-deoxy-1,5-di-O-acetyl-α-L-mannofuranose (**7**) is obtained in 75% yield. Further O-acetylation

Scheme II



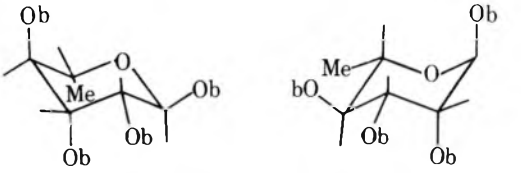
yields tetra-O-acetyl-6-deoxy-α-L-mannofuranose (**8a**). **7** can also be O-benzoylated to give pure 6-deoxy-1,5-di-O-acetyl-2,3-di-O-benzoyl-α-L-mannofuranose (**8b**) in 69% yield.

D. 6-Deoxy-2,3-O-isopropylidene-L-mannose (9) with Ethylboroxine. Reaction of 6-deoxy-2,3-O-isopropylidene-L-mannofuranose (**9**)[9,10] with ethylboroxine gives 6-deoxy-1,5-O-ethylboranediyl-2,3-O-isopropylidene-β-L-mannofuranose (**10**) as a vacuum distillable product. The facile deboronation of **10** under mild conditions with methanol at room temperature gives **9** in 96% yield. Although several structures



are possible, it is evident that **10** has the proposed structure with a seven-membered ring. A quantitative intramolecular transesterification of the 2,3-O-isopropylidene group can be ruled out under the mild, neutral conditions of methanolysis.

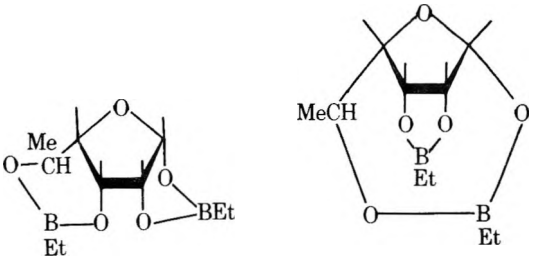
E. Determination of the Structures of 2, 3a, 4, 5 and 10. Structure of 2a. The ^1H NMR spectrum of **2a** shows that it is contaminated with <4% of the β isomer **2b**. It is fully consistent with the pyranose assignment because $J_{3,4}$ = 9 Hz and not 3.5–5 Hz as for furanose forms. The H^1H^2 coupling con-



b = BEt_2

stant (1 Hz) rules out an axial–axial relationship and a C1 conformation. The observed H^4H^5 coupling constant (9 Hz) clearly demonstrates an axial–axial coupling constant as required by the 1C conformation. The coupling constants are very similar to those found for methyl 6-deoxy-2,3,4-tri-O-acetyl-α-L-mannopyranoside,[12] which also adopts the 1C conformation.

Structure of 4. The combination of the B, B_C, and H^+ determinations of **4** show that this derivative contains two O-ethylboranediyl rings and no free hydroxy groups. In the ^{13}C NMR spectrum the C^1 signal lies at δ = 105 ppm, which is in the characteristic range for the furanose forms of monosaccharides.[26] **4** can, therefore, only have either structure A or B.



As both of these possible structures contain one five-membered 1,3,2-dioxaborolane ring and one larger boron ring (a 6- and a 7-ring, respectively, for A and B), it is not possible

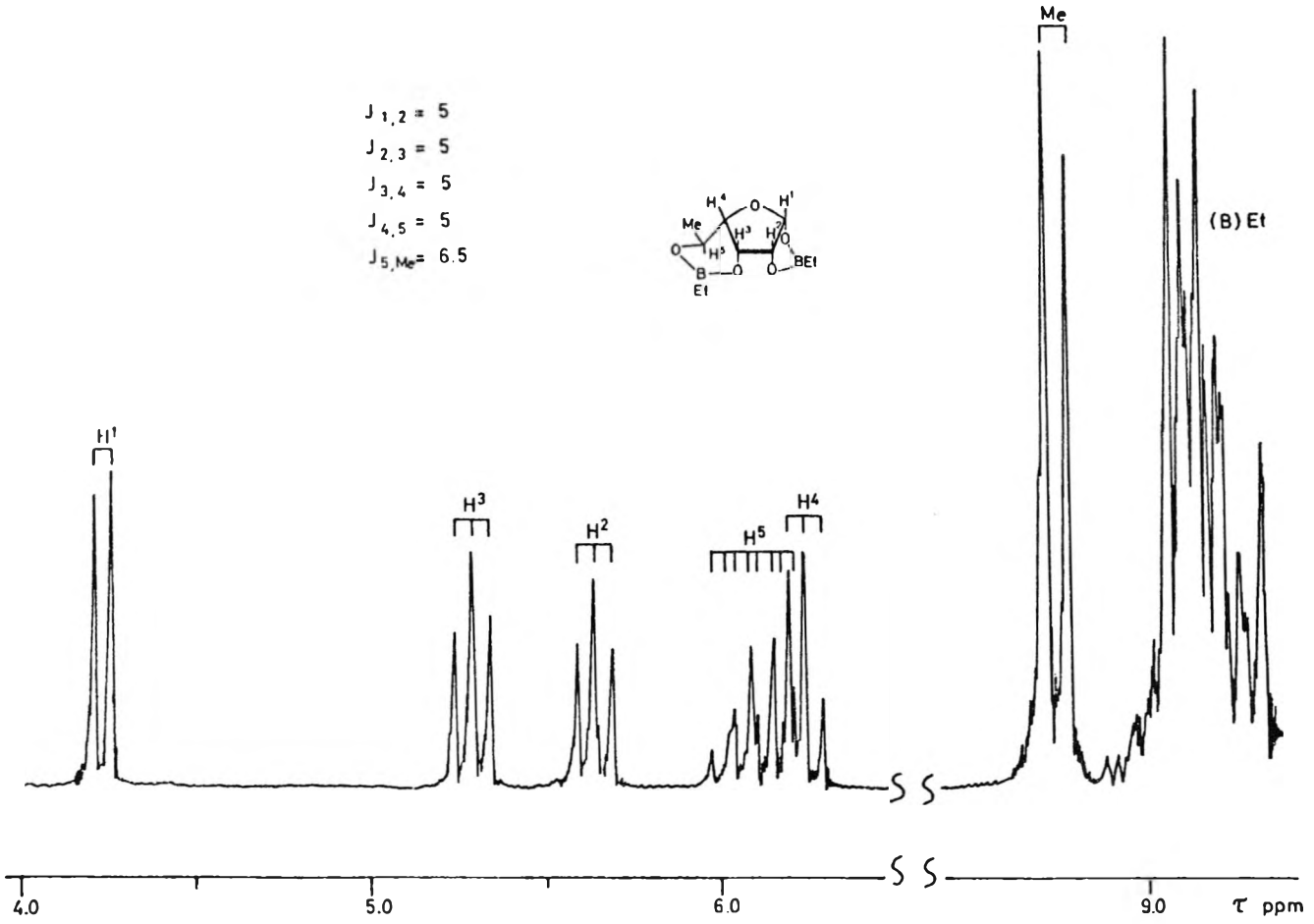


Figure 1. The 100-MHz ^{1}H NMR spectrum of 6-deoxy-1,2:3,5-bis-*O*-ethylboranediyl-β-L-mannofuranose (**4**) in CCl_4.

to differentiate between these alternatives using ^{11}B NMR, because only the boron in a five-membered ring gives rise to a signal at $\delta \sim 34.5$[13] and the six and higher membered rings have signals at $\delta \sim 31$. The structure was ascertained by comparing the ^{1}H NMR spectra of **4** (Figure 1) and **10.** As the ^{1}H NMR spectra of **9** and **5** are very similar, one would expect the spectrum of **10** to bear a close resemblance to that of its bisboron analogue (B), as both contain a seven-membered boron ring. This is, however, not the case (see Experimental Section, parts C and E). The correct structure, therefore, is A.

Structures of 5 and 3a. The presence of two hydroxy groups in **5** was confirmed gas volumetrically by reaction with activated triethylborane[7,11] to give **3a.** The B and B_C values are also in accord with a mono-*O*-ethylboranediyl derivative of **1.**

In the ^{1}H NMR spectrum of **5** in Me_2SO-d_6 a low-field doublet is observed at τ 3.60 ppm with $J_{1,OH}$ = 4.5 Hz. As this signal is indicative of a free anomeric hydroxy group,[14] possible structures containing a 1,2-*O*-ethylboranediyl group can be ruled out. The characteristic coupling constants in the ^{1}H NMR spectrum of **5** are always found when a 1,3,2-dioxaborolane ring is fused to a furanose sugar ring with C^2 and C^3.[17]

The ^{1}H NMR spectrum bears a close resemblance to those of 2,3-*O*-isopropylidene-L-erythrose[15] and 5-aldo-D-lyxofuranose 2,3-*O*-carbonate,[15] in which the only type of fused ring system possible is one that contains two five-membered rings. These ^{1}H NMR spectra, in turn, bear a strong similarity in general spectral characteristics to those of D-mannofuranose 2,3-carbonate,[15] 2,3-*O*-ethylboranediyl-α-D-mannofuranose,[16] 6-deoxy-2,3-*O*-isopropylidene-L-mannofuranose,[15] 2,3-*O*-ethylboranediyl-α-D-lyxofuranose,[17] and D-lyxofuranose 2,3-carbonate.[18]

Thus, the kind of bicyclic structure which is present in all of these compounds, i.e., a five-membered ring fused to the furanose form of the sugar ring, must be substantially more stable than the form in which the five-membered ring is fused to a pyranose sugar ring. Although the assignment of peaks to H^1 and H^3 in the ^{1}H NMR spectrum of **5** is unproblematic, H^4 and H^5 give rise to a rather complex overlapping multiplet. It is convenient to convert **5** to **3a,** as its spectrum allows an unequivocal assignment to be made of all the protons (see Figure 2). The O-diethylborylation to **3a** causes a downfield shift of the signals for H^1 and H^5 and hence they are separated from other signals.

The ^{13}C NMR spectrum of **5** is also consistent with the furanose assignment. The signals at δ 80.0, 83.3, and 85.6 fall in a range which is characteristic for ethylboranediylfuranose derivatives of sugars.[17] The absence of notable peaks, beside the seven signals observed, provides further evidence for a relatively high degree of purity of **5.**

The ^{11}B NMR spectrum of **3a** confirms the presence of a five-membered 1,3,2-dioxaborolane ring,[13] higher membered rings having signals at $\delta \sim 30$.

Structure of 10. Proof for the structural assignment is given by the fact that the high yield deboronation of **10** gives **9.**

The ^{1}H NMR spectrum of **10** shows some interesting features. The signal assigned to H^3 is observed as a triplet of doublets at τ 5.35. The additional splitting is due to long-range coupling between H^3 and H^5 ($J_{3,5}$ = 1.5 Hz). The four bonds involved must, therefore, be in the so-called "W conformation" [19] with $\angle H^4H^5 \sim 90°$.

F. Hydride Values (HZ)[20] of 1·H_2O, 3a, 4, 5, 7, 8a, and 9. The 6-deoxy-L-mannose derivatives were further characterized by their so-called hydride numbers (HZ). The HZ of a compound is the number of >BH equivalents consumed, per

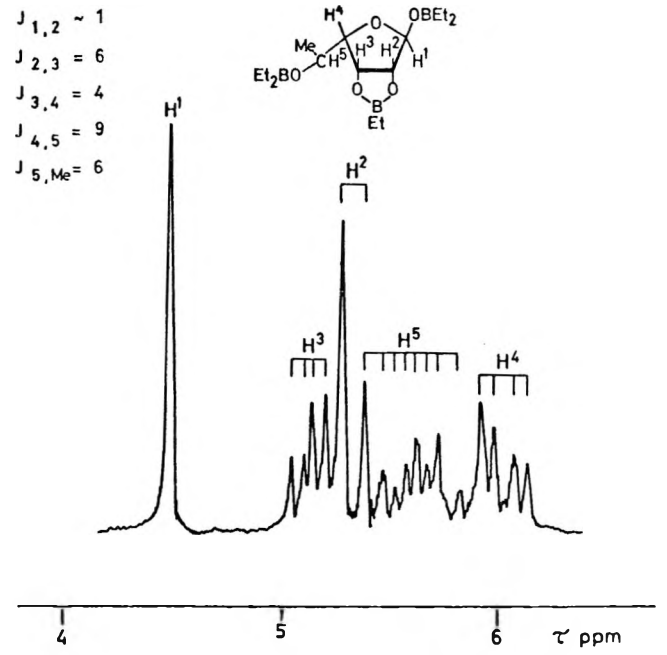


Figure 2. Ring proton region in the 60-MHz ^1H NMR spectrum of 6-deoxy-1,5-bis-*O*-diethylboryl-2,3-*O*-ethylboranediyl-α-L-mannofuranose (**3a**) in CCl_4.

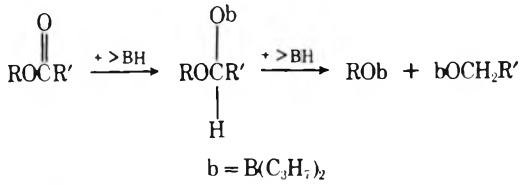
mole of compound, on reaction with an excess of propyldiborane(6) at 130 °C. This HZ consists of the two parts HZ_{gas} and HZ_{red}:

$$HZ_{gas} = \frac{\text{mol of } H_2 \text{ evolved}}{\text{mol of compd}} \text{ (O-dipropylborylation)}$$

$$HZ_{red} = \frac{\text{mol of BH reducing}}{\text{mol of compd}} \text{ (hydroboration)}$$

The values found using propyldiboranes(6), having hydride contents of 10–15% H^-, at 130 °C for ca. 3 h are listed in Table I. It is evident from the HZ_{red} values listed in Table I that all the compounds are quantitatively reduced to derivatives of 6-deoxy-L-mannitol.

The *O*-acyl containing derivatives **7** and **8a** have HZ_{red} = 5 and 9, respectively. This shows that, in addition to the sugar reduction, each *O*-acyl function reacts with exactly two >BH equivalents.



This method can be used to accurately determine *O*-acyl groups in a molecule and to deacylate *O*-acyl derivatives preparatively.[20]

G. Comparison of *O*-Ethylboranediyl with *O*-Isopropylidene Derivatives. At first, there appears to be close analogy between *O*-isopropylidene and *O*-ethylboranediyl derivatives. A closer critical comparison, however, reveals notable differences between these protective groups. Thus, for example, treatment of **1** with a 50- to 100-fold excess of acetone only results in the formation of 6-deoxy-2,3-*O*-isopropylidene-L-mannofuranose (**9**) in 50–68% yield.[9,10,21] The *O*-ethylboranediyl analogue **5**, on the other hand, is obtained in >95% yield by stoichiometric reaction of **1** with either BEPDIB or ethylboroxine. Addition of more BEPDIB or ethylboroxine immediately results in formation of the compound **4**. Yields of **4** and **5** are excellent, whereas only a moderate yield (65%) of **9** is obtained. This fact clearly demonstrates the versatility of the *O*-ethylboranediyl protective group, which is also capable of forming both intra- and intermolecular[2,16] linkages in yield of over 90%.

Table I. Hydride Numbers (HZ)[20] of the 6-Deoxy-L-mannose Derivatives (See Table II)

Compd	Registry no.	HZ_{gas}	HZ_{red}	HZ
1·H_2O	3615-41-6	6	1	7
3a	62930-51-2	0	1	1
4	62930-52-3	0	1	1
5	62930-53-4	2	1	3
7	62930-54-5	2	5	7
8a	62930-55-6	0	9	9
9	4926-05-0	2	1	3

Table II. Hydride Numbers (HZ)[20] of O-Derivatives of 6-Deoxy-L-mannose (1)

Compd no.	mg	mmol	>BH(H_2), mmol	$>BH_{red}$, mmol	$>BH_{total}$, mmol	HZ_{obsd}
1·H_2O	179.2	0.98	6.0	0.93	6.93	7.07
3a	300.3	0.89	0	0.93	0.93	1.04
4	260.5	1.09	0	1.13	1.13	1.04
5	315.2	1.56	3.2	1.69	4.89	3.13
7	403.9	1.73	3.48	9.0	12.48	7.21
8a	357.1	1.075	0	9.9	9.9	9.21
9	202.1	0.99	2.16	1.0	3.16	3.13

A further, possibly more important, factor is that the *O*-ethylboranediyl group can be removed under mild, neutral conditions. Whereas both 1,5-di-*O*-benzoyl-[10] and 1,5-di-*O*-methyl-2,3-*O*-isopropylidene-L-rhamnofuranose[22] can be prepared, the removal of the *O*-isopropylidene protective group requires acidic conditions and hence the 1,5-O-derivatives are not obtained. Instead, the labile O^1 substituents are lost and one obtains 5-*O*-benzoyl-[10] and 5-*O*-methyl-L-rhamnofuranose.[22] As *O*-acetyl groups are less stable toward acids than either *O*-benzoyl or *O*-methyl groups, it is noteworthy that 1,5-di-*O*-acetyl-α-L-rhamnofuranose (**7**) is obtained in good yield. This demonstrates the advantage of having a protective group, which can be removed under mild conditions.

Experimental Section

General. All experiments were carried out in dry, deoxygenated solvents under an atmosphere of argon.

Analyses. The purity of **4** and **6** was determined gas chromatographically[23] with a Carlo Erba (50-m column, OV 101). The ^1H NMR[24] and mass spectra[25] were obtained using the Varian A-60 or HA-100 and Varian MAT CH5 spectrometers, respectively. ^{13}C NMR spectra[26] were recorded at 25.2 MHz using a Varian XL-100-15 spectrometer with Me_4Si as an internal standard (deshielding $\delta > 0$). ^{11}B NMR spectra[26] were obtained with the latter instrument at 32.1 MHz with Et_2O–BF_3 as an external standard (deshielding $\delta > 0$). Optical rotations were measured using a OLD 5 from Carl Zeiss. Boron was determined by flame photometry of methanol solutions with a M4QIII. The B_C values were obtained using anhydrous trimethylamine *N*-oxide in boiling benzene.[27] C,H analyses were carried out by Dornis and Kolbe, Mülheim-Ruhr. The hydroxy groups were determined using activated triethylborane.[7,13]

Reagents. 6-Deoxy-L-mannose (**1**) was obtained from the monohydrate (Senn Chemicals, Switzerland) (found HZ = 7.1, see Table II) by dehydration in vacuo at 100 °C. 6-Deoxy-2,3-*O*-isopropylidene-L-mannose (**9**) was prepared by the acid-catalyzed condensation of **1** with acetone.[10,21] Triethylborane,[28] diethylboryl pivalate,[7] bis(ethylpivaloyloxy)diboroxane,[7,29] and ethylboroxine[30] have been synthesized in our pilot plant and laboratory, respectively.

Preparation. A. Ethylboroxine (from triethylborane and diboron trioxide). Triethylborane (147 g, 1.5 mol) was added to anhydrous diboron trioxide (70 g, 1 mol) in an autoclave and the mixture was heated, with rolling, to 250 °C for 5 h. The autoclave was allowed to cool to room temperature and the contents were siphoned out by means of argon pressure. After distilling off the triethylborane in

vacuo, bp <25 °C (12 Torr), ethylboroxine (160 g, 95%) was obtained as a colorless liquid: bp 55 °C (12 Torr); ^{1}H NMR (60 MHz, neat) τ 9.16 (m).

Anal. Calcd for $C_6H_{15}B_3O_3$ (168.0): B, 19.3; B_C, 6.43. Found: B, 19.0; B_C, 6.39.

B. 6-Deoxy-1,2,3,4-tetrakis-*O*-diethylboryl-α-L-mannopyranose (2a). From 1·H$_2$O with Activated Triethylborane. Triethylborane (64.4 g, 0.66 mol), activated by 0.5 mL of diethylboryl pivalate, is added dropwise (3 h) to 1·H$_2$O (20 g, 0.11 mol) in heptane (100 mL). Ethane (14.9 nL) is evolved. The heptane is removed in vacuo to give **2a** (47 g, 98%) as colorless liquid residue: MS (70 eV) no M$^+$, found *m/e* 407 (B_4, rel intensity ~1), 351 (B_3, 15), 253 (B_2, 17), 209 (B_2, 42), 83 (B_0, 100); ^{1}H NMR (100 MHz, neat) τ 4.70 (d, $J_{1,2}$ ~ 1 Hz, H^1), 5.35 (dd, $J_{2,3}$ = 2.5, $J_{3,4}$ = 9 Hz, H^3), [5.65 (t, $J_{3,4}$ = 9, $J_{4,5}$ = 9 Hz, H^4), 5.69 (dd, $J_{1,2}$ = 1, $J_{2,3}$ = 2.5 Hz, H^2)], 6.08 (dq, $J_{4,5}$ = 9, $J_{5,Me}$ = 6 Hz, H^5), 8.85 (d, $J_{5,Me}$ = 6 Hz, CMe), 9.13 (m, BEt) in the ratio 1:1:2:1:3:40, small signal at 4.95 (br s, H^1 of **2b**).

Anal. Calcd. for $C_{22}H_{48}B_4O_5$ (435.9): B, 9.92; B_C, 6.6. Found: B, 9.95; B_C, 6.41.

With Ethyldiborane(6) (elimination of triethylborane). A mixture of **2a** (16.3 g, 37.4 mmol) and ethyldiborane (2 g, 25.56‰ H$^-$, 52.1 mmol) is stirred for 3 h at room temperature. All volatile components are then removed in vacuo and further distillation yielded a mixture (8.8 g) with bp 90 °C (10^{-3} Torr) consisting of ~60% **3a**, 10% **4**, and equal amounts of three further isomers **3b–d** (^{1}H NMR). Viscous residue (3.9 g) remained after the distillation: ^{1}H NMR (100 MHz, CCl_4) τ 4.24 (d, $J_{1,2}$ = 5 Hz, H^1 of **4**), 4.38 (br s, H^1 **3a**), 4.50 (br s, H^1 **3b**), 4.70 (br s, H^1 **3d**), 4.99 (br s, H^1 **3c**), 5.2–6.3 (m), 8.77 (d, $J_{5,Me}$ = 6 Hz, CMe), 9.10 (m, BEt) in the ratio 0.1:0.1:0.6:0.1:0.1:5:3.3:23.7.

C. *O*-Ethylboron Derivatives 3a, 4, and 5. 6-Deoxy-1,5-bis-*O*-diethylboryl-2,3-*O*-ethylboranediyl-α-L-mannofuranose (3a). From 5 with Activated Triethylborane. Triethylborane (10.5 g, 107 mmol), which was activated by 0.1 mL of diethylboryl pivalate, was added dropwise (40 min) to **5** (5.7 g, 28.2 mmol) in heptane (20 mL). Ethane (1.3 nL) was evolved. The excess triethylborane and heptane were removed in vacuo and the residue was distilled to give colorless **3a** (8.4 g, 88%): bp 92–95 °C (10^{-3} Torr); $[\alpha]^{20}_D$ −1.8° (*c* 4, CCl_4); ^{1}H NMR (100 MHz, CCl_4) (Figure 2) τ 4.53 (s, $J_{1,2}$ = 1 Hz, H^1), 5.17 (dd, $J_{2,3}$ = 6, $J_{3,4}$ = 4 Hz, H^3), 5.36 (d, $J_{2,3}$ = 6 Hz, H^2), 5.65 (dq, $J_{4,5}$ = 9, $J_{5,Me}$ = 6 Hz, H^5), 6.06 (dd, $J_{3,4}$ = 4, $J_{4,5}$ = 9 Hz, H^4), 8.76 (d, $J_{5,Me}$ = 6 Hz, C^5$_{Me}$), 9.10 (m, BEt) in the ratio 1:1:1:1:1:3:25; ^{11}B NMR (CH_3CN) δ 35.2 ± 1 (half-width ~ 750 Hz), 54.1 ± 1 ppm (half-width ~ 600 Hz) in the ratio 1:2.

Anal. Calcd for $C_{16}H_{33}B_3O_5$ (337.8): B, 9.60; B_C, 5.33. Found: B, 9.45; B_C, 5.20; HZ^{20} = 1.04.

With Methanol. Methanol (5 mL) is added dropwise in 3 min to a solution of **3a** (3.4 g, 10.1 mmol) in hexane (20 mL). After removal of the volatile components in vacuo (12 Torr) **5** (2 g, 98%) was obtained as residue.

6-Deoxy-1,2:3,5-bis-*O*-ethylboranediyl-β-L-mannofuranose (4). Route IV (1 and ethylboroxine in the ratio 3:2). Ethylboroxine (5.3 g, 31.5 mmol) was added to a stirred suspension of **1** (4.1 g, 25 mmol) in benzene (25 mL) and the benzene/water azeotrope was distilled off. The remaining benzene was removed in vacuo and **4** (5.4 g, 92%), bp 76–78 °C (10^{-3} Torr), was obtained.

Route V (1 and BEPDIB in the ratio 1:1). A solution of BEPDIB (7.4 g, 24.8 mmol) in benzene (15 mL) was added dropwise to a stirred solution of **1** (4.1 g, 25 mmol) in pyridine (10 mL) in 10 min at room temperature. The volatile components were removed in vacuo and after distillation of the residue colorless **4** (5.7 g, 96%) 99% pure (GLC) was obtained: bp 77–78 °C (10^{-3} Torr); $[\alpha]^{20}_D$ −10.2° (*c* 2.9, CCl_4).

Route VI (5 and ethylboroxine). Ethylboroxine (3 g, 20.2 mmol) was added to **5** (4.4 g, 21.8 mmol) in benzene (20 mL) and the benzene/water azeotrope was distilled off. After removal of the remaining benzene in vacuo, **4** (4.8 g, 92%) was obtained; bp 75 °C (10^{-3} Torr); MS (70 eV) M$^+$ 240 (B_2, rel intensity ~1), 167 (B_2, 17), 140 (B_1, 32), 111 (B_1, 100); ^{1}H NMR (100 MHz, CCl_4) (Figure 1) τ 4.24 (d, $J_{1,2}$ = 5 Hz, H^1), 5.30 (t, $J_{1,2}$ = 5, $J_{2,3}$ = 5 Hz, H^3), 5.65 (t, $J_{2,3}$ = 5, $J_{3,4}$ = 5 Hz, H^2), 6.09 (oct, $J_{4,5}$ = 5, $J_{5,Me}$ = 6.5 Hz, H^5), 6.25 (t, $J_{3,4}$ = 5, $J_{4,5}$ = 5 Hz, H^4), 8.73 (d, $J_{5,Me}$ = 6.5 Hz, Me), 9.1 (m, BEt) in the ratio 1:1:1:1:3:10; ^{13}C NMR (Me_2SO-d_6) δ 105.0 (C^1), 68.3 (C^2), 80.7 (C^3), 78.7 (C^4), 66.9 (C^5), 20.7 (CH_3), 2.9 (BCH_2CH_3), 7.73 and 7.47 (BCH_2CH_3).

Anal. Calcd for $C_{10}H_{18}B_2O_5$ (239.9): B, 9.01; B_C, 3.00. Found: B, 8.90; B_C, 2.97; HZ^{20} = 1.04.

6-Deoxy-2,3-*O*-ethylboranediyl-α-L-mannofuranose (5). Route I (1 and ethylboroxine in the ratio 3:1). Ethylboroxine (7.1 g, 42.3 mmol) was added to a stirred suspension of **1** (20.8 g, 126.7 mmol) in benzene (70 mL) and the benzene/water azeotropic mixture was distilled off. The remaining benzene was removed in vacuo, leaving **5** (24.4 g, 95%) as residue.

Route II (1 and BEPDIB in the ratio 2:1). A solution of BEPDIB (4.9 g, 16.4 mmol) in benzene (20 mL) was added dropwise to a stirred solution of **1** (5.4 g, 32.8 mmol) in pyridine (20 mL) at room temperature. The reaction mixture was concentrated in vacuo to give **5** (6.4 g, 98%) as residue, $[\alpha]^{20}_D$ 4.7° (*c* 7, Me_2SO).

Route III (5 from 4 with methanol). Three portions of a methanol/hexane mixture (~10 mL, 1:1 mixture) were added to **4** (3.6 g, 15 mmol) and after stirring for 10 min at room temperature the dimethoxyethylborane, methanol, and hexane mixtures (6.5 g with 1.23% B, 5.8 g with 0.68% B, and 6.6 g with 0.53% B) were removed in vacuo (12 Torr). **5** (3 g, 99%) was obtained as a residue: ^{1}H NMR (100 MHz, Me_2SO-d_6) τ 3.60 (d, $J_{1,OH}$ = 4.5 Hz, C^{1}OH), 4.83 (d, $J_{1,OH}$ = 4.5 Hz, H^1), 5.07 (dd, $J_{2,3}$ = 6, $J_{3,4}$ = 4 Hz, H^3), 5.39 (d, $J_{2,3}$ = 6 Hz, H^2). 5.4–6.4 (m, H^{4}H^5, C^5$_{OH}$), 8.83 (d, $J_{5,Me}$ = 5.5 Hz, C^5$_{Me}$), 9.1 (m, BEt) in the ratio 1:1:2:3:3:5; ^{13}C NMR (Me_2SO-d_6) δ 21.2 (Me), 63.3, 80.0, 83.3, 85.6, 100.7 (C^1), 7.6 (BCH_2CH_3), 1.7 (BCH_2CH_3).

Anal. Calcd for $C_8H_{15}BO_5$ (202.0): B, 5.35; B_C, 1.78; H$^+$, 0.99. Found: B, 5.26; B_C, 1.80; H$^+$, 1.05; HZ^{20} = 3.1.

Pyrolysis of 5 to 1 and 4 (conversion ~43%). 1a (4.8 g, 23.8 mmol) was heated to 130 °C (bath temp) in vacuo (10^{-3} Torr) and a mixture of **5** and **4**, 2.6 g with 0.57% H$^+$, 57% **5**, and 43% **4** conversion (^{1}H NMR) with bp 58–65 °C (10^{-3} Torr), distilled over. Crude **1** (1.0 g, 51% with 2.25% H$^+$) was obtained as a residue.

5 from 1 and 4. A mixture of **1** (1.2 g, 7.1 mmol) and **4** (1.7 g, 7.1 mmol) was dissolved in a benzene (10 mL)/pyridine (5 mL) mixture by heating to 80 °C for 10 min. The solvents were removed in vacuo, leaving **5** (2.8 g, 98%) as residue (^{1}H NMR).

D. O-Acylation of 5. 6-Deoxy-1,5-di-*O*-acetyl-2,3-*O*-ethylboranediyl-α-L-mannofuranose (6). Acetic anhydride (20 mL) was added dropwise in 40 min to a stirred solution of **5** (5.8 g, 28.7 mmol) in pyridine (20 mL) at 0 °C. The mixture was stirred for 20 min at room temperature and concentrated in vacuo. Distillation yielded 89% (GLC) **6** (7.6 g, 93%): bp 106 °C (10^{-3} Torr); $[\alpha]^{20}_D$ 59.2° (*c* 2.3, CCl_4); ^{1}H NMR (100 MHz, CCl_4) τ 3.93 (s, $J_{1,2}$ ~ 1 Hz, H^1), 5.0 (m, $J_{4,5}$ = 7.5, $J_{5,Me}$ = 6 Hz, H^5), 5.12 (dd, $J_{2,3}$ = 6, $J_{3,4}$ = 4 Hz, H^3), 5.28 (d, $J_{2,3}$ = 6 Hz, H^2) 6.00 (dd, $J_{4,5}$ = 7.5, $J_{3,4}$ = 4 Hz, H^4), 7.99 (s, C^{5}OAc), 8.03 (s, C^{1}OAc), 8.72 (d, $J_{5,Me}$ = 6 Hz, C^{5}Me), 9.15 (m, BEt) in the ratio 1:2:1:1:6:3:5.

Anal. Calcd for $C_{12}H_{19}BO_7$ (286.1): B_C, 1.26. Found: B_C, 1.21.

6-Deoxy-1,5-di-*O*-acetyl-α-L-mannofuranose (7). 7 from 6 with Ethane-1,2-diol. Ethane-1,2-diol (ca. 5 mL) was added twice to **6** (1.7 g, 5.9 mmol) and the mixture was evaporated to dryness in vacuo (10^{-3} Torr). Crude **4** (1.1 g, 75%), mp 85 °C, was obtained. Pure **7** is obtained after recrystallization from ethanol: mp 127 °C; $[\alpha]^{20}_D$ −80° (*c* 1, Me_2SO); ^{1}H NMR (60 MHz, Me_2SO-d_6) τ 4.09 (d, $J_{1,2}$ = 2 Hz, H^1), 4.8–5.1 (m), 5.9 (m), 6.3–6.7 (m), 7.95 (s, OAc), 8.02 (s, OAc), 8.81 (d, $J_{5,Me}$ = 6.5 Hz) in the ratio 1:2:3:1:3:3:3.

Anal. Calcd for $C_{10}H_{16}O_7$ (248.2): C, 48.39; H, 6.50; H$^+$, 0.81. Found: C, 48.42; H, 6.47; H$^+$, 0.83; HZ^{20} = 7.2.

6-Deoxytetra-*O*-acetyl-α-L-mannofuranose (8a). From 4 with Acetic Anhydride. Acetic anhydride (5 mL) was added dropwise to **7** (0.5 g, 2 mmol) in pyridine (5 mL) at room temperature. The mixture was left overnight and the pyridine and acetic anhydride were removed in vacuo (10^{-3} Torr). The residue was crystallized by dissolving in ethanol (3 mL) and cooling to 0 °C and pure (GLC) **8a** (0.4 g, 60%) was obtained by filtration and drying in vacuo: mp 53 °C, $[\alpha]^{20}_D$ −101.7° (*c* 0.7, C_2H_5OH); MS (70 eV) no M$^+$, found *m/e* 273 (rel intensity 2), 245 (2), 170 (7), 157 (3), 143 (8), 43 (100); ^{1}H NMR (100 MHz, $CDCl_3$) τ 3.77 (d, $J_{1,2}$ = 3.5 Hz, H^1), 4.38 (dd, $J_{2,3}$ = 5, $J_{3,4}$ = 4 Hz, H^3), 4.63 (dd, $J_{1,2}$ = 3.5, $J_{2,3}$ = 5 Hz, H^2), 4.86 (dq, $J_{4,5}$ = 9, $J_{5,Me}$ = 6 Hz, H^5), 5.75 (dd, $J_{3,4}$ = 4, $J_{4,5}$ = 9 Hz, H^4), 7.91 (s, OAc), 7.95 (s, 2 OAc), 8.03 (s, OAc), 8.68 (d, $J_{5,Me}$ = 6 Hz, C^5$_{Me}$) in the ratio 1:1:1:1:9:3:3.

Anal. Calcd for $C_{14}H_{20}O_9$ (332.3): C, 50.60; H, 6.07. Found: C, 50.90; H, 6.13; HZ^{20} = 9.2.

6-Deoxy-1,5-di-*O*-acetyl-2,3-di-*O*-benzoyl-α-L-mannofuranose (8b). From 7 with Benzoyl Chloride. Benzoyl chloride (2.4 g, 16.8 mmol) was added dropwise in 15 min to a stirred solution of **7** (1.9 g, 7.66 mmol) in pyridine (5 mL) at 0 °C. The mixture was then stirred for 2 h at room temperature. Water (20 mL) was added and the product was extracted with diethyl ether (two 20-mL portions). Pure needles of **8b** (2.4 g, 69%) were obtained after filtration and vacuum drying: mp 158 °C, $[\alpha]^{20}_D$ −41.8° (*c* 1.6, $CHCl_3$); ^{1}H NMR (100 MHz, $CDCl_3$) τ [2.13 (m), 2.65 (m), COPh], 3.54 (d, $J_{1,2}$ = 2.5 Hz, H^1), 3.97 (dd, $J_{2,3}$ = 5.5, $J_{3,4}$ = 4.5 Hz, H^3), 4.29 (dd, $J_{1,2}$ = 2.5, $J_{2,3}$ = 5.5 Hz, H^2), 4.72 (dq, $J_{4,5}$ = 8.5, $J_{5,Me}$ = 6 Hz, H^5), 5.44 (dd, $J_{3,4}$ = 4.5, $J_{4,5}$ = 8.5 Hz, H^4), 7.88 (s, C^{1}OAc), 8.20 (s, C^{5}OAc), 8.60 (d, $J_{5,Me}$ = 6 Hz, CMe) in the ratio [4:6] 1:1:1:1:1:3:3:3.

Anal. Calcd for $C_{24}H_{24}O_9$ (456.4): C, 63.15; H, 5.30. Found: C, 63.30; H, 5.05.

E. *O*-Ethylboranediyl Derivative (10) of 6-Deoxy-2,3-isopropylidene-L-mannofuranose (9). 6-Deoxy-1,5-*O*-ethylboranediyl-2,3-*O*-isopropylidene-β-L-mannofuranose (10) from 9 and Ethylboroxine. Ethylboroxine (5 g, 16.7 mmol) was added to **9** (2.9 g, 14.2 mmol) in toluene (20 mL) and the azeotropic mixture of water/toluene was distilled off. The remaining toluene was removed in vacuo (10^{-3} Torr) and the residue was distilled to give **10** (2.6 g, 77%): bp 68 °C (10^{-3} Torr), $[\alpha]^{20}_D$ 39.7° (*c* 3.7, CCl_4); 0.8 g residue; MS (70 eV) M^+ 242 (B_1, rel intensity ~ 1), 227 (B_1, 16), 138 (B_1, 37), 111 (B_1, 100); ^1H NMR (100 MHz, CCl_4) τ 4.99 (br s, half-width = 2.5 Hz, H^1), 5.35 (ddd, $J_{2,3}$ = 7.5, $J_{3,4}$ = 3.5, $J_{3,5}$ = 1.5 Hz, H^3), 5.73 (dd, $J_{1,2}$ = 1.5, $J_{2,3}$ = 7.5, H^2), 5.75 (dq, $J_{3,5}$ = 1.5, $J_{5,Me}$ = 7, H^5), 6.00 (d, $J_{3,4}$ = 3.5 Hz, H^4), 8.55 (s, CMe), 8.65 (d, $J_{5,Me}$ = 7 Hz, $C^5{}_{Me}$), 8.70 (s, CMe), 9.16–9.34 (m, BEt) in the ratio 1:1:2:1:9:5.

Anal. Calcd for $C_{11}H_{19}BO_5$ (242.0): B, 4.47. Found: B, 4.38.

9 from 10 with Methanol. Two 5-mL portions of methanol were added to **10** (1.8 g, 7.4 mmol) and the dimethoxyethylborane/methanol mixture was removed in vacuo (0.1 Torr), leaving **9** (1.45 g, 96%) as residue: mp (from ether/hexane) 87 °C, $[\alpha]^{20}_D$ 17.8° (*c* 2.9, H_2O); found HZ^{20} = 3.19.

F. Determinations of Hydride Numbers (HZ). The hydride numbers (HZ) were obtained by heating the compounds, listed in Table II, to 130 °C for ~3 h with an excess of propyldiborane(6) having 11–15‰ H^-.[20] The volume of hydrogen, evolved after each determination, was measured after cooling to room temperature, and the excess >BH remaining after reaction was then determined volumetrically by addition of 2-ethylhexanol.

Registry No.—**2a**, 62930-56-7; **3b**, 62930-57-8; **3c**, 62930-58-9; **3d**, 62930-59-0; **6**, 62930-60-3; **8b**, 62930-61-4; **10**, 62962-24-7; ethylboroxine, 3043-60-5; triethylborane, 97-94-9; diboron trioxide, 1303-86-2; ethyldiborane, 12081-54-8; dimethoxyethylborane, 7318-82-3; ethane-1,2-diol, 107-21-1; benzoyl chloride, 98-88-4.

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Diterpenes from *Dolabella californica*

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Fourteen diterpenes have been isolated from the digestive gland of the opisthobranch mollusc *Dolabella californica*. Twelve of the diterpenes have been related through a series of chemical conversions to a compound whose structure was previously determined by x-ray analysis. The structure of the remaining compound was determined by analysis of spectroscopic data. The configurations of ten of the new diterpenes were determined by the LIS method. The compounds are all based on the dolabellane skeleton, which contains an 11-membered ring fused to a five-membered ring.

We have previously shown[1] that the digestive gland of the sea hare *Aplysia californica* contained a variety of interesting halogenated metabolites which were found to be of dietary origin.[2] Two collections of *Dolbella californica* (Sterns),[3] a related anaspidean opisthobranch mollusc, have yielded a number of diterpenes, all of which have the same novel carbon skeleton. One of the diterpenes was shown by x-ray analysis[4] to have the structure **2** and was named 10-acetoxy-18-hydroxy-2,7-dolabelladiene. We wish to report the structural determinations of the remaining diterpenes isolated from the digestive gland of *D. californica*.

The two collections of *D. californica* were made at Isla Espiritu Santo in April 1975 and March 1976. The acetone extracts of the digestive glands were chromatographed on Florisil. Rechromatography of selected fractions on silica gel gave 6 compounds from the first collection and 12 compounds from the second collection, four compounds being found in both collections. Details of the composition of the two collections, together with the molecular formulas and melting points, are shown in Table I.

An initial examination of the molecular formulas, infrared spectra, and ^1H NMR spectra (Table II) revealed that we had isolated a series of very similar compounds which differed primarily in the numbers and positions of acetate and hydroxyl groups. By reduction of the acetates to alcohols using lithium aluminum hydride in ether, we were able to relate each compound to one of four alcohols. The diacetate **1** and monoacetate **2** were both converted to the diol **3**; the triacetate **4**, three diacetates **5–7**, and a monoacetate **8** were all reduced to triol **9**; the diacetate **10** and two monoacetates **11** and **12** were related to an isomeric triol **13**; the remaining compound was an alcohol **14**.

The monoacetate **2** was the major crystalline constituent of the first collection. The molecular formula $C_{22}H_{36}O_3$, to-

Table I. Diterpenes Isolated from *Dolabella californica*

Collection					1975	1976
No. of animals					40	100
Total weight of digestive gland extracts					16 g	65 g
Registry no.	Compd	Molecular formula	Mp, °C	$[\alpha]^{20}_D$, deg	Wt, g	Wt, g
62861-12-5	1	$C_{24}H_{38}O_4$		−80.5	0.25	1.69
60259-77-0	2	$C_{22}H_{36}O_3$	78	−101	0.5	6.0
60259-76-9	3	$C_{20}H_{34}O_2$	152–153	−71.8		0.4
62861-13-6	4	$C_{26}H_{40}O_6$		−33.6		0.6
62861-14-7	5	$C_{24}H_{38}O_5$	136–137	−56.7		1.94
62861-15-8	6	$C_{24}H_{38}O_5$		−33.3	1.5	
62861-16-9	7	$C_{24}H_{38}O_5$		−26.4		0.4
62861-17-0	8	$C_{22}H_{36}O_4$		−45	1.75	7.0
62861-18-1	9	$C_{20}H_{34}O_3$	168–169	−86	1.3	
62861-19-2	10	$C_{24}H_{38}O_5$		−4.7		0.5
62861-20-5	11	$C_{22}H_{36}O_4$	153–154	−0.4		1.5
62861-21-6	12	$C_{22}H_{36}O_4$		+21.2		1.0
62861-22-7	13	$C_{20}H_{34}O_3$	157–158	−29		1.5
62861-23-8	14	$C_{20}H_{34}O$		−75.1	0.1	0.95
				Total recovery	5.4 (34%)	23.5 (36%)

Table II. ^{1}H NMR Spectra (Selected Signals) of the Diterpenes 1–14

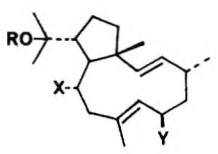
	H at C									
Compd	2	3	6	7	10	15	16	17	19	20
1	5.09	5.26		5.11	4.75	0.84	0.95	1.66	1.42	1.59
2	5.07	5.22		5.10	4.81	0.82	0.94	1.62	1.18	1.25
3	5.02	5.18		4.98	3.41	0.95	0.93	1.59	1.20	1.25
4						0.81	1.09	1.58	1.36	1.49
5	4.92	5.09	5.59	5.23	4.77	0.77	1.08	1.13	1.39	1.59
6	4.95	5.23	5.23	5.51	3.77	0.95	1.05	1.50	1.55	1.55
7	5.30	5.16	5.30	5.44	5.09	0.90	1.06	1.51	1.18	1.26
8	5.00	5.18	5.18	5.48	3.94	0.95	1.05	1.20	1.50	1.55
9	4.92	5.32	5.09	5.75	3.89	0.95	1.05	1.16	1.23	1.25
10	4.97	5.47	5.60	5.27	4.81	0.85	1.10	1.79	1.18	1.27
11	4.98	5.48	4.50	5.30	4.80	0.84	1.06	1.70	1.16	1.26
12	4.95	5.40	4.53	5.16	3.51	0.98	1.06	1.68	1.54	1.58
13	4.90	5.33	4.50	5.08		0.98	1.05	1.70	1.20	1.27
14	5.16	5.16		5.02		0.89	0.92	1.45	1.22	1.22

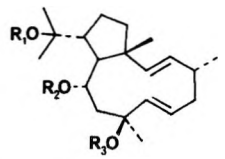
gether with an acetate signal in the ^{1}H NMR at δ 2.05 ppm and infrared bands at 3500 and 1740 cm^{-1}, strongly suggested that **2** was a monoacetate of a diol. The presence of two signals in the ^{1}H NMR at δ 1.18 and 1.25 ppm, together with a signal in the ^{13}C NMR spectrum at 72.7 ppm due to a quaternary carbon, indicated the presence of an isopropyl alcohol moiety. The ^{1}H NMR spectrum also contained signals due to methyl groups at δ 0.82 (s), 0.94 (d, J = 7 Hz), and 1.62 (bs), an α-acetoxy proton at 4.81, and vinyl protons at 5.07 (d, J = 16 Hz), 5.10 (t, J = 7 Hz), and 5.22 (dd, J = 16, 9 Hz). Irradiation at δ 2.32 caused the doublet at δ 0.94 to collapse to a singlet and the double doublet at δ 5.22 to become a doublet (J = 16 Hz). The ^{13}C NMR spectrum confirmed the presence of disubstituted and trisubstituted double bonds and contained a quaternary carbon signal at 20.8 ppm. From these data we deduced that **2** was bicyclic, containing the partial structure **15** where the quaternary carbon was at the bridgehead or at a side-chain junction. Since the coupling constant indicated a trans-disubstituted olefin, the partial structure must be in a large ring or in a side chain. Since we could not find a known carbon skeleton which contained this feature,[5] the structure of the monoacetate **2** was determined by single-crystal x-ray analysis[4].

The diacetate **1** was isolated as an oil. The ^{1}H NMR spectrum contained two acetate methyl signals at δ 2.04 and 1.91 and two signals at 1.59 and 1.42 ppm due to the methyl groups on a carbon atom bearing acetoxy. The diol **3** could be prepared from either **1** or **2** and was also a natural product. The ^{1}H NMR spectrum of **3** indicated the presence of the isopropyl alcohol side chain (δ 1.20 and 1.25) and the secondary alcohol functionality (δ 3.41).

The second group of compounds, a triacetate **4**, three diacetates **5–7**, a monoacetate **8**, and a triol **9**, all have the same carbon skeleton. All acetates **4–8** were converted into the triol **9** by reduction with lithium aluminum hydride in diethyl ether. Since the monoacetate of **8** was the major constituent in both collections, we first confined our studies to the structural elucidation of **8** and the corresponding triol **9**.

The monoacetate **8**, obtained as an oil, had the molecular formula $C_{22}H_{36}O_4$. On reduction with lithium aluminum hydride in ether, the monoacetate gave the triol **9** having a molecular formula $C_{20}H_{34}O_3$. The ^{1}H NMR spectrum of the monoacetate contained many signals which could be assigned to functional groups found in compounds **1–3**. The partial structure **15** was identified from signals at δ 0.95 (s, 3 H), 1.05 (d, 3 H, J = 7 Hz), 5.00 (d, 1 H, J = 16 Hz), and 5.18 (m, 1 H), the α-hydroxy proton gave rise to a multiplet at δ 3.94, and the isopropyl acetate side chain was represented by methyl signals at 2.02, 1.55, and 1.50 ppm. The major difference was that the trisubstituted olefin signal and the accompanying methyl signal in **2** were replaced by a methyl signal at δ 1.20, typical of a methyl group on a carbon atom bearing oxygen, and signals due to a trans-disubstituted olefinic bond at δ 5.48 (d, 1 H, J = 16 Hz) and 5.18 (m, 1 H). By careful decoupling of the ^{1}H NMR spectrum of the triol **9**, we were able to establish the presence of the 1,5-diene system. Irradiation at δ 2.57 collapsed the double doublet at δ 5.32 to a doublet, the doublet at δ 1.05 (3 H) to a singlet, and a two-proton multiplet at δ 2.16 to a broad doublet. Irradiation at δ 2.16 collapsed the multiplet at δ 5.09 to a sharp doublet and altered the multiplicity of the signal at δ 2.57. We therefore concluded that the trisubstituted olefin in **2** was replaced by an allylic tertiary alcohol in **8**.





1 R = Ac X = OAc Y = H

2 R = H X = OAc Y = H

3 R = H X = OH Y = H

10 R = H X = OAc Y = OAc

11 R = H X = OAc Y = OH

12 R = Ac X = OH Y = OH

13 R = H X = OH Y = OH

14 R = H X = H Y = H

16 R = Ac X = OAc Y = Br

4 R_1 = Ac R_2 = Ac R_3 = Ac

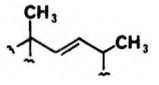
5 R_1 = Ac R_2 = Ac R_3 = H

6 R_1 = Ac R_2 = H R_3 = Ac

7 R_1 = H R_2 = Ac R_3 = Ac

8 R_1 = Ac R_2 = H R_3 = H

9 R_1 = H R_2 = H R_3 = H



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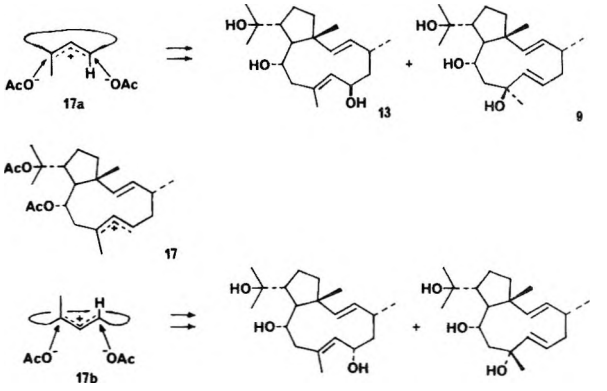
Acetylation of the secondary alcohol substituent in **8** with acetic anhydride in pyridine gave the diacetate **5**, identical in all respects with the natural material. Treatment of the diacetate with phosphorus tribromide and pyridine in hexane at −40 °C[6] gave the rearranged allylic secondary bromide **16** in 70–80% yield. The bromide **16** proved to be quite unstable and was therefore used without purification. Reduction of the bromide **16** with sodium in tetrahydrofuran containing *tert*-butyl alcohol gave the diol **3**, identical in all respects with an authentic sample, as the major product, albeit in low yield. An attempted reduction of the bromide **16** with lithium aluminum hydride gave no recognizable products, suggesting that the geometry of the medium-sized ring prevented the concerted displacement of bromide by hydride. The conversion of **8** to **3** established the structures of **4–9** with the exception of the stereochemistry at C-8, which was determined from a lanthanide-induced shift study (see below).

The triacetate **4** was obtained as an oil. The ^{1}H NMR spectrum contained three acetoxy methyl signals at δ 2.07, 1.98, and 1.95 and three signals due to methyl on a carbon atom bearing acetoxy at 1.58, 1.49, and 1.36 ppm. The diacetate **6**, obtained as an oil, contained a secondary alcohol substituent, as indicated by the ^{1}H NMR signal at δ 3.77 (m, 1 H) and three methyl groups on carbon atom bearing acetoxy which gave rise to signals at δ 1.55 (6 H) and 1.50 (3 H). The remaining diacetate **7** contained the isopropyl alcohol side chain, which gave rise to two methyl signals at δ 1.26 and 1.18 in the ^{1}H NMR spectrum.

A third group of compounds, a diacetate **10**, two monoacetates **11** and **12**, and a triol **13**, was found only in the second collection. The acetates **10–12** were all converted into the triol **13** by reduction with lithium aluminum hydride in ether. The ^{1}H NMR spectrum of the triol **13** was similar to that of the diol **3**, except in the low-field region, which contained signals at δ 4.90 (d, J = 16 Hz) and 5.33 (dd, J = 16, 7 Hz) due to a trans-disubstituted olefin and a doublet at δ 5.08 (J = 9 Hz) coupled to a multiplet at 4.50 ppm. In the diacetate **10**, the corresponding multiplet was at δ 5.60, suggesting that the multiplets were due to allylic α-hydroxy and allylic α-acetoxy protons, respectively. The similarity between the ^{1}H NMR spectra of **10–13** and that of the bromide **16** led to the hypothesis that all compounds had the same carbon skeleton and substitution pattern. The bromide **16** was therefore treated with silver acetate in aqueous tetrahydrofuran containing acetic acid at 0 °C to obtain an inseparable mixture of two triacetates, which were reduced directly with lithium aluminum hydride in ether to obtain a 3:2 mixture of triols **9** and **13**.

Scheme I. Possible Configurations of the Triols **9** and **13** Arising from the Solvolysis of Bromide **16**



The solvolysis proceeded by way of the carbonium ion intermediate **17**, which reacted with acetate to give the expected mixture of a secondary and tertiary allylic acetates. Depending on the geometry of the carbonium ion intermediate **17a** or **17b**, either of two possible pairs of triacetates might have been formed (Scheme I). Since the conformation of the acetate **2**, as determined by x-ray analysis, closely resembled intermediate **17a**, we expected the diols **9** and **13** to have the configurations shown.

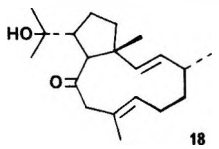
The diacetate **10** was obtained as an oil and could be prepared by acetylation of the diol **13** with acetic anhydride in pyridine at room temperature. The ^{1}H NMR spectrum of **10** contained two α-acetoxy proton signals at δ 4.81 and 5.60 and two methyl signals at δ 1.18 and 1.27 due to the isopropyl alcohol side chain. The monoacetate **11** contained an allylic secondary alcohol group which could be acetylated at room temperature to give the diacetate **10**. The ^{1}H NMR spectrum of **11** contained an α-acetoxy proton signal at δ 4.80 and an α-hydroxy proton signal at δ 4.50 which was coupled to an olefinic proton signal at δ 5.30 (d, J = 9 Hz). The ^{1}H NMR spectrum of the remaining monoacetate **12** contained two methyl signals at δ 1.54 and 1.58, due to the isopropyl acetate side chain, and α-hydroxy proton signals at δ 3.51 and 4.53.

Since we had obtained only two of four possible isomers from the solvolysis of the bromide **16**, we had predicted that the configuration at C-8 in compounds **4–9** and at C-6 in compounds **10–13** was as drawn. In order to confirm the assignments, we measured lanthanide-induced shifts[7] in the ^{1}H NMR spectra of compounds **5** and **11**. A solution of each compound in $CDCl_3$ was treated with aliquots of $Eu(fod)_3$ reagent and the induced shifts were measured. Because of the lack of rigidity in the 11-membered ring, we did not attempt a quantitative treatment of the LIS data. In the case of diacetate **5**, the proton at C-6 experienced the greatest shift, indicating that the europium atom was associated with the hydroxyl group. Examination of molecular models revealed that the relative shifts of the bridgehead methyl and the secondary methyl group would indicate whether the hydroxyl group, and therefore the europium atom, were above or below the plane of the 11-membered ring. Since the induced shift of the bridgehead methyl (49% of C-6 proton shift) was much greater than that of the secondary methyl (12% of C-6 proton shift), the configuration of **5** must be as shown. In the spectra of monoacetate **11**, the α-hydroxy proton at C-6 experienced the greatest induced shift, indicating that the europium was associated with the secondary alcohol. The induced shift of the bridgehead methyl (15.1% of C-6 proton shift) was again greater than that of the secondary methyl (12.8% of C-6 proton shift) but the difference was less pronounced. However, had the secondary hydroxyl and secondary methyl groups been on the same face of the 11-membered ring, we predicted that the induced shift of the secondary methyl signal would be

considerably greater than that of the bridgehead methyl. The configuration of 11 must therefore be as shown.

The alcohol 14 has a single hydroxyl group. The ^{1}H NMR spectrum of 14 contained a six-proton singlet at δ 1.22 due to the isopropyl alcohol side chain, together with signals at δ 0.89 (s, 3 H), 0.92 (d, 3 H, J = 7 Hz), and 5.16 (m, 2 H) due to fragment 15 and at δ 1.45 (s, 3 H) and 5.02 (t, J = 7 Hz) due to a trisubstituted olefinic group. On the basis of the spectral evidence, we proposed that 14 had the same carbon skeleton and configuration as the diol 3 but lacked the C-10 hydroxyl group. Our attempts to interconvert 3 and 14 have all failed. The diol was converted into a ketone 18 with Jones reagent, but the ketone could not be converted into the corresponding thioketal. The ketone 18 was converted into the corresponding *p*-toluenesulfonylhydrazone, but this derivative could not be reduced[8] to the alcohol 14.

During the course of these experiments, we made some observations which implied that the 11-membered ring was more rigid than predicted from examination of molecular models. The ketone 18 did not undergo rearrangement to give a conjugated ketone, even in the presence of strong acids and bases. When the ketone 19, obtained by Jones oxidation of 9, was treated with *p*-toluenesulfonic acid in dry benzene, the expected dienone 20 was not formed. These results indicated that the 11-membered ring cannot accommodate a third olefinic bond, although examination of molecular models suggested that this should be possible.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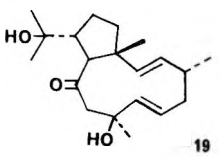
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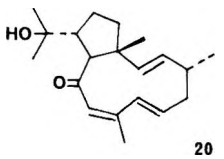
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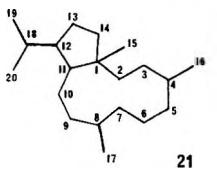
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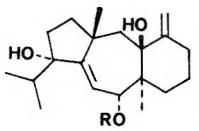
22 R = H
23 R = Ac

The dolabellane carbon skeleton 21 has not been encountered previously. However, at the same time that we communicated the structure of the monoacetate 2, Pettit et al.[9] published the structures of dolatriol 22 and its acetate 23, which were obtained from a related opisthobranch, *Dolabella auricularia*. The tricyclic skeleton of dolatriol 22 is formally related to the dolabellane skeleton by addition of a bond between carbons 3 and 8. Addition of a bond between carbons 4 and 10 in the dolabellane skeleton would give the cyathane skeleton.[10]

The dietary origin of the dolabellanes, if, like all other known opisthobranch metabolites,[11] they are indeed of dietary origin, remains a mystery. *Dolabella californica* is a nocturnal feeder. We did not observe any obvious food source while collecting the animals and concluded that *D. californica* must graze on the small algae which form a mat on the substratum. The isolation of diterpenes from two geographically separated *Dolabella* species suggests that *Dolabella* may be feeding on a specific genus of algae. Since *D. californica* produced copious quantities of purple ink, we suspect that it must eat predominantly red algae.[12,13]

Experimental Section

^{1}H NMR spectra were recorded on a Varian HR-220 spectrometer, ^{13}C NMR spectra were recorded on a Varian CFT-20 spectrometer, infrared spectra were recorded on a Perkin-Elmer Model 700 spectrophotometer, and optical rotations were measured on a Perkin-Elmer Model 141 polarimeter, using a 10-cm microcell. Low-resolution mass spectra were recorded on a Hewlett-Packard 5930A mass spectrometer. High-resolution mass measurements were supplied by the Analytical Facility at California Institution of Technology. Melting points were measured on a Fisher-Johns apparatus and are reported uncorrected. All solvents used were either spectral grade or distilled from glass prior to use.

Collection and Extraction of *Dolabella californica*. *Dolabella californica* were collected using scuba at night at Isla Espiritu Santo in the Gulf of California (24°31'N, 110°23'W) in April 1975 and March 1976. Each collection was extracted separately. The sea hares were anesthetized by injection of a saturated aqueous magnesium sulfate solution (20 mL) between the rhinophores. The digestive glands were removed by dissection, and the combined material was homogenized in acetone. The resulting suspension was filtered, and the solids were rehomogenized in acetone, allowed to stand at 5 °C for 20 h, and again filtered. The combined extracts were evaporated in vacuo to obtain an aqueous suspension of organic materials. The aqueous residue was extracted with the ether (3 × 1 L). The combined ether extracts were dried over sodium sulfate and evaporated in vacuo to obtain a brown, viscous oil.

First Collection (April 1975). Forty *Dolabella californica* gave 20 g of ether-soluble material. The brown oil (18 g) was chromatographed on a column of Florisil (40 × 6 cm diameter). The material was eluted with solvent mixtures of increasing polarity from hexane to ethyl acetate. Elution with 100% benzene gave a fraction (500 mg) which was rechromatographed on silica gel, using 25% ether in hexane as eluent, to obtain the diacetate 1 (250 mg) and the alcohol 14 (100 mg). The material which was eluted with 20% ether in benzene was crystallized from hexane to give the monoacetate 2 (500 mg). The fraction (3.0 g) which was eluted with 50% ether in benzene was rechromatographed on silica gel, using 50% ether in hexane as eluent, to obtain the diacetate 6 (1.5 g). The material (3.0 g) eluted with 10% ethyl acetate in ether was rechromatographed on silica gel, using ether as eluent, to obtain the monoacetate 8 (1.75 g). The fraction (2.0 g) eluted with 50% ethyl acetate in ether was crystallized from hexane to yield the triol 9 (1.30 g).

Second Collection (March 1976). One hundred *Dolabella* gave 70 g of ether-soluble material. The oil (65 g) was chromatographed on a column of Florisil (90 × 6 cm diameter). Material (14 g) eluted with benzene was rechromatographed on silica gel to obtain the diacetate 1 (1.5 g), the alcohol 14 (900 mg), and the monoacetate 2 (4.5 g). The fraction (19 g) eluted with 20% ether in benzene was rechromatographed on silica gel to separate the monoacetate 2 (2.0 g), the triacetate 4 (600 mg), the diacetate 5 (1.9 g), the diacetate 10 (500 mg), the diol 3 (400 mg), and the diacetate 7 (400 mg). The material (15 g) eluted with 50% ether in benzene was rechromatographed on silica gel to obtain the monoacetate 8 (7.0 g), the monoacetate 11 (1.5 g), and the monoacetate 12 (1.0 g). The material eluted with 10% ethyl acetate in ether recrystallized from ether to give the triol 13 (1.5 g).

(1*R,2*E*,4*R**,7*E*,10*S**,11*S**,12*R**)-10,18-Diacetoxy-2,7-dolabelladiene (1):** $[\alpha]^{20}_D$ −80.5° (*c* 2.6, $CHCl_3$); IR ($CHCl_3$) 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.84 (s, 3 H), 0.95 (d, 3 H, J = 7 Hz), 1.42 (s, 3 H), 1.59 (s, 3 H), 1.66 (s, 3 H), 1.91 (s, 3 H), 2.04 (s, 3 H), 3.05 (m, 1 H), 4.75 (m, 1 H), 5.09 (d, 1 H, J = 16 Hz), 5.11 (t, 1 H, J = 7 Hz), 5.26 (dd, 1 H, J = 16, 9 Hz); ^{13}C NMR ($CDCl_3$) δ 170.1, 169.0, 135.4, 134.4, 130.5, 127.3, 84.9, 70.7, 55.3, 47.2, 45.0, 38.9, 37.3, 36.0, 26.8, 26.3, 26.1, 25.7, 25.5, 23.4, 22.8, 21.0, 19.1, 18.0; mass spectrum *m/e* 390 (M^+·), 330 (M^+· − AcOH), 288, 271, 256, 228, 174, 43 (base peak); high-resolution mass measurement, observed 390.2766 ($C_{24}H_{38}O_4$ requires 390.2770).

(1*R,2*E*,4*R**,7*E*,10*S**,11*S**,12*R**)-10-Acetoxy-18-hydroxy-2,7-dolabelladiene (2):** mp 78 °C; $[\alpha]^{20}_D$ −101° (*c* 1.32, $CHCl_3$); IR ($CHCl_3$) 3500, 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.82 (s, 3 H), 0.94 (d, 3 H, J = 7 Hz), 1.18 (s, 3 H), 1.25 (s, 3 H), 1.62 (s, 3 H), 2.05 (s, 3 H), 4.81 (dt, 1 H, J = 9, 1, 1 Hz), 5.07 (d, 1 H, J = 16 Hz), 5.10 (t, 1 H, J = 7 Hz), 5.22 (dd, 1 H, J = 16, 9 Hz); ^{13}C NMR (C_6D_6) δ 168.9, 135.8, 131.2, 128.3, 127.4, 73.0, 71.9, 56.1, 50.0, 47.7, 46.1, 40.1, 38.3, 36.4, 32.5, 27.9, 27.3, 23.9, 22.0, 20.0, 18.8; mass spectrum *m/e* 346 (M^+·), 328, 287, 269. Anal. Calcd for $C_{22}H_{36}O_3$: C, 75.83; H, 10.4. Found: C, 75.90; H, 10.51.

(1*R,2*E*,4*R**,7*E*,10*S**,11*S**,12*R**)-10,18-Dihydroxy-2,7-dolabelladiene (3):** mp 152–153 °C; $[\alpha]^{20}_D$ −71.8° (*c* 0.92, $CHCl_3$); IR ($CHCl_3$) 3500 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93 (d, 1 H, J = 7 Hz), 0.95 (s, 3 H), 1.20 (s, 3 H), 1.25 (s, 3 H), 1.59 (s, 3 H), 2.55 (m, 1 H), 4.98

(t, 1 H, J = 7 Hz), 5.02 (d, 1 H, J = 16 Hz), 5.18 (dd, 1 H, J = 16, 9 Hz); mass spectrum m/e 306 (M^+·) 288, 270, 255, 227, 163; high-resolution mass measurement, observed 306.2560 ($C_{20}H_{34}O_2$ requires 306.2558).

(1*R,2*E*,4*R**,6*E*,8*S**,10*S**,11*S**,12*R**)-8,10,18-Triacetoxy-2,6-dolabelladiene (4):** $[\alpha]^{20}_D$ −33.6° (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 (s, 3 H), 1.09 (d, 3 H, J = 7 Hz), 1.36 (s, 3 H), 1.49 (s, 3 H), 1.58 (s, 3 H), 1.96 (s, 3 H), 1.98 (s, 3 H), 2.07 (s, 3 H), 2.67 (dd, 1 H, J = 15, 4 Hz), 3.07 (m, 1 H), 5.18 (m, 3 H), 5.45 (m, 2 H); mass spectrum m/e 448 (M^+·); high-resolution mass measurement, observed 448.2819 ($C_{26}H_{40}O_6$ requires 448.2824).

(1*R,2*E*,4*R**,6*E*,8*S**,10*S**,11*S**,12*R**)-10,18-Diacetoxy-8-hydroxy-2,6-dolabelladiene (5):** mp 136–137 °C; $[\alpha]^{20}_D$ −56.7° (*c* 0.94, $CHCl_3$); IR ($CHCl_3$) 3500, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.77 (s, 3 H), 1.08 (d, 3 H, J = 7 Hz), 1.18 (s, 3 H), 1.39 (s, 3 H), 1.59 (s, 3 H), 1.91 (s, 3 H), 2.05 (s, 3 H), 2.25 (m, 1 H), 4.20 (s, 1 H), 4.77 (d, 1 H, J = 8 Hz), 4.92 (d, 1 H, J = 16 Hz), 5.09 (dd, 1 H, J = 16, 9 Hz), 5.59 (m, 1 H). Anal. Calcd for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42. Found: C, 71.00; H, 9.64.

(1*R,2*E*,4*R**,6*E*,8*S**,10*S**,11*S**,12*R**)-8,18-Diacetoxy-10-hydroxy-2,6-dolabelladiene (6):** $[\alpha]_D$ −33.3° (*c* 0.40, $CHCl_3$); IR ($CHCl_3$) 3500, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (s, 3 H), 1.05 (d, 3 H, J = 7 Hz), 1.50 (s, 3 H), 1.55 (s, 6 H), 2.00 (s, 3 H), 2.07 (s, 3 H), 2.50 (m, 2 H), 2.77 (dd, 1 H, J = 14, 8 Hz), 3.77 (m, 1 H), 4.95 (d, 1 H, J = 16 Hz), 5.23 (m, 2 H), 5.51 (d, 1 H, J = 16 Hz); ^{13}C NMR ($CDCl_3$) δ 170.5, 169.9, 139.5, 138.4, 131.9, 125.5, 86.1, 83.5, 65.8, 58.6, 53.7, 49.4, 46.8, 38.9, 38.0, 34.6, 25.8, 25.4, 23.0, 22.6, 20.3, 17.4, 17.3, 16.9; mass spectrum m/e 406 (M^+·), 287, 206, 187; high-resolution mass measurement, observed 460.2719 ($C_{24}H_{38}O_5$ requires 406.2719).

1*R,2*E*,4*R**,6*E*,8*S**,10*S**,11*S**,12*R**)-8-10-Diacetoxy-18-hydroxy-2,6-dolabelladiene (7):** $[\alpha]^{20}_D$ −26.4° (*c* 0.36, $CHCl_3$); IR ($CHCl_3$) 3500, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (s, 3 H), 1.06 (d, 3 H, J = 7 Hz), 1.18 (s, 3 H), 1.26 (s, 3 H), 1.51 (s, 3 H), 1.99 (s, 3 H), 2.05 (s, 3 H), 2.66 (dd, 1 H, J = 16, 6 Hz), 5.09 (m, 1 H), 5.16 (d, 1 H, J = 16 Hz), 5.30 (m, 2 H), 5.44 (d, 1 H, J = 16 Hz); high-resolution mass measurement, observed 406.2719 ($C_{24}H_{38}O_5$ requires 406.2719).

(1*R,2*E*,4*R**,6*E*,8*S**,10*S**,11*S**,12*R**)-18-Acetoxy-8,10-dihydroxy-2,6-dolabelladiene (8):** $[\alpha]^{20}_D$ −45° (*c* 1.9, $CHCl_3$); IR 3500, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (s, 3 H), 1.05 (d, 3 H, J = 7 Hz), 1.20 (s, 3 H), 1.50 (s, 3 H), 1.55 (s, 3 H), 2.02 (s, 3 H), 2.50 (m, 1 H), 2.89 (br s, 1 H), 3.94 (br s, 1 H), 5.00 (d, 1 H, J = 16 Hz), 5.18 (m, 2 H), 5.48 (d, 1 H, J = 16 Hz); ^{13}C NMR ($CDCl_3$) δ 169.5, 142.1, 138.6, 132.8, 126.4, 86.6, 74.1, 66.8, 58.0, 56.5, 49.5, 46.9, 39.2, 37.3, 35.1, 30.1, 26.1, 25.9, 23.2, 20.1, 18.0; mass spectrum m/e 364 (M^+·), 286, 206; high-resolution mass measurement, observed 364.2619 ($C_{22}H_{36}O_4$ requires 364.2613).

(1*R,2*E*,4*R**,6*E*,8*S**,10*S**,11*S**,12*R**)-8,10,18-Trihydroxy-2,6-dolabelladiene (9):** mp 168–169 °C; $[\alpha]^{20}_D$ −86° (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (s, 3 H), 1.05 (d, 3 H, J = 7 Hz), 1.16 (s, 3 H), 1.23 (s, 3 H), 1.25 (s, 3 H), 1.95 (m, 2 H), 2.16 (m, 2 H), 2.34 (m, 2 H), 2.57 (br s, 1 H), 3.89 (d, 1 H, J = 9 Hz), 4.92 (d, 1 H, J = 16 Hz), 5.09 (m, 1 H), 5.32 (dd, 1 H, J = 16, 10 Hz), 5.75 (d, 1 H, J = 16 Hz); ^{13}C NMR ($CDCl_3$) δ 143.1, 137.4, 132.4, 125.5, 75.0, 72.7, 67.0, 57.1, 56.8, 49.4, 47.1, 38.2, 37.9, 34.1, 31.5, 29.3, 26.0, 23.2, 16.6, 16.4. Anal. Calcd for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63. Found: C, 74.70; H, 10.63.

(1*R,2*E*,4*R**,6*R**,7*E*,10*S**,11*S**,12*R**)-6,10-Diacetoxy-18-hydroxy-2,7-dolabelladiene (10):** $[\alpha]^{20}_D$ −4.7° (*c* 0.17, $CHCl_3$); IR ($CHCl_3$) 3500, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (s, 3 H), 1.10 (d, 3 H, J = 7 Hz), 1.18 (s, 3 H), 1.27 (s, 3 H), 1.78 (s, 3 H), 2.00 (s, 3 H), 2.07 (s, 3 H), 2.32 (d, 1 H, J = 7 Hz), 4.81 (m, 1 H), 4.97 (d, 1 H, J = 16 Hz), 5.27 (d, 1 H, J = 10 Hz), 5.47 (dd, 1 H, J = 16, 7 Hz), 5.60 (m, 1 H); high-resolution mass measurement, observed 406.2715 ($C_{24}H_{38}O_5$ requires 406.2719).

(1*R,2*E*,4*R**,6*R**,7*E*,10*S**,11*S**,12*R**)-10-Acetoxy-6,18-dihydroxy-2,7-dolabelladiene (11):** $[\alpha]^{20}_D$ −0.4° (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) 3500, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (s, 3 H), 1.06 (d, 3 H, J = 7 Hz), 1.16 (s, 3 H), 1.26 (s, 3 H), 1.70 (s, 3 H), 2.05 (s, 3 H), 4.50 (m, 1 H), 4.80 (m, 1 H), 4.98 (d, 1 H, J = 16 Hz), 5.30 (d, 1 H, J = 9 Hz), 5.48 (dd, 1 H, J = 16, 7 Hz); high-resolution mass measurement, observed 364.2623 ($C_{22}H_{36}O_4$ requires 364.2613).

(1*R,2*E*,4*R**,6*R**,7*E*,10*S**,11*S**,12*R**)-18-Acetoxy-6,10-dihydroxy-2,7-dolabelladiene (12):** mp 153–154 °C; $[\alpha]^{20}_D$ +21.2° (*c* 1.06, $CHCl_3$); IR ($CHCl_3$) 3500, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (s, 3 H), 1.06 (d, 3 H, J = 7 Hz), 1.54 (s, 3 H), 1.58 (s, 3 H), 1.68 (s, 3 H), 2.02 (s, 3 H), 2.70 (m, 1 H), 2.98 (d, 1 H, J = 10 Hz), 3.51 (m, 1 H), 4.53 (m, 1 H), 4.95 (d, 1 H, J = 16 Hz), 5.16 (d, 1 H, J = 9 Hz), 5.40 (dd, 1 H, J = 16, 7 Hz); ^{13}C NMR ($CDCl_3$) δ 169.0, 135.6, 134.1, 133.0, 130.2, 86.8, 71.5, 65.3, 54.2, 47.5, 46.2, 43.1, 39.8, 31.2, 26.0, 21.9, 20.0, 18.9, 16.9, 16.0. Anal. Calcd for $C_{22}H_{36}O_4$: C, 72.49; H, 10.04. Found: C, 72.30; H, 10.04.

(1*R,2*E*,4*R**,6*R**,7*E*,10*S**,11*S**,12*R**)-6,10,18-Trihydroxy-2,7-dolabelladiene (13):** mp 157–158 °C; $[\alpha]_D$ −29° (*c* 0.9, $CHCl_3$); IR 3500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (s, 3 H), 1.05 (d, 1 H, J = 7 Hz), 1.20 (s, 3 H), 1.27 (s, 3 H), 1.70 (s, 3 H), 1.93 (m, 1 H), 2.14 (d, 1 H, J = 11 Hz), 2.41 (m, 1 H), 2.53 (m, 1 H), 4.50 (m, 1 H), 4.90 (d, 1 H, J = 16 Hz), 5.08 (d, 1 H, J = 9 Hz), 5.33 (dd, 1 H, J = 16, 7 Hz). Anal. Calcd for $C_{20}H_{34}O_3 \cdot CH_3OH$: C, 71.15; H, 10.80. Found: C, 71.43; H, 10.73. (Sample for analysis was recrystallized from methanol.)

(1*R,2*E*,4*R**,7*E*,11*S**,12*R**)-18-Hydroxy-2,7-dolabelladiene (14):** $[\alpha]^{20}_D$ −75.1° (*c* 1.35, $CHCl_3$); IR ($CHCl_3$) 3550 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (s, 3 H), 0.92 (d, 3 H, J = 7 Hz), 1.22 (s, 6 H), 1.45 (s, 3 H), 1.82 (m, 3 H), 2.09 (m, 4 H), 5.02 (t, 1 H, J = 7 Hz), 5.16 (m, 2 H); mass spectrum m/e 290 (M^+·), 272, 257, 229, 175; high-resolution mass measurement, observed 290.258 ± 0.010 ($C_{20}H_{34}O$ requires 290.261).

Reduction of Acetates with Lithium Aluminum Hydride. A solution of the diacetate **1** (20 mg, 0.05 mmol) in anhydrous tetrahydrofuran (1 mL) was added to a stirred suspension of lithium aluminum hydride (20 mg, 0.53 mmol) in anhydrous tetrahydrofuran (9 mL) at room temperature. The reaction mixture was stirred at reflux for 1 h, cooled to 0 °C, and quenched with water (3 mL), followed by 15% sodium hydroxide solution (3 mL). The inorganic salts were removed by filtration and the tetrahydrofuran was evaporated in vacuo. The aqueous residue was extracted with ether (3 × 20 ml), and the combined ether extracts were dried over sodium sulfate and evaporated in vacuo to obtain the diol **3** (12 mg, 79% theoretical) identical in all respects with the natural material.

Using identical reaction conditions and workup procedures: **2** (30 mg, 0.08 mmol) gave **3** (20 mg, 85% theoretical); **4** (24 mg, 0.054 mmol) gave **9** (15 mg, 85% theoretical); **5** (20 mg, 0.05 mmol) gave **9** (12 mg, 74% theoretical); **6** (30 mg, 0.073 mmol) gave **9** (19 mg, 81% theoretical); **7** (15 mg, 0.037 mmol) gave **9** (10 mg, 84% theoretical); **8** (25 mg, 0.065 mmol) gave **9** (17 mg, 80% theoretical); **10** (15 mg, 0.037 mmol) gave **13** (9 mg, 73% theoretical); **11** (35 mg, 0.092 mmol) gave **13** (23 mg, 77% theoretical); **12** (15 mg, 0.039 mmol) gave **13** (9 mg, 72% theoretical).

Acetylation of Monoacetate 8. Acetic anhydride (1 mL) was added to a solution of the monoacetate **8** (80 mg, 0.21 mmol) in pyridine (3 mL), and the reaction mixture was stirred under a nitrogen atmosphere for 24 h. The excess reagents were removed in vacuo, and the residue was partitioned between water and ether. The ether extracts were dried over sodium sulfate and the solvent was evaporated to yield a solid which was recrystallized from hexane to obtain the diacetate **5** (70 mg, 81% theoretical), identical in all respects with the natural material.

6-Bromo-10,18-diacetoxy-2,7-dolabelladiene (16). A solution of phosphorus tribromide (150 μL, 1.5 mmol) in hexane (5 mL) was added dropwise over 10 min to a cooled solution of the diacetate **5** (30 mg, 0.079 mmol) and pyridine (50 μL, 0.62 mmol) in hexane (10 mL) at −30 °C. The reaction mixture was stirred for 1 h at −30 °C, then quenched with water (5 mL). The mixture was extracted with ether (3 × 20 mL), the combined ether extracts were dried over the sodium sulfate, and the solvent was evaporated to yield the bromide **16** (25 mg, 67% theoretical). All attempts to purify the bromide **16** by chromatography resulted in extensive degradation. ^1H NMR ($CDCl_3$) δ 0.80 (s, 3 H), 1.05 (d, 3 H, J = 7 Hz), 1.35 (s, 3 H), 1.59 (s, 3 H), 1.70 (s, 3 H), 1.89 (s, 3 H), 2.02 (s, 3 H), 3.12 (m, 1 H), 4.70 (d, 1 H, J = 10 Hz), 4.82 (d, 1 H, J = 16 Hz), 4.98 (m, 1 H), 5.48 (dd, 1 H, J = 16, 8 Hz), 5.59 (d, 1 H, J = 10 Hz).

Reduction of Bromide 16. Sodium (30 mg, 1.3 mmol) was added to a solution of the bromide **16** (26 mg, 0.054 mmol) in tetrahydrofuran (10 mL) containing *tert*-butyl alcohol (50 μL, 0.7 mmol) and the reaction mixture was boiled under reflux for 3 h. The product was cooled and quenched with water (5 mL). The organic material was extracted with ether (3 × 15 mL), and the combined extracts were dried over sodium sulfate and evaporated in vacuo to yield an oil (8 mg). Chromatography of the oil on silica gel gave the diol **3** as the major product (4 mg, 24% theoretical).

Solvolysis of Bromide 16. A solution of silver acetate (50 mg, 0.33 mmol) in aqueous acetic acid [50 μL (0.87 mmol) in 1 mL] was added to the bromide **16** (40 mg, 0.083 mmol) in tetrahydrofuran (5 mL) at 0 °C, and the mixture was stirred for 2 h. The mixture was partitioned between water (5 mL) and ether (3 × 10 mL). The combined ether extracts were dried over sodium sulfate and the solvent was evaporated to yield a mixture of triacetates (28 mg). The product was treated with lithium aluminum hydride according to the established procedures to yield a mixture of triols (20 mg). Chromatography of the triols on silica gel gave the triols **9** (12 mg, 44% theoretical) and **13** (8 mg, 29% theoretical), both identical with authentic samples.

Jones Oxidation of the Diol 3. One equivalent of Jones reagent

(24 μL, 0.025 mmol) was added dropwise to a solution of the diol **3** (7 mg, 0.023 mmol) in anhydrous acetone (5 mL) at 0 °C. The reaction mixture was stirred for 10 min, then quenched with excess 2-propanol (1 drop) and water (5 mL). The acetone was removed in vacuo and the aqueous residue extracted with ether (3 × 10 mL). The combined ether extracts were dried over sodium sulfate and the solvent was evaporated to yield the ketone **18** (4 mg, 57% theoretical) as an oil: IR ($CHCl_3$) 3500, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (d, 3 H, J = 7 Hz), 0.96 (s, 3 H), 1.18 (s, 6 H), 1.44 (s, 3 H), 2.62 (m, 1 H), 2.80 (d, 1 H, J = 10 Hz), 2.93 (d, 1 H, J = 10 Hz), 3.23 (d, 1 H, J = 10 Hz), 5.20 (m, 2 H).

Jones Oxidation of Triol 9. One equivalent of Jones reagent was added to a solution of the triol **9** (14 mg, 0.043 mmol) in acetone (5 mL) and the reaction was allowed to proceed according to the procedure above to give the ketone **19** (8 mg, 58% theoretical): IR ($CDCl_3$) 3500, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (d, 3 H, J = 7 Hz), 1.09 (s, 3 H), 1.13 (s, 3 H), 1.14 (s, 3 H), 1.23 (s, 3 H), 1.50 (m, 4 H), 1.93 (m, 2 H), 2.16 (m, 1 H), 2.59 (m, 2 H), 2.48 (m, 2 H), 2.83 (d, 1 H, J = 10 Hz), 5.16 (d, 1 H, J = 16 Hz), 5.23 (m, 1 H), 5.30 (m, 1 H), 5.47 (d, 1 H, J = 16 Hz).

Jones Oxidation of Triol 13. One equivalent of Jones reagent was added to a solution of the triol **13** (20 mg, 0.062 mmol) in acetone (5 mL) and the reaction was allowed to proceed according to the procedure above to give the dione (11 mg, 56% theoretical): IR ($CHCl_3$) 3500, 1710, 1680 cm^{-1}; λ_{max} 247 nm; ^1H NMR ($CDCl_3$) δ 1.03 (s, 3 H), 1.10 (d, 3 H, J = 7 Hz), 1.21 (s, 3 H), 1.91 (s, 3 H), 2.46 (br s, 2 H), 2.70 (m, 1 H), 2.95 (d, 1 H, J = 11 Hz), 3.05 (d, 1 H, J = 11 Hz), 3.39 (d, 1 H, J = 11 Hz), 5.19 (d, 1 H, J = 16 Hz), 5.49 (dd, 1 H, J = 16, 7 Hz), 5.98 (s, 1 H).

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Registry No.—**13** dione, 62861-24-9; **16**, 62861-25-0; **18**, 62861-26-1; **19**, 62861-27-2.

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A Convenient Synthesis of γ-Lactams via Michael Addition

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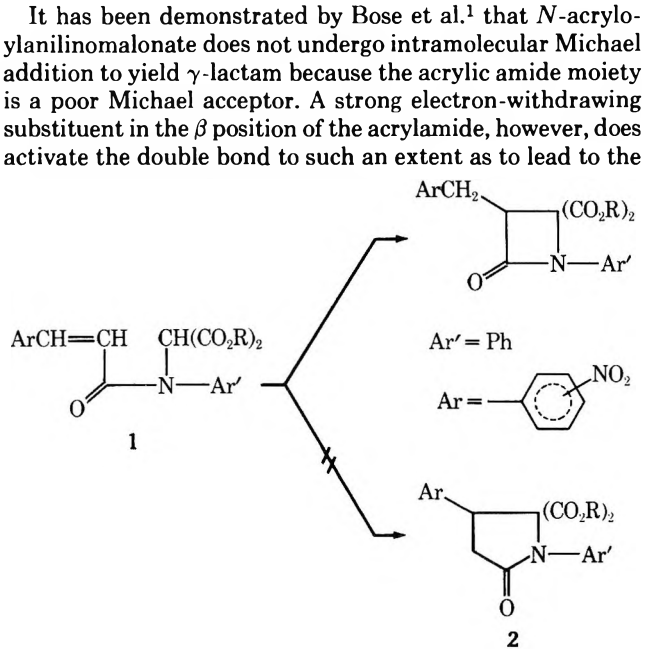
A convenient synthesis of 1-aryl-2,2-dicarboalkoxy-5-pyrrolidinones from substituted anilinomalonates by way of intermolecular Michael addition followed by amidification has been developed. This is probably the first report on a Michael addition involving an acid chloride as a Michael acceptor. The mechanism suggested has been convincingly established. A large number of γ-lactam derivatives have been prepared in good to excellent yields.

It has been demonstrated by Bose et al.[1] that *N*-acryloylanilinomalonate does not undergo intramolecular Michael addition to yield γ-lactam because the acrylic amide moiety is a poor Michael acceptor. A strong electron-withdrawing substituent in the β position of the acrylamide, however, does activate the double bond to such an extent as to lead to the formation of β- and γ-lactams[2] from suitable substrates by way of Michael addition.



Though much work has not been reported on the formation of β- or γ-lactams by intramolecular Michael addition, many γ-lactams have been conveniently synthesized by intermolecular Michael addition. Cocolas and Hartung[3] have reported that the Michael adduct between diethyl acetamidomalonate and ethyl acrylate or crotonate in ethanol gave 2-pyrrolidinones at reflux temperature. The formation of γ-lactams from the simple Michael adduct has been explained on the basis that the conformation of the molecule places the groups in question in very close proximity with each other for the attack of nitrogen on the γ-carbonyl carbon.

A detailed and exhaustive study on the synthesis of γ-lactams has been made by Pachaly et al.[4] It has been shown that *N*-acetylglycine esters also undergo similar intermolecular Michael addition provided that a strong base such as sodium hydride is used. The reaction follows a stereoselective path leading to the formation of the trans isomer of the γ-lactam.

An attempt to throw some light on the intramolecular Michael addition leading to γ-lactam formation led us to work on amide **1e** (Ar = Ph; Ar′ = *p*-nitrophenyl).

Table I.[a] 1-Aryl-2,2-dicarboalkoxy-3-phenyl-5-pyrrolidinone (2)

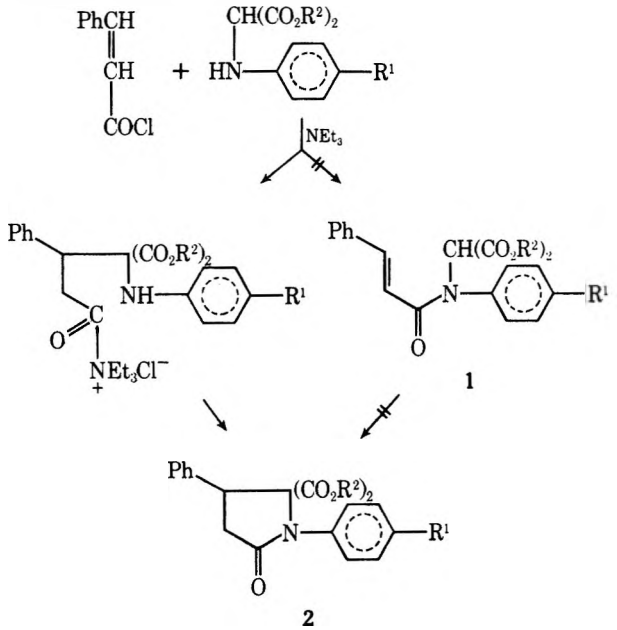
Registry No.	Compd	Yield, %	Mp, °C	IR, cm^{-1} ν C=O	NMR[b] C_3 proton (t)	NMR[b] C_4 protons (d)
62851-28-9	**2a**	36.0	92	1730, 1721, 1718	5.48	7.15
32285-86-2	**2b**[7]	24.0	128–129	1735, 1720, 1710	5.58	7.23
62851-29-0	**2c**	66.7	125–127	1740, 1730, 1715	5.43	7.02
62851-30-3	**2d**	71.6	108–110	1742, 1720, 1706	5.41	6.97
62851-31-4	**2e**	85.4	106	1742, 1735, 1710	5.63	6.97
62905-87-7	**2f**	76.1	134–135	1739, 1724, 1714, 1698	5.46	6.97
19038-40-5	**2g**[8]	45.0	130	1758, 1740, 1720	5.34	6.91
62882-93-3	**2h**	78.7	135–136	1760, 1740, 1720	5.47	6.92
62851-32-5	**2i**	75.1	100–101	1759, 1724, 1709	5.40	6.92
62905-88-8	**2j**	79.7	136–137	1754, 1724, 1706	5.46	7.01

[a] All compounds presented here have satisfactory elemental analyses. [b] $CDCl_3$, Me_4Si as internal standard. Chemical shift in τ.

Chatterjee and co-workers[5] have shown that the carbonyl character of similar nitro-substituted amides is greatly enhanced because of the increased delocalization of Np electrons across the π orbital of the *p*-nitrophenyl system causing a decrease in the strength of N-p:C=O π overlap. Amide **1e**, therefore, is expected to be a suitable substrate for intramolecular Michael addition.

When *p*-nitroanilinomalonate could not be amidified with cinnamoyl chloride under nonbasic conditions,[6] the reaction was carried out in the presence of triethylamine. We hoped that amidification would be followed by intramolecular Michael addition in presence of the base, resulting in the formation of γ-lactam. The product from the above reaction was isolated in excellent yield and was characterized to be a γ-lactam by IR and NMR spectra as well as the elemental analysis.

A conceivable mechanism, however, for the formation of γ-lactam involves intermolecular Michael addition followed by intramolecular amidification.



2a, R^1 = H; R^2 = Et
b, R^1 = CH_3; R^2 = Et
c, R^1 = Cl; R^2 = Et
d, R^1 = Br; R^2 = Et
e, R^1 = NO_2; R^2 = Et
f, R^1 = CO_2Et; R^2 = Et
g, R^1 = H; R^2 = Me
h, R^1 = Cl; R^2 = Me
i, R^1 = Br; R^2 = Me
j, R^1 = CO_2Et; R^2 = Me

A conclusive evidence for this alternative mechanism will be to experimentally rule out the first one. The amide **1e** was ultimately prepared in 80% yield from *p*-nitroanilinomalonate with cinnamoyl chloride in the presence of pyridine, a base weak enough not to create complications by abstracting the methine proton. We were surprised to find that the amide **1e** did not yield γ-lactam in the presence of various bases normally used as catalysts in the Michael addition. This establishes the alternative mode of γ-lactam formation suggested by us.

Since the yield of lactam **2e** was about 85%, it follows that addition–elimination reaction leading to the formation of α,β-unsaturated ketone does not seriously compete with the Michael addition.

In order to study the effect of substituents on the formation of γ-lactams, a number of substituted anilinomalonates were prepared. It was observed (Table I) that with an electron-withdrawing substituent which decreased the basicity of aminomalonate the yields obtained ranged from 67 to 86%, whereas with electron-releasing groups such as CH_3 the yields were tremendously reduced because of simultaneous formation of α,β-unsaturated amides. Amidification, therefore, does compete with Michael addition and the amides if formed do not isomerize to γ-lactams.

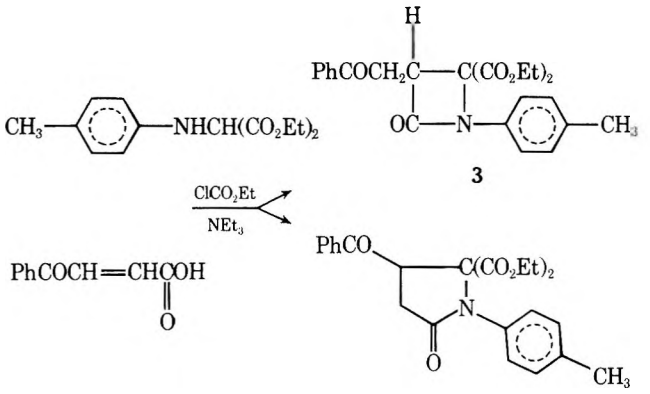
Recently Baldwin[9] has examined a number of polyfunctional molecules as substrates for the 5-endo-trigonal ring-forming reaction. It has been found that for first-row elements this is a disfavored process. The failure of amide **1e** to undergo intramolecular Michael addition to form **2e** is an additional reinforcement to Baldwin's hypothesis.[10]

The mechanism suggested by us shows the final step to be a 5-exo-trigonal ring-forming process and hence it will be favored.

Since α,β-unsaturated acid chlorides have never been employed in Michael addition, we felt that additional convincing evidences were necessary in support of the mechanism suggested by us.

The mixed anhydride from β-benzoylacrylic acid and ethyl chloroformate was treated with ethyl *p*-toluidinomalonate in the presence of triethylamine. If the keto carbonyl group alone be responsible for the activation of the double bond, then both intermolecular Michael addition followed by amidification and amidification followed by intramolecular Michael addition would lead only to the formation of β-lactam **3**. But if γ-lactam be isolated even in minor yield from this comparatively more basic amino ester, it would definitely establish the validity of the mechanism suggested by us.

The reaction product as expected was a mixture from which we isolated a solid product by chromatography in 10% yield. Since β- and γ-lactams are isomeric, elemental analysis cannot differentiate them. Since both of them contain four carbonyl functions, the IR spectrum too could not be profitably used



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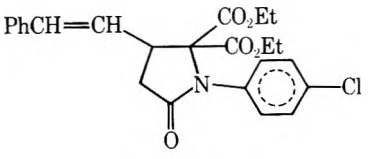
for eliminating one structure in favor of the other. The NMR spectrum, however, was helpful in characterizing the product as a γ-lactam (4). Since this reaction product was characterized as a γ-lactam, no attempt was made to investigate the nature of other products of the reaction.

In all NMR spectra of the γ-lactams prepared by us we find the ring methine proton as a triplet between τ 5.4 and 5.6 and the ring methylene proton as multiplets between τ 6.9 and 7.2. The spectrum of the isolated product shows a triplet centered at τ 4.93 (1 H) and a multiplet at τ 7.03. A keto group present adjacent to the ring methine proton in this compound obviously is responsible for the shift in position from τ 5.4 to τ 4.93. The β-lactam ring methine proton in a similar environment has never been observed by us at such low field.

Encouraged by our above results, we tried to investigate the comparative ease of formation of five- vs. seven-membered rings. β-Styrylacryloyl chloride was reacted with *p*-chloroanilinomalonate in the presence of triethylamine. The NMR spectrum of the reaction product shows the following pattern: τ 2.81 (m, 9 H), 3.72 (m, 2 H), 5.97 (m, 5 H), 7.36 (d, 2 H), and 8.97 (m, 6 H). The doublet at τ 7.36 can be assigned to the ring methylene protons of a γ-lactam. The ring methine proton, which also is an allylic proton, appears merged with the ester methylene (4 H) protons giving a complicated splitting pattern. The characteristic splitting pattern centered at τ 3.72 of two protons is very similar to that of a β-substituted styrene derivative.[11] The NMR spectrum, therefore, is compatible with the formulation of the product as a γ-lactam (5) rather than a seven-membered cyclic amide.



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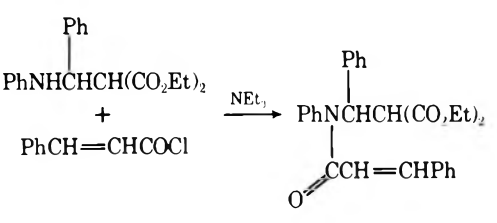
We wish to report here that an attempt to synthesize a 2-piperidinone derivative from ethyl β-anilinobenzylmalonate and cinnamoyl chloride by the method developed by us was not met with success. An α,β-unsaturated amide (6) was ob-



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tained in 70% yield. This suggests that amidification outweights other competitive processes in the case of this basic amino ester.

Experimental Section[12]

A Typical Preparation of γ-Lactam. 1-(*p*-Nitrophenyl)-2,2-dicarboethoxy-3-phenyl-5-pyrrolidinone (2e). A mixture of 3.0 g (10 mmol) of *p*-nitroanilinomalonate,[5] 3.03 g (30 mmol) of triethylamine, and 2.46 g (15 mmol) of freshly distilled cinnamoyl chloride in 60 mL of anhydrous benzene was refluxed for 6 h. The reaction mixture was cooled and washed successively with 2 N HCl, 5% $NaHCO_3$ solution, and finally with water. After drying (Na_2SO_4), the solvent was stripped out to give a crude solid which on fractional crystallization from methanol (two times) afforded 3.68 g (85.4%) of off-white, crystalline solid: mp 106 °C; IR (Nujol) 1742, 1735, 1710 cm^{-1}; NMR ($CDCl_3$) τ 1.72 (d, 2 H), 2.52 (m, 7 H), 5.63 (t, 1 H), 5.88 (q, 2 H), 6.39 (q, 2 H), 6.97 (d, 2 H), 9.05 (t, 3 H), and 9.2 (t, 3 H).

Anal. Calcd for $C_{22}H_{22}N_2O_7$: C, 61.97; H, 5.16; N, 6.74. Found: C, 61.67; H, 5.47; N, 6.40.

Ethyl *N*-Cinnamyl-*p*-nitroanilinomalonate (1e). A mixture of 0.9 g (3 mmol) of *p*-nitroanilinomalonate and 0.67 g (4 mmol) of cinnamoyl chloride in 10 mL of pyridine and 20 mL of benzene was refluxed on a water bath for 6 h. It was washed with 2 N HCl and water, dried (Na_2SO_4), and evaporated at reduced pressure to give a crude solid. This on repeated fractional crystallization from ethanol and petroleum ether mixture yielded 1.29 g (79.8%) of light green needles: mp 99–100 °C; IR (Nujol) 1740, 1728, 1665 cm^{-1}; NMR ($CDCl_3$) τ 2.1 (d, 2 H), 2.54 (m, 7 H), 3.37 (d, 1 H, J = 10 Hz), 3.47 (d, 1 H), 5.17 (d, 1 H), 5.67 (q, 4 H), and 9.03 (t, 6 H).

Anal. Calcd for $C_{22}H_{22}N_2O_7$: C, 61.97; H, 5.16. Found: C, 62.00; H, 4.88.

1-(*p*-Tolyl)-2,2-dicarboethoxy-3-benzoyl-5-pyrrolidinone (4). A solution of 1.33 g (5 mmol) of β-benzoylacrylic acid[13] and 1.54 g (15 mmol) of triethylamine in 30 mL of anhydrous chloroform was maintained at 0 °C with stirring. To this, 0.56 g of ethyl chloroformate was added at a time. After 20 min of stirring, a solution of 1.33 g (5 mmol) of ethyl *p*-toluidinomalonate in 20 mL of anhydrous chloroform was added dropwise while not allowing the temperature of the reaction mixture to rise above 5 °C. The stirring was continued for 0.5 h after the addition was over. The product, isolated in the usual fashion, was a viscous, dark brown liquid which on chromatography over silica gel with ethyl acetate–petroleum ether afforded 0.36 g (10%) of colorless cubes (recrystallized from ethanol): mp 138–139 °C; IR (Nujol) 1758, 1738, 1728, 1688 cm^{-1}; NMR ($CDCl_3$) τ 2.00 (m, 2 H), 2.53 (m, 2 H), 2.90 (m, 5 H), 4.93 (t, 1 H), 5.87 (q, 2 H), 6.07 (q, 2 H), 7.03 (q, 2 H), 7.65 (s, 3 H), 9.00 (t, 3 H), and 9.08 (t, 3 H).

Anal. Calcd for $C_{24}H_{25}NO_6$: C, 68.11; H, 5.91. Found: C, 68.70; H, 5.33.

1-(*p*-Chlorophenyl)-2,2-dicarboethoxy-3-styryl-5-pyrrolidinone (5). β-Styrylacryloyl chloride (obtained by heating 1.7 g of the acid[14] with 3 mL of thionyl chloride in 20 mL of benzene) was taken in 25 mL of benzene and to it was added 1.3 g (5 mmol) of ethyl *p*-chloroanilinomalonate and 5 mL of triethylamine. The mixture was refluxed for 5 h, cooled, and washed successively with 2 N HCl, 5% $NaHCO_3$, and water. After drying over Na_2SO_4, the solvent was stripped off to yield 2.1 g of a viscous liquid which on chromatography over alumina using petroleum ether–ethyl acetate as eluent afforded 0.95 g (22.2%) of a golden yellow, viscous liquid: IR ($CHCl_3$) 1740, 1720, 1690 cm^{-1}; NMR (CCl_4) τ 2.81 (m, 9 H), 3.72 (m, 2 H), 5.97 (m, 5 H), 7.36 (d, 2 H), and 8.97 (m, 6 H).

Diethyl *N*-Cinnamyl-β-anilinobenzylmalonate (6). A mixture of 1.71 g (5 mmol) of ethyl β-anilinobenzylmalonate,[15] 1.0 g (6 mmol) of cinnamoyl chloride, and 2.02 g (20 mmol) of triethylamine in 40 mL of benzene was refluxed on a water bath for 6 h. The reaction mixture was worked up by the usual procedure to afford 1.38 g of colorless needles (recrystallized from benzene–petroleum ether): mp 144–145 °C; IR (Nujol) 1745, 1724, 1637 cm^{-1}. Identical product was obtained when the reaction was carried out under nonbasic condition.

Anal. Calcd for $C_{29}H_{29}NO_5$: C, 73.89; H, 6.15. Found: C, 73.50; H, 6.09.

Acknowledgment. The authors wish to express their sincere thanks to Professors A. K. Bose and M. S. Manhas of Stevens Institute of Technology, and Professor P. K. Bhattacharya and Mr. A. Sarkar of I. I. S., Bangalore, India, for kindly supplying some of the IR and NMR spectra.

Registry No.—**1e**, 62851-33-6; **4**, 62851-34-7; **5**, 62851-35-8; **6**, 62851-36-9; cinnamoyl chloride, 102-92-1; β-benzoylacrylic acid, 583-06-2; ethyl chloroformate, 541-41-3; ethyl *p*-toluidinomalonate, 5634-67-3; β-styrylacryloyl chloride, 40926-86-1; ethyl *p*-chloroanilinomalonate, 5203-01-0; ethyl β-anilinobenzylmalonate, 58929-06-9; diethyl anilinomalonate, 6414-58-0; diethyl *p*-nitroanilinomalonate,

22815-39-0; diethyl *p*-chloroanilinomalonate, 5203-01-0; diethyl *p*-bromoanilinomalonate, 5500-48-1; diethyl *p*-ethoxycarbonylanilinomalonate, 28268-31-7; dimethyl anilinomalonate, 35757-92-7; dimethyl *p*-chloroanilinomalonate, 62851-37-0; dimethyl *p*-bromoanilinomalonate, 62851-38-1; dimethyl *p*-ethoxycarbonylanilinomalonate, 62851-39-2.

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Exploitation of the Vinylogous Wolff Rearrangement. An Efficient Total Synthesis of (±)-Mayurone, (±)-Thujopsene, and (±)-Thujopsadiene

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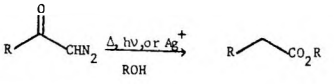
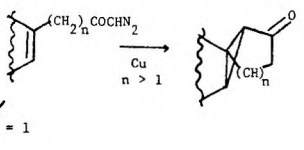
A synthetic route to (±)-mayurone, (±)-thujopsene, and (±)-thujopsadiene employing in turn a vinylogous Wolff rearrangement, a photochemical Wolff rearrangement, and an intramolecular copper-catalyzed cyclopropanation reaction is described.

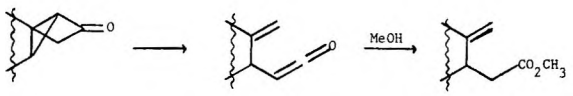
Since the pioneering studies of Arndt and Eistert in the early 1940's α-diazo ketones have found wide application in organic syntheses.[1] Principal among the synthetically useful reactions of this functionality are the Wolff rearrangement (eq 1) and the intramolecular insertion into olefinic bonds (eq 2). The former transformation can be effected thermally,[2] photochemically,[3] and by silver ion[1] catalysis, while the latter is best effected by copper.[4] Recently, we and others have described what appears, formally at least, to be a special case of the latter reaction.[5-7] Specifically, β,γ-unsaturated diazo ketones in the presence of a nucleophile and under the influence of copper lead efficiently via skeletal rearrangement to γ,δ-unsaturated acid derivatives (eq 3). This transformation, a synthetic alternative to the Claisen rearrangement (eq 4),



(1)



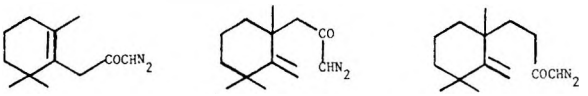
(2)



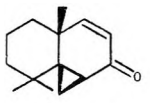
(3)

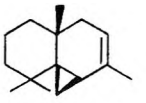
(4)

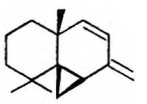
was termed[5] the vinylogous Wolff rearrangement and was suggested to involve the intermediacy of a bicyclo[2.1.0]pentanone, which under the reaction conditions fragments to a β,γ-unsaturated ketene (eq 3).[5-7] In order to illustrate dramatically the synthetic flexibility of the diazo ketone functionality in general, and the use of the vinylogous Wolff rearrangement in particular, we describe here an efficient route to the thujopsene class of sesquiterpenes including mayurone, thujopsene, and thujopsadiene (**1**–**3**). Our approach, employing the three diazo ketones listed below, exploits in turn a vinylogous Wolff rearrangement, a photochemical Wolff rearrangement, and an intramolecular copper-catalyzed cyclopropanation reaction.

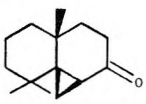


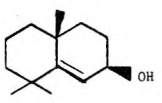
The salient structural feature of the thujopsene class of sesquiterpenes is the cis disposition of the angular methyl group and the cyclopropane ring. Dihydromayurone (**4**) occupies a central place in any synthetic strategy to this class of natural products as it embodies the requisite stereochemical features and furthermore is easily transformed to each member of this class. The first solution of this interesting architectural problem was achieved in 1963 by Dauben and Ashcraft through application of their then recent discovery: the hydroxyl-mediated stereospecific Simmons–Smith reaction (**5** → **6**).[8] Subsequent oxidation yielded (±)-dihydromayurone (**4**), which was transformed into (±)-thujopsene. The second approach, solely to (±)-thujopsene and avoiding the intermediacy of dihydromayurone, was elegantly conceived by Buchi to involve intramolecular cyclization of the carbene derived from tosyl hydrazone **7**.[9] Finally, Anderson[10a] and more recently Mori[10b] and McMurry[11] demonstrated that the intramolecular cyclization of δ,ϵ-unsaturated diazo ketones


MAYURONE (1)


THUJOPSENE (2)


THUJOPSADIENE (3)


DIHYDROMAYURONE (4)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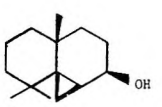
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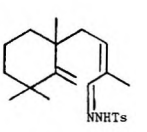
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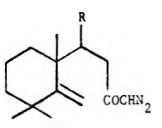
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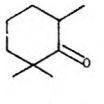
a) R = H

b) R = CO_2CH_3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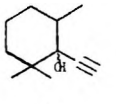
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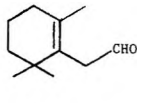
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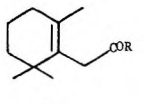
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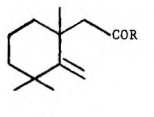
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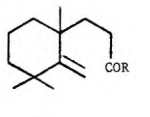
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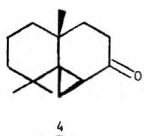
4

a) R = OH c) R = Cl

b) R = OCH_3 d) R = CHN_2

8a and **8b** leads efficiently to dihydromayurone and its β-carbomethoxy derivative.

Our approach to the thujopsene class, envisioned to incorporate in turn the vinylogous Wolff rearrangement, the photochemical Wolff rearrangement, and the intramolecular cyclopropanation reaction, called initially for preparation of the β,γ-unsaturated acid **12a**. This acid appeared at the outset to be easily available by dehydration of the epimeric mixture of alcohols derived from the addition of the lithium enolate of ethyl acetate[12] to 2,2,6-trimethylcyclohexanone. Unfortunately, all attempts (ca. 12 in all) at this dehydration led only to complex mixtures consisting of various amounts of the two α,β-, the β,γ-, and the two γ,δ-unsaturated acid derivatives. Successful acquisition of the desired β,γ-unsaturated acid (**12a**) was finally achieved via Jones oxidation[13] of aldehyde **11**,[14] now readily available through application of the vanadium(V)-catalyzed Meyer–Schuster rearrangement[14,15] of α-acetylenic alcohol **10**.[16] Successive treatment of this crystalline carboxylic acid (**12a**) (mp 55–58 °C) with oxalyl chloride and excess diazomethane afforded diazo ketone **12d** in 65% overall yield.

At this point we were ready to exploit the various diazo ketone transformations discussed above. The first, the vinylogous Wolff rearrangement [i.e., $Cu(acac)_2$; C_6H_{12}–MeOH (0.2% v/v); Δ], afforded ester **13b** in 55% yield. This ester proved to be identical in all respects with that prepared previously by McMurry and Blaszczak via a Claisen rearrangement sequence.[11] With this ester in hand homologation to the corresponding chain lengthened methyl ester (**14b**) via a photochemical Wolff rearrangement, the second utilization of a diazo ketone, was now straightforward. To this end, **13a** was converted in the usual manner [(a) ClCOCOCl; (b) CH_2N_2] to diazo ketone **13d** in 87% yield. Subsequent irradiation of **13d** in methanol through Pyrex ($\lambda \geq 2800$ Å) gave the desired methyl ester (**14b**) in 75% yield. The stage was now set for the third and final diazo ketone transformation, namely the previously reported Mori–McMurry copper-catalyzed intramolecular cyclopropanation reaction.[10,11] This reaction sequence proceeded without event to yield (±)-dihydromayurone (**4**) in 47% yield.

With completion of this efficient approach to dihydromayurone (i.e., 8% overall from 2,2,6-trimethylcyclohexanone), there remained only the conversions to (±)-mayurone, (±)-thujopsene, and (±)-thujopsadiene to fulfill our synthetic goal. To this end dihydromayurone was readily transformed to (±)-thujopsene and (±)-thujopsadiene in 72 and 58% yield, respectively, as originally outlined by Dauben[8] and McMurry.[11] The synthetic samples were identical in all respects (IR, NMR, and VPC retention data) with the natural products.[17,18] Transformation of dihydromayurone to mayurone, on the other hand, had not previously been described. Initial attempts here to utilize the Sharpless–Reich selenoxide elimination[19] sequence lead only to partial conversion. Efforts at this point to effect separation of (±)-dihydromayurone and (±)-mayurone proved unsuccessful. (±)-Mayurone, identical in all respects with natural mayurone,[17] was finally prepared in 75% yield by selenium dioxide oxidation of dihydromayurone.

Experimental Section

Materials and Methods. Vapor-phase chromatography (VPC) was performed with a Varian Aerograph Model 920 gas chromatograph on one of the following columns: A, 25% QF-1, 10 ft × 0.375 in.; B, 6% SE-30, 10 ft × 0.375 in.; C, 25% SE-30, 10 ft × 0.375 in.; D, 6% DEGS, 10 ft × 0.375 in.; E, 12.5% OV 101, 10 ft × 0.375 in. The helium carrier gas flow rate was 100–120 mL/min and the oven temperature ranged from 160 to 190 °C. Compounds isolated by preparative VPC were obtained as either colorless oils or white solids. Melting points were taken on a Thomas Hoover capillary melting point apparatus and are corrected. Boiling points are uncorrected. Solutions were dried over $MgSO_4$ unless specified otherwise. IR and NMR spectra were obtained for CCl_4 solutions, the former on a Perkin-Elmer Model 337 spectrophotometer and the latter on either a Varian A-60 (60 MHz) or HR-220 (220 MHz) spectrometer. Photochemical experiments were carried out with a Hanovia Model L mercury lamp (No. 679A-36) in a quartz immersion well using Pyrex 7740 as filter.

2,2,6-Trimethylcyclohexanone was readily prepared from 2-carbethoxycyclohexanone.[21] The lithium acetylide–ethylenediamine complex was obtained from Research Organic/Inorganic Chemicals Co. and was stored under N_2. Samples of triphenylsilanol and tris(triphenylsiloxy)vanadate were kindly supplied by Hofmann-La Roche. Triphenylsilanol is commercially available from Arapahoe Chemicals and tris(triphenylsiloxy)vanadate can be conveniently prepared from V_2O_5 and Ph_3SiOH.[22]

2,6,6-Trimethyl-1-cyclohexeneacetaldehyde (11). To a suspension of 10.8 g (1.5 equiv) of $LiC{\equiv}CH{\cdot}(CH_2NH_2)_2$ in 60 mL of anhydrous C_6H_6–THF (1:1) warmed to 39 °C under N_2 was added a solution of 11.1 g (79.2 mmol) of ketone **9** in 25 mL of C_6H_6–THF (1:1). During the course of the addition (~10 min) the reaction temperature was maintained at 39 °C by slight cooling. The resulting mixture was then stirred at room temperature for 10 h. After careful addition of 15 mL of H_2O the mixture was refluxed for 1 h. The reaction mixture

was then poured into saturated aqueous NH_4Cl and extracted with Et_2O. The organic phase was separated, washed with H_2O and brine, and dried. Removal of the solvent in vacuo followed by distillation of the residue afforded 11.9 g (90%) of an oily liquid boiling at 56–58 °C (1.4 torr) which consisted of a 75:25 (NMR; relative area for acetylenic hydrogen's) epimeric mixture of the corresponding propynols (10): IR 3650 (m), 3550–3400 (w, br), 3310 (m), 2970 (s), 2940 (s), 1460 (m), 1030 (s) cm^{-1}.

A solution consisting of 3.87 g (23.3 mmol) of the propynols and 1.44 g of Ph_3SiOH in 20 mL of paraffin oil ($d^{20} = 0.86$) was heated to 144 °C under N_2. To this was added 450 mg of tris(triphenylsiloxy) vanadate (91%). The resulting solution was stirred for 5 h at 144–146 °C under N_2, cooled to 40 °C, and then distilled under reduced pressure. The colorless oil [3.42 g, 88%, 75–82 °C (1.0 Torr)] obtained was found to be a 9:1 mixture (VPC on column A) of **11** and the α,β-unsaturated isomers, respectively. An analytical sample of **11** obtained by VPC on column A had the following spectral data: IR 2940 (s), 2860 (s), 2830 (s), 2720 (m), 1720 (s), 1460 (m) cm^{-1}; NMR (60 MHz) δ 0.95 (s, 6 H), 1.33–2.30, 1.58 (m, s, 9 H), 3.05 (s, 2 H), 9.50 (t, J = 2.5 Hz, 1 H).

2,6,6-Trimethyl-1-cyclohexeneacetic acid (12a). A solution of 330 mg (2.0 mmol) of aldehyde **11** in 15 mL of acetone was chilled to 0–5 °C and then treated with 740 μL (1.0 equiv) of CrO_3–H_2SO_4 (2.7 M). After stirring at 0–5 °C for 30 min the reaction mixture was poured into water and extracted with Et_2O. The organic phase was washed with two 25-mL portions of 5% (w/v) aqueous NaOH. The aqueous phase was separated, acidified (dilute HCl), and extracted with ether. The organic phase was washed with H_2O and brine, and dried. Removal of the solvent in vacuo yielded 300 mg (83%) of crude crystalline **12**. An analytical sample was obtained by recrystallization from petroleum ether (30–60 °C) at low temperature. The resulting white, crystalline solid had mp 55–58 °C and the following spectral data; IR 3500–2600 (s, br), 1705 (s), 1455 (m), 1405 (m), 1380 (w), 1360 (w), 1290 (m), 1220 (m) cm^{-1}; NMR (60 MHz) δ 0.97 (s, 6 H), 1.30–2.50, 1.62 (m, s, 9 H), 3.06 (s, 2 H), 11.0 (br s, 1 H); *m/e* 182.1298 (M^+, calcd for $C_{11}H_{18}O_2$, 182.1306).

Methyl 1,3,3-Trimethyl-2-methylenecyclohexaneacetate (13b). A solution consisting of 3.00 g (16.7 mmol) of acid **12a** in 20 mL of dry benzene was treated with 2.20 mL (1.50 equiv) of oxalyl chloride and then stirred at room temperature for 8 h. The resulting solution was concentrated in vacuo and the residue distilled (Kuglerohr), yielding 2.77 g (83%) of the corresponding acid chloride (**12c**) [IR 2940 (s), 2870 (s), 1800 (s), 1460 (m), 1360 (m), 950 (s) cm^{-1}].

A solution of 2.17 g (10.8 mmol) of **12c** in 50 mL of anhydrous ether was added dropwise with stirring to a chilled, ethereal solution of CH_2N_2 (5–6 equiv). After the addition, the resulting solution was allowed to stand overnight at room temperature. The excess diazomethane was then removed on a steam bath and the remaining solution was dried and concentrated in vacuo to yield 2.23 g (100%) of diazo ketone **12d** [IR 3130 (w), 2940 (s), 2105 (s), 1640 (s), 1350 (s) cm^{-1}]. This diazo ketone (435 mg, 2.12 mmol) was dissolved in 56 mL of cyclohexane and then treated with 40 mg of $Cu(acac)_2$ and 112 μL of MeOH (1.1 equiv). The resulting mixture was heated at reflux for 1 h, cooled, washed with three 50-mL portions of 2 N HCl, and dried. Removal of the solvent in vacuo yielded 395 mg of a dark oil which contained 244 mg (55%, VPC) of ester **13b**. An analytical sample obtained by VPC on column A possessed the following spectral data which were identical in all respects with the spectral data provided by Prof. McMurry for this ester: IR 3110 (w), 2960 (s), 2940 (s), 2875 (m), 1740 (s), 1630 (w), 1460 (m), 1440 (m), 1190 (m), 1005 (m), 902 (m) cm^{-1}; NMR (60 MHz) δ 0.92–2.10, 1.10, 1.22 (m, s, s, 15 H), 2.43 (s, 2 H), 3.53 (s, 3 H), 4.83 (s, 1 H), 4.96 (s, 1 H).

Methyl 1,3,3-Trimethyl-2-methylenecyclohexanepropionate (14b). A solution of 1.47 g (7.0 mmol) of ester **13b** in 15 mL of MeOH was treated with 10 mL of 5% (w/v) aqueous NaOH and refluxed for 2 h under a N_2 atmosphere. The reaction mixture was then cooled, poured into water, and extracted with ether. The aqueous phase was separated, acidified (dilute HCl), and extracted with ether. The resulting organic phase was washed with H_2O and brine, and dried. Removal of the solvent in vacuo afforded 1.27 g (93%) of carboxylic acid **13a** [IR 3700–2600 (s, br), 1705 (s), 1610 (w), 1460 (m), 1400 (m), 1295 (m), 1235 (m), 902 (m) cm^{-1}].

This acid (1.27 g, 6.5 mmol) was dissolved in 5 mL of benzene and treated with 1.0 mL (1.8 equiv) of oxalyl chloride. The resulting solution was then stirred for 5 h at room temperature, concentrated under reduced pressure, and distilled (Kuglerohr) to yield 1.29 g (93%) of acid chloride **13c** [3100 (w), 2960 (s), 2945 (s), 1800 (s), 1620 (w), 908 (m) cm^{-1}].

A solution of this acid chloride (1.29 g, 6.00 mmol) in 50 mL of anhydrous ether was added dropwise with stirring to a chilled, ethereal solution of CH_2N_2 (4.5 equiv). The resulting solution was allowed to stand overnight at room temperature and then after removal of excess diazomethane on a steam bath, the remaining solution was concentrated in vacuo to yield 1.38 g (100%) of diazo ketone **13d** [IR 3120 (w), 2970 (s), 2945 (s), 2110 (s), 1645 (s), 1350 (s), 900 (m) cm^{-1}]. Without further purification diazo ketone **13d** was dissolved in 70 mL of MeOH and irradiated for 1.3 h. The photolysate was poured into H_2O and extracted with ether. The organic phase was washed with H_2O and brine, and dried. Removal of the solvent in vacuo afforded 1.23 g of a yellow oil which on distillation (Kuglerohr, 110–115 °C) afforded 1.05 g (75%) of ester **14b**. An analytical sample obtained by VPC on column B had the following spectral characteristics: IR 3100 (w), 2950 (s), 2870 (s), 1740 (s), 1670 (m), 1460 (m), 1440 (m), 1380 (m), 1360 (m), 1200 (s), 1175 (s), 902 (s) cm^{-1}; NMR (60 MHz) δ 1.00–2.40, 1.06, 1.11 (m, s, s, 19 H), 3.59 (s, 3 H), 4.83 (s, 1 H), 5.03 (s, 1 H).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78, Found: C, 74.77; H, 10.74.

Dihydromayurone (4). A solution consisting of 545 mg of diazo ketone **14d** [IR 3100 (w), 2960 (s), 2100 (s), 1645 (s), 1350 (s), 900 (m) cm^{-1}], prepared in 86% overall yield [NaOH, MeOH; $(ClCO)_2$, C_6H_6; CH_2N_2, Et_2O] from ester **14b**, in 10 mL of cyclohexane was added dropwise to a refluxing suspension of 720 mg of Cu powder, 214 mg of $CuSO_4$ (anhydrous), and 60 mL of cyclohexane. The resulting mixture was stirred at reflux for 1 h following the addition. After cooling, the reaction mixture was washed with three 50-mL portions of 2 N HCl, dried, and concentrated in vacuo to afford 525 mg of a dark oil. This oil was chromatographed on silica gel. Elution with hexane–benzene (1:1) and then hexane–benzene (3:7) yielded 224 mg (47%) of crystalline ketone **4**. An analytical sample obtained by VPC on column D had a mp of 100 °C and the following spectral data which were in good agreement with literature data[10] for this ketone: IR 3075 (w), 3020 (m), 2950 (s), 2870 (s), 2860 (s), 1680 (s), 1470 (m), 1275 (s), 1100 (m), 910 (m), 870 (m) cm^{-1}; NMR (60 MHz) δ 0.64 (s, 3 H), 0.91 (m, 1 H), 1.04–2.32, 1.13, 1.21 (m, s, s, 18 H).

(±)-Thujopsene (2). A solution of 42 mg (0.2 mmol) of ketone **4** dissolved in 5 mL of anhydrous ether under a nitrogen atmosphere was first treated with 5 equiv of MeMgI and then refluxed for a period of 40 min. The reaction mixture was cooled to room temperature and carefully treated with 2.0 mL of saturated aqueous NH_4Cl. The resulting suspension was poured into ether and water and the aqueous phase was separated. The organic phase was washed with H_2O and brine, and dried. Removal of the solvent in vacuo yielded 48 mg of a yellow oil which consisted mainly of thujopsene (**2**) and a small amount (12%; VPC) of ketone **4**. The yield based on recovered **4** was 72% (VPC). A sample obtained by preparative VPC on column C was identical [VPC retention properties, IR, NMR] with an authentic sample of natural (±)-thujopsene.[17]

(±)-Mayurone (1). A solution consisting of 32.2 mg (0.16 mmol) of ketone **4**, 112 mg of SeO_2, and 15 mL of *t*-BuOH was heated at reflux under an atmosphere of N_2 for 41 h. After filtration, the mixture was evaporated in vacuo and the residual material was dissolved in 15 mL of MeOH and agitated for 3 h in the presence of 450 mg of Raney Ni (deactivated).[23] The mixture was then filtered and the filtrate evaporated under reduced pressure. The remaining residue was washed with three 10-mL portions of ether. The ether washings were combined, washed with brine, and dried. Removal of the solvent in vacuo afforded 44.5 mg of a dark oil which contained 24.5 mg (75%; VPC) of enone **1**. An analytical sample obtained by VPC on column D was found to be identical (IR, 220 MHz NMR, and VPC retention properties) with an authentic sample of mayurone.[17]

(±)-Thujopsadiene (3). A solution containing 41.2 mg (0.2 mmol) of enone **1** in 5 mL of dry ether (distilled from $LiAlH_4$) was first treated with 4 mL (36.8 equiv; 1.84 M) of methyllithium and then gently refluxed under a nitrogen atmosphere for 3 h. After cooling to 0–5 °C 15 mL of saturated aqueous NH_4Cl was then added. The resulting mixture was poured onto water–pentane (1:1 v/v) and the aqueous layer separated. The organic phase was washed with H_2O and brine, and dried. Removal of the solvent in vacuo afforded 41 mg of an oil containing 31.9 mg (78.5%; VPC) of diene **3**. An analytical sample obtained by VPC on column E possessed spectral data (IR and NMR) which were identical in all respects with those provided by Professor McMurry for (±)-thujopsadiene.[18]

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Regional NMR Facility (NIH No. RR542) at the University of Pennsylvania, where the 220-MHz NMR spectra were obtained.

Registry No.—**1**, 51446-90-3; **2**, 17974-52-6; **3**, 51446-91-4; **4**, 28890-28-0; **9**, 62861-88-5; *cis*-**10**, 62861-89-6; *trans*-**10**, 62861-90-9; **11**, 472-66-2; **12a**, 472-68-4; **12c**, 62861-91-0; **12d**, 62861-92-1; **13a**, 62861-93-2; **13b**, 51417-31-3; **13c**, 62861-94-3; **13d**, 62861-95-4; **14b**, 62861-96-5; **14d**, 62861-97-6.

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A Conformational Analysis of Cyclopropanodecalin Derivatives by Carbon-13 Nuclear Magnetic Resonance Spectroscopy[1]

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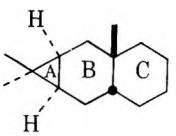
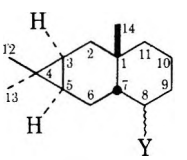
The ^{13}C NMR spectra of 18 cyclopropanodecalins based on the carane skeleton and containing a *cis*-decalin configuration have been recorded and all carbon shifts assigned. The β-deuterium isotope effect of some multiply deuterated compounds aided the shift assignment. On the basis of the shift data the hydrocarbons, alcohols, and acetates could be classified in terms of the two possible *cis*-decalin conformations.

The stereochemical and conformational features of a series of tricyclic substances derived from (−)-*cis*-caran-3-one have been the subject of recent chemical[3] and spectroscopic[3,4] studies, circular dichroism,[3] ^1H NMR,[3] IR,[3] and, in one instance, x-ray crystallographic, data[4] having been gathered on trimethylcyclopropanodecalin derivatives (**1**). The present communication represents an extension of the earlier ^{13}C NMR investigation of bicyclic carane derivatives[5] and reports the chemical shift assignment and conformational assessment of tricycles based on structure **1**.



1

The compounds chosen for study consisted of the hydrocarbon **1**, nine derivatives possessing a single methyl, hydroxy, or acetoxy substituent on ring C (**2**–**6** and **15**–**18**) and eight derivatives containing two of these functions on ring C (**7**–**14**). For four of these substances, **1**, **5**, **15**, , and **16**, the assignment of seven of the decalin ring carbons has been obtained by a minimum number of deuteration experiments, making extensive use of the deuterium β-effect.[5,6] This technique has permitted the characterization of the conformationally impure members of this class of compounds.



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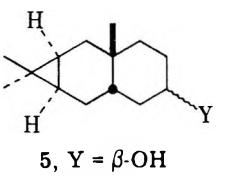
3, Y = α-OH
4, Y = α-OAc
17, Y = β-OH
18, Y = β-OAc



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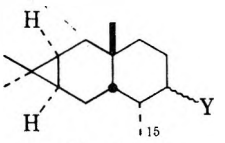
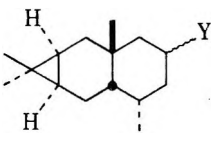
6, Y = β-OAc
15, Y = α-OH
16, Y = α-OAc



7, Y = β-OH
8, Y = β-OAc
11, Y = α-OH
12, Y = α-OAc



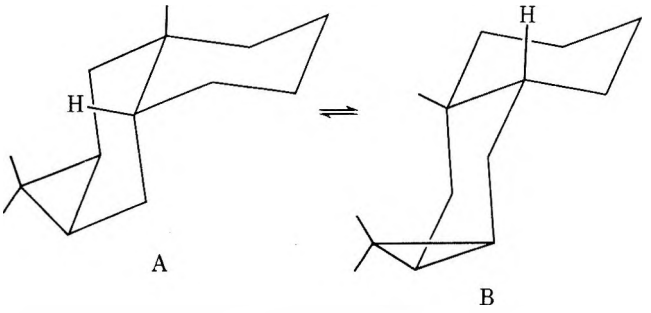
9, Y = α-OH
10, Y = α-OAc
13, Y = β-OH
14, Y = β-OAc

The B/C cis ring junction of these substances allows the skeleton to adopt conformation A or B or exist as a mixture of the two forms.[7] On the basis of conformational analysis, A is expected to be of lower energy in view of its avoidance of the severe nonbonded interaction of C(12) and C(14) in B. Furthermore, in the monofunctional derivatives possessing either

Table I. Chemical Shifts of Tricycles 1–10[a,c]

	1	2	3	4	5	6	7	8	9	10
C(1)	30.7	31.8	32.6	32.7	30.1	30.0	31.6	31.4	33.0	33.0
C(2)	34.9	35.2	34.7	34.6	33.7	33.6	34.1	34.1	34.9	34.8
C(3)	17.5	17.0	16.9	16.9	17.1	17.6	16.6	16.6	16.7	16.7
C(4)	16.7	16.6	16.7	16.7	16.7	16.6	16.7	16.5	16.6	16.7
C(5)	18.9	18.4	17.7	17.7	18.4	18.2	18.2	18.0	18.2	18.1
C(6)	20.4[b]	14.9	14.1	15.1	21.5	21.2	16.6	16.5	14.9	14.9
C(7)	36.2	41.6	42.4	39.8	36.8	36.6	42.7	42.5	40.5	40.5
C(8)	26.7	29.7	69.5	73.1	36.4	32.3	37.5	34.4	29.2	29.0
C(9)	19.6	27.4	28.2	24.7	66.4	69.8	71.4	74.3	37.5	33.0
C(10)	21.6[b]	21.7	20.2	20.0	31.1	27.0	31.1	27.3	67.7	71.1
C(11)	31.3	30.2	29.7	29.7	30.2	29.8	30.1	29.5	40.0	35.9
C(12)	15.5	15.5	15.4	15.5	15.3	15.2	15.3	15.2	15.5	15.2
C(13)	28.7	28.6	28.4	28.5	28.5	28.4	28.5	28.4	28.4	28.5
C(14)	27.0	26.8	26.6	26.5	26.9	26.7	26.9	26.7	27.5	27.3
C(15)		19.1					14.8	14.7	18.2	18.1
C=O				170.2		170.2		170.5		170.4
Ac Me				21.3		21.2		21.1		21.4

[a] In ppm downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b] Assignments may be reversed. [c] Registry no.: **1**, 62961-16-4; **2**, 62961-17-5; **3**, 62961-18-6; **4**, 62961-19-7; **5**, 62961-20-0; **6**, 62961-21-1; **7**, 62961-22-2; **8**, 62961-23-3; **9**, 62961-24-4; **10**, 62961-25-5.



a *cis*-H(7)–H(8) or a *trans*-H(7)–H(9) configuration, the substituent adopts an equatorial stance in A, hence yielding to this conformer even greater preference over form B. This prediction has been borne out for the *p*-bromobenzoate of alcohol **5** in the solid state.[4] On the assumption of substances having only equatorial substituents in conformer A showing similar conformational behavior, these tricycles were submitted to ^{13}C NMR analysis first.

Chemical Shift Assignments

The dimethylcyclopropyl moiety is recognized readily from the equivalence of the carbon resonances of this group with those previously characterized among carane derivatives.[5] Thus, the *endo*- and *exo*-methyl signals appear at 15.4 ± 0.1 and 28.5 ± 0.1 ppm, respectively, and the resonance of their common quaternary carbon neighbor at 16.8 ± 0.2 ppm. The high-field cyclopropyl methines, C(3) and C(5), resonate over two narrow ranges, 17.1 ± 0.5 and 18.3 ± 0.6 ppm. Within each substance the low-field signal is allocated to C(5) on the basis of deuteration experiments (vide infra). While the methine values apply strictly only to substances with equatorial ring C substituents, deviations from these ranges exceed not more than a few tenths of a part per million in any of the derivatives.

After recognition of the *gem*-dimethylcyclopropyl signals, the angular methyl group and the bridgehead quaternary center in the 8α and 9β derivatives **2**–**4** and **5**–**6**, respectively, are unique carbon types identified by the multiplicity patterns of their single-frequency off-resonance decoupled (SFORD) spectra. The angular methyl group of **2** displays a sharp quartet pattern similar to that of each of the *gem*-methyl groups, whereas the components of the C(8) methyl quartet show greater half-widths due to residual two-bond carbon–hydrogen and/or second-order coupling.[8,9] The hydroxymethine and bridgehead methine signals in **3**–**6** are assigned routinely. The differentiation of the latter from C(8) in **2** follows from the practically equivalent β-effects of the hydroxy and methyl groups (cf. **2** and **3**). These considerations leave only the methylene signals of **2**–**6** to be assigned.

Comparison of the spectra of the alcohols **3** and **5** with their respective acetates identifies the centers attached to the carbinol carbon, i.e., C(9) of **3** and C(8) and C(10) of **5**, but does not differentiate the latter pair. Between **3** and **5** C(6) experiences the loss of a peri interaction and C(10) gains a β-effect. Hence these two carbons are expected to resonate at lower field in **5**, while two additional methylene peaks, C(2) and C(11), remain unaffected in the two alcohols and their acetates. These interrelationships specify the assignments given in Table I for C(6), C(9), and C(10) of the 8α-substituted compounds and C(6), C(8), and C(10) of the 9β-functionalized substances. Since alcohol **3** differs trivially from **2** at only the functionalized ring carbon, tentative assignments, except for the differentiation of C(2) from C(11), are complete for **2**–**6**.

The above shift allocations are corroborated by consideration of the *trans*-H(8)–H(9) and *cis*-H(8)–H(10) disubstituted derivatives **7** and **9** and their acetates. With reference to **2**, the introduction of an equatorial hydroxy group into **7** and **9** causes the perturbation of two ring carbons aside from the newly substituted site. The methylene carbons β to the hydroxy group in **9** are shifted downfield 10 ppm from their position in **2**. The C(11) shift identifies, by difference, the ca. 35 ppm resonance as the only methylene signal remaining constant in **2**–**10** and, hence, as the signal of C(2).

Apart from the resonances of the C(6)–C(9) fragment of **1**, the spectrum of this hydrocarbon bears a strong resemblance to that of **2**. However, three methylene signals within 2 ppm of each other leave the assignments based solely on chemical shift correlations uncertain. The resonances of four of the six methylene centers in this substance have been proven by deuteration experiments (vide infra). Carbon(10) is assigned tentatively the 21.6-ppm signal, a value identical with the C(10) resonance of **2**. All carbons shifts of compounds **1**–**10** are listed in Table I.

The conformation of the above substances is implicit in the chemical shift relationships between the mono- and disubstituted derivatives. Thus, for example, on comparison of **9** and **2**, the hydroxy group causes insignificant perturbations at all sites other than C(9), C(10), and C(11), the substituted and β carbons. The conspicuous absence of γ-effects relegates the oxygen function to an equatorial orientation. This fact and

Table II. Chemical Shifts of Tricycles 11–18[a,e]

	11	12	13	14	15	16	17	18
C(1)	31.6	31.4	31.3	31.3	29.2	29.4	31.0	30.7
C(2)	35.1	35.0	35.4	35.1	28.0	29.4	31.4[b]	32.4
C(3)	17.1	16.8	17.1	17.0	19.0	18.6	18.5	17.9
C(4)	16.7	16.7	16.9	17.0	17.9	17.7	17.4	17.2
C(5)	18.4	18.3	18.6	18.4	18.8	18.7	18.4	17.9
C(6)	16.7	16.5	14.6	14.6	22.1	21.8	18.5[c]	19.0[d]
C(7)	40.9	40.6	41.2	40.8	38.2	37.3	45.7	41.4
C(8)	33.7	32.8	24.7	25.5	37.4	33.0	71.4	74.1
C(9)	70.9	72.9	34.4	31.4	69.6	71.7	30.9[b]	26.4
C(10)	29.9	26.9	68.1	71.2	31.3	27.3	18.7[c]	18.1[d]
C(11)	25.3	25.8	37.5	34.0	37.4	34.8	36.3	34.1
C(12)	15.4	15.4	15.4	15.4	15.5	15.4	15.3	15.3
C(13)	28.5	28.4	28.5	28.4	29.0	28.8	28.6	28.4
C(14)	26.7	26.6	30.0	29.1	30.0	29.2	30.3	29.3
C(15)	15.1	14.8	18.6	18.4				
C=O		170.2		170.2		170.0		170.1
Ac Me		21.3		21.6		21.3		21.4

[a] In ppm downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b,c,d] Assignments may be reversed. [e] Registry no.: **11**, 62961-26-6; **12**, 62961-27-7; **13**, 62961-28-8; **14**, 62961-29-9; **15**, 62961-07-3; **16**, 62961-08-4; **17**, 62961-09-5; **18**, 62961-10-8.

the known relative configuration of these substances[3] are sufficient to define their conformation as A. The possibility of some members of the series **1–10** being conformer mixtures, with significant proportions of B present, is excluded by the constant C(2) resonance which, as shown below, is highly sensitive to conformational change. Examination of Table I reveals the C(2) resonance appears over the narrow range of 35.0 ± 0.4 ppm, exclusive of compounds **5–8**. The latter four substances, whose C(2) signal is ca. 1 ppm upfield, have a common equatorial C(9) oxy substituent. This perturbation is likely the result of polarization of the C(1)–C(2) bond by the carbon–oxygen dipole, which should show its strongest effect on the C(1)–C(2) axis when emanating from an equatorial C–O bond [cf. the C(2) shifts in the hydroxy epimers of **5** and **7** in Table II]. Additional examples of long-range, ϵ shieldings attributable to hydroxy substitution in equivalent molecular arrays, i.e., *trans*-4-alkylcyclohexanols contained within conformationally rigid skeleta, indicate the regularity of the effect and require an explanation that does not invoke atomic interaction or conformational mobility.[10]

Four disubstituted derivatives of **1**, i.e., **11–14**, possess one axial and one equatorial substituent on ring C. Hence, irrespective of the conformational disposition of these substances, the axial group interacts 1,3-diaxially with a single alkyl substituent, either the angular methyl group or C(6). While 1,3-diaxial alkyl–alkyl and alkyl–hydroxyl interactions need not be energetically equivalent, the overriding factor determining the conformer preference remains, to a first approximation, the C(1)–C(4) methyl–methyl interaction. On this basis it may be anticipated that compounds **11–14** are further representatives of conformer A, in which the oxygen function assumes an axial orientation. Spectral comparison of **11** and **13** with their epimeric hydroxy counterparts, **7** and **9**, respectively, confirms this assessment. In particular, the conformational weathervane C(2) (vide supra) is equivalent, except as noted above, for both of these substances and their acetates. The axial hydroxy group of **11** is revealed by mild shielding of C(8), C(9), and C(10) and the strong γ-effect (5 ppm) suffered by C(11) relative to **7**. A cogent argument establishing the axial orientation of the hydroxy group is the insignificant shift of C(8) accompanying acetylation. In three of the four possible stereoisomers of unsymmetrical, chair-like, vicinally hydroxylated and methylated cyclohexanes acetylation results in 2.5–4.0 ppm shielding of the centers bound to the carbinol carbon. These shieldings are examples of γ-effects in which the oxygen substituent interacts sterically with the hydrogen at the oxycarbon sites. This interaction is not possible with the hydrogen of the methine holding the methyl group in the cis isomer in which the oxygen function is axial. Analogous behavior is observed in cases of O-methylation.[11,12]

The C(8) methyl resonance of **13** and **14** is the same as that of **9** and **10**, while the angular methyl group is shifted ca. 2.5 ppm downfield from its location in the latter substances. The magnitude of this δ-effect is typical of the response of methyl functions opposed by a *syn*-diaxial hydroxy group.[13] This effect and the normal magnitude of γ-effects of the same group in **11** and **13** [cf. C(11) of **11** and **7** and C(8) of **9** and **13**] suggests the absence of any unusual deformation of ring C in these substances. The foregoing considerations establish that all substances **1–14** have a common, unique conformation in which the angular methyl group is axial with respect to ring C, as in A. All chemical shifts of compounds **11–14** are listed in Table II.

An unambiguous assessment of the ground-state energy difference of the alternate conformers of **15–18** is impossible. These substances contain a single ring C substituent stereochemically oriented in such a way as to introduce a destabilizing *syn*-diaxial oxygen–alkyl interaction into the otherwise preferred conformer A. In fact, the spectra of these substances do not correlate with **1–14** except for the conformationally insensitive *gem*-dimethylcyclopropyl moiety. Furthermore, the curious behavior of both **15** and **17** accompanying acetylation indicates these compounds to be represented not by a unique conformation, but rather to be conformer mixtures. Comparison of **15** and **16**, for instance, shows four of the five methylene signals to undergo 2–4-ppm shifts, a result which defies simple explanation unless a change in the equilibrium concentration of alternate conformers exists between **15** and its acetate.

This circumstance negates the usual criteria employed in signal assignment and requires an alternate method of chemical shift evaluation. The technique chosen for this purpose entails inspection of deuterated analogues of the protio compounds under carefully controlled conditions to allow recognition of the small deuterium β-effects (2–3 Hz per deuterium in the absence of proximate heteroatoms) as well as the directly deuterated carbons.

The pentadeuterio hydrocarbon **25** and alcohols **22** and **23** were prepared by known literature procedures (Scheme I). The starting material (−)-*cis*-caran-3-one was converted into its trideuterio derivative **19** with loss of stereochemical integrity at C(4) by carbonate-induced exchange in deuterium oxide–dioxane solution. After Robinson annelation and two

Table III. Chemical Shift and Shift Differences Between Protio and Deuterio Tricycles[a]

	1	25[f]	Δδ[b]	5	22[f]	Δδ	15	23	Δδ	16[c]	24[c,f]	Δδ
C(1)	30.70	30.67	–	30.09	30.02	−2	29.15	*d*		29.36	*d*	
C(2)	34.91	34.89	–	33.72	33.70	–	28.03	28.10	+2	29.36	29.44	+2
C(3)	17.50	17.50	–	17.11	17.11	–	18.95	18.93	–	18.56	18.51	–
C(4)	16.67	*d*		16.65	*d*		17.91	17.84	–	17.69	17.64	–
C(5)	18.88	18.69	−5	18.41	18.25	−4	18.78	18.64	−4	18.66	18.51	−4
C(6)	20.35	*e*		21.49	*e*		22.05	*e*		21.81	*e*	
C(7)	36.19	35.93	−7	36.84	36.60	−6	38.20	37.96	−6	37.28	36.99	−7
C(8)	26.70	26.46		36.41	*e*		37.39	*e*		33.04	*e*	
C(9)	19.63	19.34	−7	66.39	66.39	0	69.64	69.42	−6	71.72	71.67	−1
C(10)	21.61	*e*		31.13	*e*		31.32	*e*		27.28	*e*	
C(11)	31.28	31.14	−4	30.16	29.92	−6	37.35	37.11	−6	34.81	34.55	−7
C(12)	15.49	15.49	–	15.27	15.27	–	15.49	15.49	–	15.37	15.39	–
C(13)	28.71	28.72	–	28.46	28.47	–	28.98	28.96	–	28.81	28.83	–
C(14)	27.00	26.95	–	26.91	26.92	–	30.02	30.02	–	29.22	29.19	–

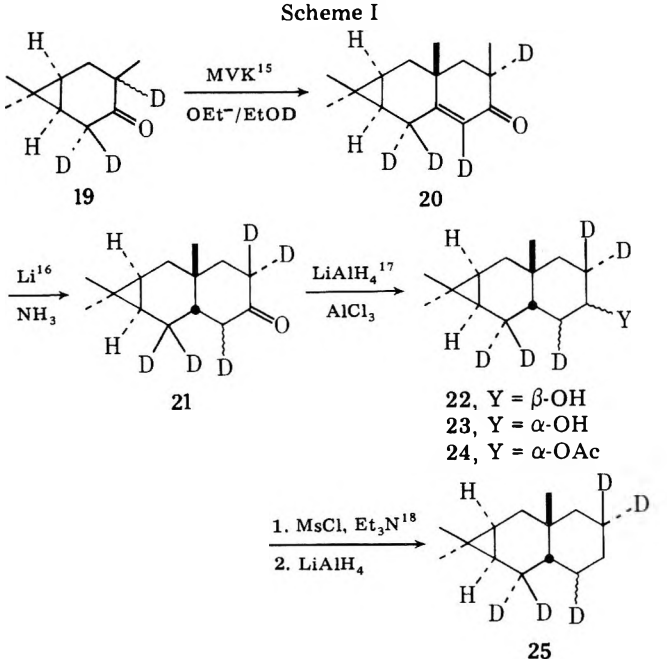
[a] Chemical shifts in ppm downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b] $\Delta\delta$ = δ(deuterio derivative) − δ(protio derivative), expressed in Hz. Digital resolution = ±0.6 Hz. Negative sign indicates an upfield shift. [c] Acetate carbonyl and methyl signals reported in Table II. [d] Signal not detected. [e] Deuterated carbon signal not detected. [f] Registry no.: **22**, 62930-39-6; **24**, 62930-40-9; **25**, 62930-41-0.

reductions alcohol **22** was reduced further to hydrocarbon **25** and alcohol **23** was acetylated, thus yielding 6,6,8,10,10-pentadeuterio analogues of **1**, **5**, **15**, and **16**.[14]

The spectrum of **25** contains two less signals than that of **1**. The slowed rate of dipolar relaxation of fully deuterated carbons, splitting of the resonance by one-bond C–^{2}H coupling, and broadening of all resonances of carbons two and three bonds from the deuterium atom contribute to the vanishingly low intensity of the C(6) and C(10) signals. The monodeuterated site, C(8), is detected as a low-intensity, broad 1:1:1 triplet centered at 26.5 ppm in the proton noise-decoupled spectrum (see Table III). In the remaining deuterated compounds, however, the monodeuterated methylene signal was not observed due to small amounts of available material and, hence, low spectral signal-to-noise ratios.

The pattern of deuterium incorporation in **25** is arranged in such a manner as to yield to each member of undeuterated methylene and methine sets a different number of β-deuterons. Thus the methylenes C(2), C(11), and C(9) and the methines C(3), C(5), and C(7) possess zero, two, and three β-deuterium neighbors, respectively. On the assumption of the small, upfield deuterium β-effects being approximately additive and γ-effects being negligible, the resonances of these six carbons can be assigned unambiguously by the magnitude of their shifts in **25** vs. those of **1**. The correlation of these spectra is presented in Table III. The assumption of insignificant γ and longer range effects is supported fully by the invariant resonances of C(2), C(3), and the methyl groups (<1 Hz change). Carbon-2 is unique, being the only methylene to remain constant in **1** and **25**. Among the two cyclopropyl methines of **25** C(3) has no deuterium neighbors and is constant, whereas C(5) experiences a 5-Hz upfield shift. This shift is due to two β-deuterons and implies that each deuterium shows a 2–3-Hz β-effect. The three β-deuterons of the unambiguous C(7) methine of **25** yield a 7-Hz perturbation of this carbon's resonance, corroborating the approximate magnitude and additivity of the β-deuterium effects. Hence, the upfield 7 and 4 Hz shifts of the 19.6- and 31.3-pp methylene resonances of **1** in its deuterated analogue relegate these signals to C(9) and C(11), respectively, and complete the assignment of this hydrocarbon.

Scheme I

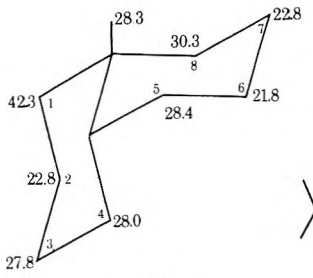


The shift changes between alcohols **5** and **22** parallel closely those of the hydrocarbons, except at the oxygenated site which does not reflect the presence of β-deuterons. Despite attempts to maintain identical conditions, the anomalous shift of the oxycarbon may reflect different degrees of hydrogen bonding, causing perturbations as large as the deuterium β-effects. The assignments dictated by the deuterium results (Table III) are in full accord with those given in Table I.

A similar correlation of **15** and **16** with their pentadeuterio derivatives **23** and **24**, respectively, yields a complete assignment of the undeuterated ring carbons of these substances independent of chemical shift relationships (see Table III). Among the directly deuterated carbon resonances of **15** the high-field 22-ppm resonance is not altered by acetylation (cf. **15** and **16**) and therefore is allocated to C(6) (vide infra). The C(8) and C(10) signals of **15** are differentiated by comparison with **5** and are discussed below with respect to the conformational stance of the compound.

In comparison to derivatives 1–14 the C(2) resonance of alcohol **15** has undergone a dramatic upfield shift. A large shift change at this position has analogy in the chemical shifts of *cis*-9-methyldecalin (**26**).[19] A strong likeness of the angular methyl and ring C carbon resonances of hydrocarbon **1** to equivalent centers in **26** is apparent on the formulas below. The flattening of ring B of **1** by the cyclopropyl function must alter the γ-effects of ring B carbons acting on ring C centers and hence exact correspondence of these resonances with those of like carbons of **26** cannot be expected. However, two sets of shifts suggest that **26** is a realistic model for the tricyclic

substances. The conformational mobility of **26** at room temperature averages the neopentyl centers C(1) and C(8) as well as C(3) and C(6). These two resonance pairs are the only conformationally diagnostic signals, since the remaining, averaging carbon pairs, C(2)–C(7) and C(4)–C(5), have nearly equal δ values in both conformers due to similar environments and accidental degeneracy, respectively. The large 12-ppm difference of the neopentyl methylenes of **26** and the approximate correspondence of ring C shifts between **26** and **1** indicate qualitatively that the C(2) and C(11) resonances of **1** exhibit probably large, inversely proportional shift perturbations between conformers A and B. While **1** exists exclusively as A, **15** does not. In fact, the C(2) and C(11) shifts of the latter display shift modifications in consonance with those predicted from model **26**. Compared with **5**, C(2) of **15** is shifted upfield 5.7 ppm and C(11) downfield 7.1 ppm. The larger shift change at C(11) must take into account also the partial loss of the γ-effect from the hydroxy group in conformer B. The fortuitous cancellation of shift perturbations which yield similar C(4) and C(5) δ values in **26** is reflected also in the conformationally insensitive C(6) resonance between **5** and **15** (vide supra).



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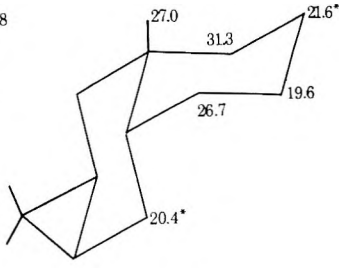


1

The proportions of the A and B contributions to the description of **15** cannot be calculated accurately, since the δ values the C(2) and C(11) resonances would possess in conformer B are not known. However, an approximate assessment is possible. The chemical shift of C(10) in **5** and **15** is nearly identical. To the extent the behavior analogous to that of *cis*-9-methyldecalin (**26**) is observed at this site, i.e., equal γ-effects at C(10) from the angular methyl group in conformer A and from C(2) in conformer B, the C(10) resonance implies that **15** is represented exclusively by conformer B. Though this center is not expected to be changed significantly by the skeletal reorientation between A and B, the C(9) hydroxy group exerts a β-effect, equivalent to that in **5**, only in an equatorial disposition. The oxymethine resonance of **15** is 3.2-ppm downfield of the same signal of **5**. In the latter substance, which adopts conformation A, the hydroxy group is equatorial and the carbinol carbon suffers a γ-effect from C(6). The oxymethine of **15**, depicted as conformer B, is environmentally equivalent to that in **5** except for the removal of the C(6) γ-effect. Whereas this difference is low for a normal γ-effect (cf. C(3) and C(6) of **26**), independent support for the weakness of the γ-effect between C(6) and C(9) is found in a comparison of **7** and **11**. The γ-effect suffered at C(6) from C(9) in **7** is replaced with a δ-effect from the hydroxy group in **11**, but the normally expected 2–3-ppm downfield δ-effect is not observed. This suggests that the terminal carbons of the C(6)–C(9) fragment may be splayed slightly from the interannular gauche geometry found in the *cis*-decalin **26**. The attenuated δ-effect strongly implies a weakened γ-effect. These qualitative correlations indicate that alcohol **15** is preponderantly conformer B.

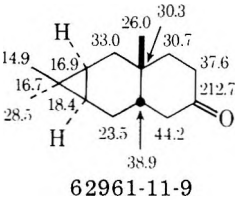
Accompanying the normal upfield shifts of C(8) and C(10) of **15** upon acetylation (**15** → **16**), C(2) shifts downfield 1.4 ppm and C(11) upfield 2.6 ppm. The latter shifts are tending toward the δ values these carbons exhibit in **5** and hence signal a shift in the equilibrium conformer proportions between **15** and its acetate **16**, increasing the contribution of form A. Since the A values of the hydroxy and acetoxy functions in hydrogen donor solvents are similar,[20] differing by <500 cal, the shift in conformational equilibrium between **15** and **16** indicates a very small ground-state energy difference between conformers A and B for these derivatives and assigns a somewhat smaller A value to the acetoxy function.

Alcohol **17**, if depicted as conformer A, possesses a single axial ring C hydroxy group involved in a 1,3-diaxial interaction with the angular methyl group, hence being energetically similar to **15**. Whereas a deuterated derivative of this substance was not prepared and thus the assignment of the methylene resonances not proved by independent means, the unusual shift modification of these signals occurring on acetylation (**17** → **18**) are analogous to those observed between **15** and **16** and indicate the substances to be conformer mixtures. The C(2) resonance of **17** lies closer to the 35-ppm value this signal assumes in A-like conformers than the same signal in **15** or **16**, indicating the further diminution of the contribution of B for **17**.

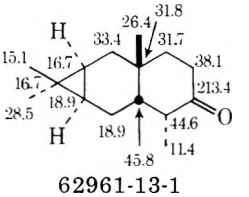
The C(6) signal can be used also to judge the conformational preference of **17**. As discussed above, in the absence of C(8) substituents the C(6) signal is insensitive to the conformational make-up of the compound and appears at 21–22 ppm. The γ-effect at C(6) from the C(8) hydroxy group of **17** should be strong in conformer B in which these centers adopt a vicinal trans-diequatorial stance and absent in A wherein they become trans-diaxial. With 5 ppm as the magnitude of the γ-effect (cf. C(6) of **1** and **7**)[21] and 21.5 ppm as the δ value of C(6) the 18.7 (or 18.5) ppm resonance of C(6) in **17** suggests A and B contribute equally to the conformational description of this substance.

In the acetate of **17**, i.e. **18**, the C(2) resonance moves downfield (to 32.4 or 34.1 ppm). This shift direction is analogous to that in the **15** → **16** change and points to an increasing contribution from form A. Simultaneously C(11) moves downfield (to 32.4 or 34.1 ppm). These requirements are fulfilled irrespective of the shift designation of C(2) and C(11) of **18**. The assignments given in Table II are preferred, since the reverse allocation, i.e., 34.1 ppm to C(2), would imply that the acetate is represented almost exclusively as conformer A, a conclusion incompatible with the intermediate C(6) resonance.

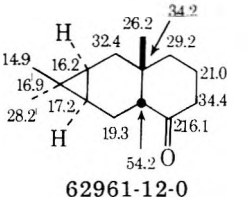
As a sidelight to the above study, the carbon shifts of the ketone precursors of the alcohols used in the investigation were determined. The δ values are depicted on the ketone formulas.



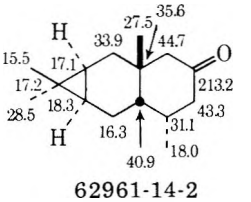
62961-11-9



62961-13-1



62961-12-0



62961-14-2

Experimental Section

The carbon shifts in the tables and the last four formulas were recorded with $CDCl_3$ solutions on a Varian XL-100-15 spectrometer operating at 25.20 MHz in the Fourier transform mode.

Registry No.—**26**, 2547-26-4.

References and Notes

(1) F.F. and A.T. are indebted to NATO and the Italian National Research Council (CNR) for support of this work.
(2) (a) Università di Perugia; (b) Rice University.
(3) F. Fringuelli, A. Taticchi, F. Fernandez, D. N. Kirk, and M. Scopes, *J. Chem. Soc., Perkin Trans. 1*, 1103 (1974), and references cited therein.
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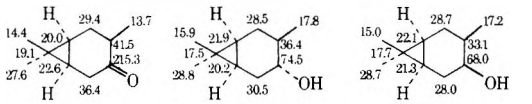
(14) Compound **19** (4β-Me) and the two epimeric alcohols derived therefrom by hydride reduction also were examined spectrally. The deuterium shifts necessitate the assignment reversal of the C(4) and *endo*-methyl resonances of the ketone and allow the previously undifferentiated cyclopropyl methines in all three substances to be assigned, as shown on the following formulas.



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(19) The chemical shifts given on formula **26** are taken from D. K. Dalling, D. M. Grant, and E. G. Paul, *J. Am. Chem. Soc.*, **95**, 3718 (1973), determined at low temperature.
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(21) The γ-effect may also be assessed as the methyl shift difference between methylcyclohexane and *trans*-2-methylcyclohexanol, i.e., 4.7 ppm.[22]
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Organic Reactions at Alumina Surfaces. A Mechanistic and Synthetic Study of Sulfonate Ester Elimination Reactions Effected by Chromatographic Alumina[1,2]

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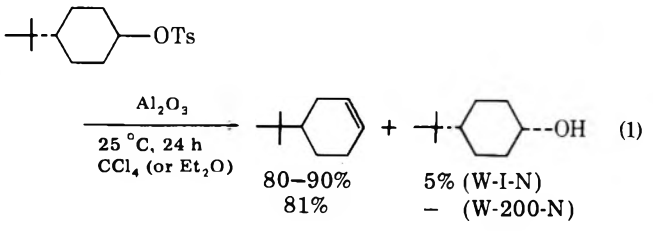
Chromatographic, neutral, highly active Woelm alumina has been used at room temperature for high-yield dehydrosulfonation of some secondary cyclic and acyclic and some primary sulfonate esters. Evidence is presented for the concertedness of these olefin-forming elimination reactions, and application is made to gram-scale chemospecific elimination of sulfonic acids from some highly functionalized esters. The scope and limitations of this heterogeneous procedure are presented, and the practical advantages and disadvantages are noted. Some practical guidelines are suggested for which activity of alumina is needed for optimal elimination reactions, and some generalizations are made concerning the structural types of sulfonate esters which would be most suitable for this alumina promoted dehydrosulfonation reaction.

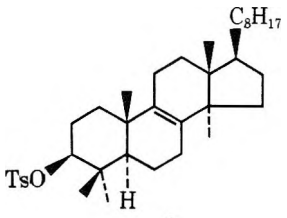
The very large number of olefin-forming elimination reactions indicates the importance of alkenes as synthetic intermediates and as ultimate target molecules.[3] Because of this importance, new reagents and new synthetic methods are constantly being sought which offer some advantages over known procedures for alkene formation.[4] Recently we have developed a very mild, convenient, and high-yield method for converting some sulfonate esters into the corresponding olefins even in the presence of normally base and acid labile (e.g., carboxylic ester) groups; even some neopentylic tosylates undergo elimination *without skeletal rearrangement*, and in all cases product isolation is easy. These concerted, heterogeneous elimination reactions are effected simply by stirring solutions of the sulfonate esters over untreated[5a] or vacuum-dehydrated[5b] commercial Woelm chromatographic alumina at room temperature. This procedure has some practical advantages over other methods for overall dehydration of alcohols, and it has been chosen recently by other laboratories to prepare some cycloalkenes.[6] We now conclude our study of this alumina procedure by illustrating its application to preparative scale (several grams) reactions, by demonstrating its chemoselectivity in converting a steroidal tetraester into the corresponding olefinic triester, and by extending its scope to conversion of primary cyclohexylmethyl tosylate esters into methylenecyclohexanes. The mechanistic and synthetic aspects of the discussion are organized according to the type of organic reactant: (1) secondary cyclic systems; (2) secondary acyclic systems; and (3) primary systems.

Results and Discussion

Secondary Cyclic Systems. Sulfonate esters are known to undergo concurrent elimination and hydrolysis reactions when exposed to chromatographic alumina.[7,8] We have studied the effect of alumina activity (i.e., dryness) on the ratio of dehydrosulfonation to hydrolysis using Woelm neutral activity I,[5a] activity super-I (W-200-N), and activity super-I-dehydrated (W-200-N-Dehydrated)[5b] alumina.[9] Of these three types of alumina, W-200-N-Dehydrated alumina converts sulfonates into the corresponding olefins with the least amount of alcohol (i.e., hydrolysis) side products; however, W-200-N-Dehydrated alumina has the operational disadvantages of having to be prepared by 400 °C vacuum dehydration of commercially available W-200-N alumina and having to be used immediately after preparation. For convenience and operational simplicity, we have therefore recently examined commercially available W-200-N alumina itself; we now report that *untreated W-200-N alumina used directly from the commercial can* is sufficiently dry to convert substituted *cyclohexyl* tosylates into the corresponding olefins with very little (<2%) or, in some cases, with no alcohol side



(1)



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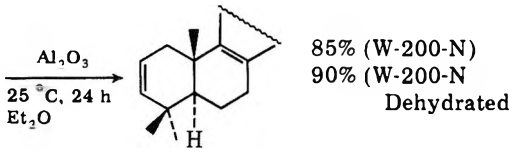


(2)

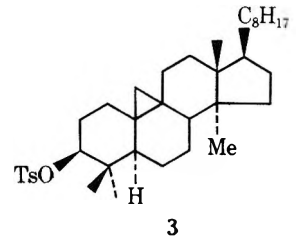
2

products. Equations 1 and 2 illustrate that activity I alumina leads to a small amount of hydrolysis, whereas W-200-N and W-200-N-Dehydrated alumina produce olefins as the only detectable products.

To illustrate the effectiveness of this synthetic method on a preparative scale, 4.2 g of 4-*tert*-butylcyclohexyl tosylate was converted over W-200-N alumina into 4-*tert*-butylcyclohexene reproducibly in 68–81% yield (eq 1). We have recently reported 2-propanol/alumina high-yield and selective reductions of *6–8 g* of some steroidal ketones.[2] Thus multigram scale organic reactions at alumina surfaces are practical, convenient, and economical. With our usual ratio of 5 g of alumina/mmol of substrate and at the current price of W-200-N alumina (approximately $25/500 g), the cost for alumina is roughly 25 cents for conversion of 1 mmol of sulfonate into olefin.

In contrast to the effectiveness of activated Woelm alumina in causing dehydrosulfonation of lanosteryl tosylate 1, Baker reagent-grade aluminum oxide powder activated at 400 °C under vacuum did not consume any of tosylate 1!

An *unexpected benefit* was associated with the use of W-200-N (or W-200-N-Dehydrated) alumina rather than some less active forms of alumina: neopentylic tosylate 1 underwent elimination *without skeletal rearrangement!*[5b] Previously, lanosteryl tosylate 1 had been observed to react on alumina to yield unrearranged diene 2 (43% yield) as well as some rearranged diene(s) (52% yield),[10] and Stevenson had reported a similar mixture of Δ^2-olefin and a 4 → 3 methyl shift product



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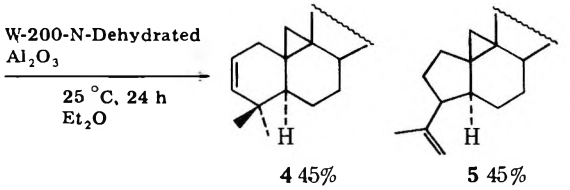
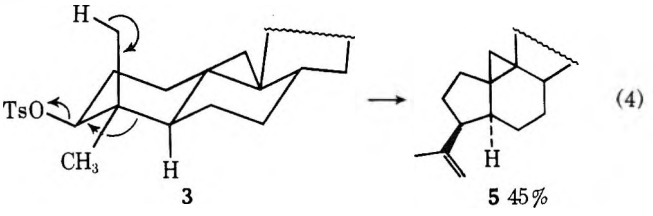


(3)

4 45% 5 45%

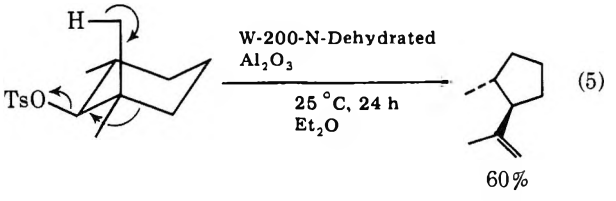
when some 4,4-dimethyl-3-tosyloxy steroids in the amyrin series were filtered through a column of Woelm W-I-N alumina.[11] Using Merck alumina and refluxing toluene, Barbier had observed the conversion of cycloartanyl tosylate 3 into cyclohexene 4 (1%) and isopropenylcyclopentane 5 (70% yield); our results, shown in eq 3, illustrate the use of W-200-N-Dehydrated alumina in promoting neopentylic tosylate dehydrotosylation to form equal amounts of rearranged and unrearranged olefins even in this especially rearrangement-prone system. These heterogeneous elimination reactions of neopentylic tosylates 1 and 3 are synthetically useful especially because even mild homogeneous conditions (e.g., PCl_5, 0 °C, 1 h;[13] NaOAc, H_2O, acetone[14]) and basic conditions (e.g., $CaCO_3$[13b]) produce rearranged products *exclusively*.

The absence (eq 2) or equal amount (eq 3) of rearranged products suggested that these elimination reactions occurring at the alumina surfaces may be, in part, *concerted* rather than ionic processes.[15] We have shown previously that optically active menthyl tosylate undergoes a concerted syn 1,2 elimination on alumina to the extent of at least 37%, and that optically active neomenthyl tosylate undergoes a concerted syn 1,3 elimination to the extent of about 11%.[5b] Indeed, rearranged steroidal isopropenylcyclopentane 5 could have arisen via a *concerted* 1,3 elimination, as shown in eq 4. The 1,3-elimination pathway may become predominant in some cases, as illustrated in eq 5.



(4)

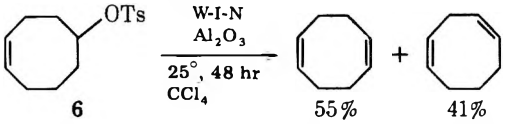
3 5 45%



(5)

60%

Another mechanistic probe for ionic (or radical[16]) intermediates involves transannular interactions in medium sized rings. We have found that cyclooctenyl tosylate 6 reacted even on unactivated W-I-N alumina to give only monocyclic diene and no bicyclic products (eq 6). In contrast, homogeneous



(6)

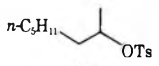
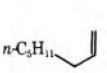
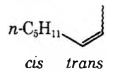
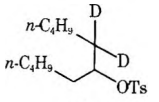
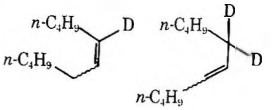
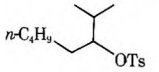
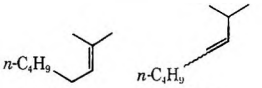
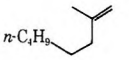
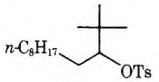
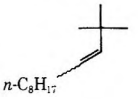
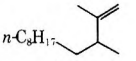
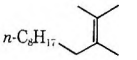
6 55% 41%

solvolysis of tosylate 6 under various conditions gave mainly bicyclic products via carbonium ion intermediates.[17]

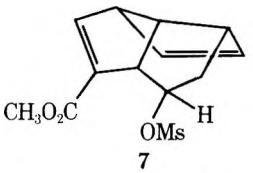
Many olefin-forming elimination reactions involve strongly acidic or strongly basic media and in some cases temperatures in excess of 200 °C.[3,4] Under such conditions many organic functional groups are unstable. We have found that W-200-N-Dehydrated alumina is highly selective for dehydrosulfonation of sulfonate esters even in the presence of such normally labile units as ketone, *carboxylic* ester, and primary and secondary iodides![5] Equations 7 and 8 illustrate the survival of *carboxylic* esters under the heterogeneous alumina reaction conditions.

Paquette has noted that preparation of triene 8 is achieved more *conveniently*, as shown in eq 7, using alumina and mesylate 7 than by direct dehydration of the corresponding alcohol using ethyl(carboxysulfamoyl)triethylammonium hydroxide inner salt.[6a] Chen has reported that transformation

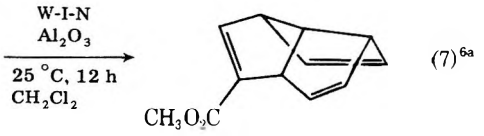
Table I. Secondary Acyclic Tosylate Esters Stirred in Et_2O over W-200-N-D Alumina at 25 °C for 24 h[a,b]

Substrate[c]	1,2-Elimination products	1,3-Elimination products	Other elimination products
 11	 22%  cis 33% trans 12%		
 12	 1:1.9		
 13	 46–51% 23–33%	 20–26%	
 14	 cis 7% trans 13–16%	 15 59–60%	 16 10–12%

[a] Virtually no alcohol products were detected in any of these reactions using W-200-N-Dehydrated alumina. [b] No olefin isomerization took place under these reaction conditions, as shown by appropriate control experiments. [c] Registry no.: 11, 27770-99-6; 12, 62862-05-9; 13, 62862-06-0; 14, 62862-07-1.

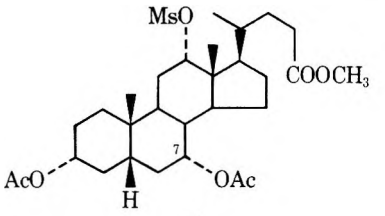


7

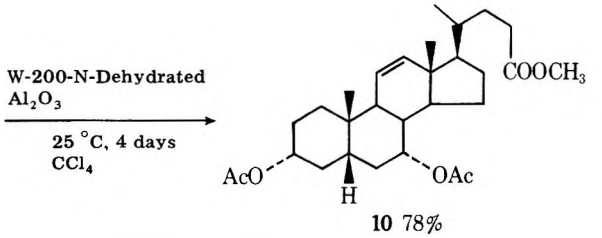


(7)[6a]

8 74%



9

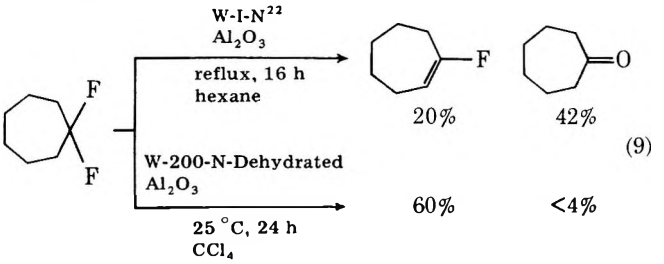


(8)

10 78%

of highly functionalized steroidal mesylate **9** into pharmacologically important cholenate **10** is very difficult using known procedures; he has therefore developed a new method to achieve specifically this conversion, which involves stirring a heterogeneous mixture of mesylate **9** in hexamethylphosphoric triamide (HMPT) containing an excess of potassium (or sodium) acetate at exactly 100 °C for 2 days; the temperature was critical and the yield of cholenate **10** was 80–85% with a small amount of concurrent elimination of the labile axial 7α-acetoxy group.[18] VPC analysis[19] indicated that the cholenate **10**, formed using our alumina procedure (eq 8), was at least as clean as that formed using Chen's procedure and that no skeletal rearrangement (13 → 12 methyl shift) had occurred during the alumina-promoted reaction of neopentylic mesylate **9**.[20,21] The chemospecificity of the alumina-promoted dehydromesylation of steroidal tetraester **9** convincingly illustrates the usefulness of this heterogeneous synthetic method for conversion of complex and polyfunctional sulfonates selectively into the corresponding olefins.

In contrast to most alkyl iodides, bromides, and chlorides, which are relatively stable to W-200-N-Dehydrated alumina at room temperature, *gem*-difluorides undergo a particularly facile dehydrofluorination to produce fluoroolefins. Boswell was the first to recognize the effectiveness of chromatographic alumina for such dehydrofluorinations, but with some particularly unreactive *gem*-difluorides he obtained mainly hydrolysis (i.e., ketone) rather than elimination products.[22] Again, using Woelm alumina dried at 400 °C, we have been able to minimize hydrolysis and to maximize dehydrofluorination, as shown with 1,1-difluorocycloheptane (eq 9).

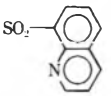


(9)

Secondary Acyclic Systems. Whereas using either W-200-N or W-200-N-Dehydrated alumina made only a small difference in the hydrolysis/elimination ratio for most *cyclic* secondary tosylates, the ratio of hydrolysis/elimination in *acyclic* secondary tosylates was more sensitive to the water content of the alumina; 2-octyl tosylate, for example, was hydrolyzed to 2-octanol in ~30, 10–15, and 0–7% yield on W-I-N, W-200-N, and W-200-N-Dehydrated alumina, respectively.[23] Therefore, if the main objective is to obtain the *highest possible yield* of olefin from an acyclic secondary sulfonate ester, then W-200-N-Dehydrated alumina should be used; if, however, the yield of olefin is not critical, but rather a sample of the olefin is desired and it can be separated easily from ~10–15% of the corresponding alcohol, then W-200-N alumina should be used directly from the commercial can.

The results summarized in Table I show that dehydrotos-

Table II. Cyclohexanemethyl Esters Stirred over W-200-N-D Alumina at 25 °C

Registry no.	Z=	Solvent	Time, h	Products, % yield[a] 18			OZ
3725-11-9	SO_2Tol (17)	CCl_4[b]	24	61	8	0	27
62862-09-3	$SO_2C_6H_4NO_2$-*p*	Et_2O	44	43	18	tr	23
62862-08-2		CCl_4[b]	24	72	23	1–2	0
57346-53-9	SO_2NMe_2	CCl_4[b]	1	58	20	0	10
	SO_2NMe_2	CH_3CN (50 °C)	1	44	3	0	42
62862-10-6	SOTol	CCl_4[b]	24	2	0	0	67
62862-11-7	$CSSCH_3$	CCl_4	24	1	19	2	49
62862-12-8	$COOCH_3$	CCl_4	24	tr	4	tr	89
33026-78-7	$PO(OPh)_2$	CCl_4	24	tr	17	tr	70
62862-13-9	$PS(OMe)_2$	CCl_4	24	1	13	4	70

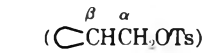
[a] VPC yields using a calibrated internal standard. [b] Alumina doped with 4% (w/w) acetonitrile.

ylation of unsymmetrical tosylates **11** and **12** over alumina proceeded preferentially, but not exclusively, in the direction of the more highly substituted β-carbon atom: methylene in preference to methyl and methine in preference to methylene. This regioselectivity represents a Saytzeff-type elimination.[3] When flanked by $-CH_2$ and $-CD_2$ as in dideuteriotosylate **12**, tosylate elimination occurred selectively in the direction of the $-CH_2$ group; k_H/k_D was about 1.88–1.94. This result is consistent with a stepwise carbonium ion mechanism or with a concerted mechanism involving little *or* much carbon–hydrogen bond heterolysis in the transitions state.[15,24] Although the carbonium ion mechanism cannot be ruled out in this case, it seems unlikely because *l*-2-octyl tosylate was not racemized when it was recovered before complete elimination over W-200-N-Dehydrated alumina had taken place. Furthermore, methanol-doped alumina converted *l*-2-octyl tosylate into *d*-2-methoxyoctane with 90–95% net inversion of configuration;[25] the high stereoselectivity of this heterogeneous displacement reaction on alumina argues against carbonium ion intermediates and argues in favor of a synchronous delivery of $-OCH_3$ and loss of $-OTs$.[26]

The stereochemistry of the olefins produced depended on the structural environment of the parent tosylate and the developing double bond: 2-octyl tosylate (**11**) yielded 2-octene in ~3:1 cis/trans ratio, whereas neopentylic tosylate **14** yielded the corresponding *tert*-butylalkenes in ~1:2 cis/trans ratio.

Encumbered tosylates **13** and **14** yielded not only 1,2-but also 1,3-elimination products; indeed the major olefinic product **15** from neopentylic tosylate **14** was a product derived from overall 1,3 elimination. Distinction between a concerted or stepwise 1,3 elimination is not possible with our data on this system. At least some carbonium ion pathway, however, must be occurring because formation of tetrasubstituted olefin **16** cannot be rationalized via any concerted elimination process;[27] a control experiment showed that tetrasubstituted alkene **16** was not formed via isomerization on alumina of terminal olefin **15**.

Primary Systems. Even with W-200-N-Dehydrated alumina, *n*-alkyl tosylates gave olefins in only very poor yields; hydrolysis was predominant. Primary tosylates having methine β-hydrogen atoms,

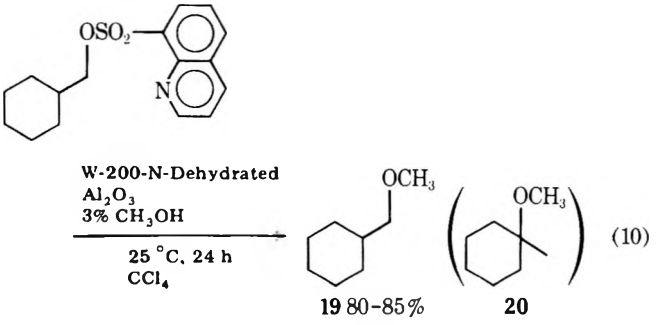


however, did undergo dehydrotosylation on W-200-N-Dehydrated alumina with virtually no accompanying hydrolysis. In this isobutylic-type of tosylate the choice of alumina activity was critical: W-I-N alumina gave 2:1 hydrolysis/elimination, whereas W-200-N-Dehydrated alumina gave olefin cleanly. Table II summarizes our results with some cyclohexanemethyl esters.

The major product in most cases in Table II was methylenecyclohexane (**18**), which is thermodynamically less stable than its double bond isomer 1-methylcyclohexene.[28] Selective formation of exocyclic alkene **18** suggested a concerted 1,2-elimination pathway rather than a stepwise ionic process which would have led mainly to 1-methylcyclohexene via a primary and then a tertiary carbonium ion. Choice of solvent was critical; under the reaction conditions, double bond isomerization from the exocyclic to the endocyclic position did not occur with diethyl ether or with CCl_4/4% CH_3CN, but such isomerization did occur with CCl_4 as solvent. Apparently Et_2O and CCl_4/4% CH_3CN were able to block the acid sites on the alumina, thus preventing double bond migration.[29]

Choice of leaving group was also important. While all sulfonate esters and even a dimethylsulfamate ester gave terminal olefin **18** in good yields, even the slight change to a *p*-tolylsulfinate ester drastically reduced the rate of ester reaction on alumina. Likewise, xanthate, carbonate, phosphate, and thiophosphate esters were found to be unreactive. We have no good explanation for the unusual difference in reactivity between the sulfonate and the other esters, especially for the large reactivity difference between sulfonate and sulfinate esters on alumina.

If 3% by weight of methanol was added to W-200-N-Dehydrated alumina and then cyclohexanemethyl 8-quinolinesulfonate was introduced in CCl_4 solution, a displacement reaction occurred cleanly to form methyl ether **19** in 80–85% yield (eq 10). That no tertiary ether **20** was formed argues in favor of a synchronous S_N2-type of substitution.[25]

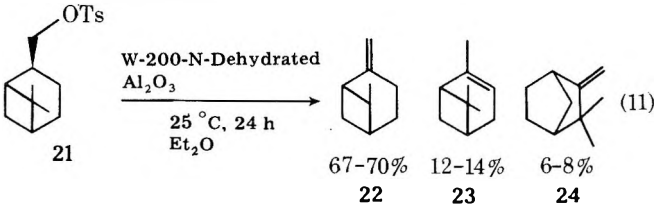


(10)

19 80–85% **20**

The synthetic utility of this conversion of primary cyclohexylmethyl tosylates into the corresponding exocyclic olefins was illustrated further with 10-pinanyl tosylate **21**, a system which is known to undergo skeletal rearrangement at the slightest provocation.[30–32] As shown in eq 11, with Et_2O (or with CCl_4/4% CH_3CN) as solvent, primary tosylate **21** reacted

at room temperature on alumina to give predominantly unrearranged β-pinene (**22**), the product of a concerted 1,2 elimination, and some α-pinene (**23**), the product of a 1,3 elimination. Camphene (**24**) probably arose via a competing ionic process; when the reaction was done in CCl_4 solvent, camphene was the major observed product. Indeed both β- and α-pinenes (**22** and **23**) isomerized to a mixture rich in camphene when they were stirred at 25 °C in CCl_4 solution over alumina, but the pinenes **22** and **23** did not isomerize over alumina with Et_2O as solvent.



(11)

Conclusions

Sulfonate ester dehydrosulfonation effected by Woelm chromatographic alumina is synthetically useful especially in the following instances: (1) when stereoelectronic factors strongly favor elimination in one of two possible directions (e.g., 3β-cholestanyl tosylate giving only 2-cholestene[5b]); (2) when elimination of a methine β-hydrogen atom does not occur because it would lead to a bridgehead double bond (e.g., sulfonate **7**); (3) when the sulfonate ester is symmetrical and elimination in either direction produces the same olefin (e.g., 4-benzoyloxycyclohexyl tosylate);[5b] (4) when a β elimination is possible in only one direction because there are no β′ hydrogen atoms (e.g., cyclic neopentylic sulfonates **1**, **3**, and **9** and cyclohexanementhyl tosylates **17** and **21**).

The major disadvantages of this heterogeneous olefin-forming procedure are as follows: (1) poor regiochemical control of olefin formation when two double bond positional isomers are possible; (2) poor stereochemical control when cis and trans alkenes are possible; (3) indirectness (i.e., alcohol → sulfonate → olefin); (4) large amount of alumina required for complete reaction (5–7 g Al_2O_3 mmol of sulfonate); and (5) the inconvenience of having to dehydrate commercial alumina in order to suppress *completely* hydrolysis of primary and acyclic secondary tosylates.

The major advantages of this sulfonate elimination procedure are as follows: (1) inertness of many acid- and base-sensitive organic functional groups; (2) concerted elimination without skeletal rearrangement of some highly rearrangement-prone tosylates; (3) convenience of using commercially available W-200-N alumina for elimination without any significant amount of hydrolysis, particularly of cyclic secondary sulfonates; and (4) ease of product isolation (i.e., filtration of alumina and evaporation of solvent).

The practical advantages of Woelm chromatographic alumina for introducing double bonds into polyfunctional and complex compounds will make this heterogeneous "reagent" useful to organic chemists.

Experimental Section

Analytical vapor-phase chromatography (VPC) was performed on a Varian Aerograph Model 1200, and preparative vapor-phase chromatography was done on a Varian Aerograph Model 90-P3.

Spectral data were obtained with a Perkin-Elmer 457-A or 337 infrared spectrometer and a Varian A-60 or Jeol MH-100 NMR spectrometer. Mass spectra (70 eV) were measured on a Hitachi RMU-6 mass spectrometer. Optical rotations were measured on solutions in a 10-cm micro cell with a Perkin-Elmer Model 141 polarimeter. Elemental analyses were done by Chemalytics, Inc. (Tempe, Ariz.), or by Micro-Tech Laboratories, Inc. (Skokie, Ill.).

All substrates and standards were best commercially available reagent grades or were prepared from such. Purity was tested before use. All solvents and doping agents were reagent grade and were dried before use (except carbon tetrachloride and freshly opened anhydrous ether, as received). Woelm aluminum oxide, W-200 neutral (activity grade super I), was obtained from ICN Pharmaceuticals, Inc. (Cleveland, Ohio).

***trans*-4-*tert*-Butylcyclohexyl Tosylate.** According to the general procedure described previously,[5b] a solution of 4.15 g (3.4 mmol) of 4-*tert*-butylcyclohexyl tosylate[33] in 120 mL of anhydrous diethyl ether was stirred over 70 g of W-200-N alumina at 25 °C for 24 h. Analytical VPC (10 ft × ⅛ in., 5% SE-30) analysis using a calibrated standard indicated the presence of 4-*tert*-butylcyclohexene (81%) and no *cis*-4-*tert*-butylcyclohexanol. Filtration through Celite, washing with 150 mL of 1:1 Et_2O/CH_2Cl_2, and evaporation of most of the solvent and bulb-to-bulb distillation (15–20 mm, 60 °C) gave 1.26 g (68%) of a clear oil: $n^{20}D$ 1.458 (lit.[34] $n^{20}D$ 1.459); NMR (CCl_4) δ 5.5 (M, 2 H, vinylic H), 0.84 (s, 9 H, *tert*-butyl), identical with that of an authentic sample.[33]

Cycloartanyl Tosylate (3). A solution of 128.3 mg (0.22 mmol) of cycloartanyl tosylate (**3**) (mp 143–146 °C; lit.[12] 144–147 °C) in 8 mL of dry ether was stirred over 7.45 g of W-200-N-Dehydrated alumina at 25 °C for 1 day. Rotary evaporation of the methylene chloride/ether (1:1) extract gave 81.5 mg (90%) of a clear colorless oil, shown by NMR to be a 1:1 mixture of olefin **4** (9,19-cyclo-9-lanost-2-ene) and olefin **5** (3β-isopropenyl-14α-methyl-9,19-cyclo-*A*-nor-5α,9β-cholestane): NMR (CCl_4) δ 5.4 (m, 2 H, Δ2 olefin **4**), 4.61 (m, 2 H, isopropenyl olefin **5**), 2.6–0.6 (m, steroid nucleus), 0.65 (d, unresolved from nucleus band; H_B of 9,19-cyclopropane[12]), 0.35 (d, 1 H, H_A of 9,19-cyclopropane[12] in Δ2 olefin **4**), −0.18 (d, 1 H, H_A of 9,19-cyclopropane[12] in isopropenyl olefin **5**).

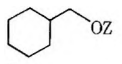
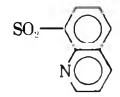
***trans*-2,2,6-Trimethylcyclohexyl Tosylate.** A solution of 265 mg (0.89 mmol) of *trans*-2,2,6-trimethylcyclohexyl tosylate (mp 69 °C, NMR δ 4.02, 4.20 (d, >CHOTs), separated by recrystallization from some *cis* isomer, NMR δ 4.4 >CHOTs][35] in 8 mL of dry ether was stirred over 6.3 g of W-200-N-Dehydrated alumina at 25 °C for 1 day. Filtration through Celite, washing with 30 mL of 1:1 Et_2O/CH_2Cl_2, and analytical VPC (10 ft × ⅛ in., 5% SE-30) analysis using *n*-decane as a calibrated internal standard indicated the presence of one major component (60% yield) along with several minor components (~25% yield). Preparative VPC (10 ft × ¼ in., 20% SE-30) gave a clear oil, *trans*-2-isopropenyl-1-methylcyclopentane;[36] IR (CCl_4) 885 cm^{-1} (=CH_2); NMR (CCl_4) δ 0.9 (d, CH_3), 1.65 (br s, allylic CH_3), 4.7 (s, =CH_2); mass spectrum (*m/e*) 124; $n^{23}D$ 1.4423 (lit.[36] $n^{25}D$ 1.4430).

4-Cyclooctenyl Tosylate (6). A solution of 280 mg (1.0 mmol) of 4-cyclooctenyl tosylate (**6**) (mp 47 °C, lit.[17b] mp 47–48 °C) in 3 mL of carbon tetrachloride was stirred over 4.0 g of W-I-N alumina at 25 °C for 48 h. Analytical VPC (10 ft × ⅛ in. FFAP) using 1-tetradecene as a calibrated internal standard showed 1,5-cyclooctadiene (55%) and 1,4-cyclooctadiene (41%). Careful distillation removed most of the CCl_4 solvent and preparative VPC gave pure 1,5-cyclooctadiene [NMR (CCl_4) δ 2.33 (m, 8 H, allylic H), 5.5 (m, 4 H, vinylic); IR (CCl_4) 3000, 2930, 2880 cm^{-1}, identical with that of an authentic sample] and 1,4-cyclooctadiene [NMR (CCl_4) δ 1.2–1.7 (m, 2 H), 2.0–3.0 (m, 6 H, allylic), 5.0–5.9 (m, 4 H, vinylic).

Methyl 3α,7α-Diacetoxy-12α-mesyloxy-5β-cholanate (9). A solution of 201.9 mg (0.34 mmol) of cholanate (**9**) (mp 83–86 °C; lit.[18] mp 85–86 °C) in 4.5 mL of carbon tetrachloride was stirred over 3.91 g of W-200-N-Dehydrated alumina at 25 °C for 3 days. Filtering and rinsing the alumina with 30 mL of ether/methylene chloride (1:1) and with 70 mL of acetonitrile in a Hirsch funnel, followed by removal of solvent by rotary evaporation, gave 158.3 mg of a slightly yellow oil, shown by NMR to contain 77% methyl 3α,7α-diacetoxy-5β-chol-11-enate (**10**) and 23% starting ester (**9**). Further reaction of the material in carbon tetrachloride over 4.82 g of fresh dehydrated alumina for 1.5 days, followed by the same product isolation, gave 141 mg of oil shown by NMR and GLC to be a 94:6 mixture of Δ^{11}-olefin **10** (78% yield) and starting ester **9** (5% recovery), with no observable diene product. Methyl 3α,7α-diacetoxy-5β-chol-11-enate (**10**): NMR[37] ($CDCl_3$) δ 6.15 and 5.44 (AB, q, 2 H, Δ^{11}-olefin), 5.00 (m, 1 H, 7β-H), 4.58 (m, 1 H, 3β-H), 3.65 (s, 3 H, methyl ester), 2.00 and 2.04 (pair of s, 6 H, acetates); mp 140–140.5 °C (lit.[18] 139–141 °C) after preparative thin-layer chromatography and recrystallization from methanol.

1,1-Difluorocycloheptane. A solution of 74.8 mg (0.55 mmol) of 1,1-difluorocycloheptane and 56.5 mg of nonane (calibrated internal standard) in 4 mL of carbon tetrachloride was stirred over 3.45 g of W-200-N-Dehydrated alumina at 25 °C for 1 day. Analysis by VPC (10 ft × ⅛ in., 5% SE-30 on Chromosorb W 100/120) of the methylene chloride/ether (1:1) extract showed 60% 1-fluorocycloheptene and 4% cycloheptanone (comparison to knowns) with no recovered starting material. Preparative VPC (10 ft × ¼ in., 20% SE-30 on Chromosorb W 45/60) of the product of a separate run afforded pure 1-fluorocycloheptene: $n^{21}D$ 1.4360 (lit.[22a] $n^{25}D$ 1.4359); NMR (CCl_4) δ 5.28 (d of

Table III. Physical and Spectral Properties of Cyclohexylmethyl Esters

 Z=	n_D, T °C	Mp or bp (torr), °C	IR, cm^{-1}	NMR (CCl_4), δ (ppm)	Comments
SO_2Tol		30–31 (lit.[42] 30–31)	(CCl_4), 1370 (br, $\nu_{AS}SO_2$), 1186 and 1174 (s, sharp, $\nu_S SO_2$)	3.74 (d, J = 6 Hz, 2 H, carbinol H)	
$SO_2C_6H_4NO_2$-p		81–83	($CHCl_3$), 1559 (s, $\nu_{AS}NO_2$), 1365 (sh, $\nu_{AS}SO_2$), 1349 (s, $\nu_S NO_2$), 1183 (s, sharp, $\nu_S SO_2$)	($CDCl_3$), 4.92 (d, J = 6 Hz, 2 H, carbinol H)	Pale yellow crystals. Anal. Calcd for $C_{13}H_{17}NO_5S$: C, 52.20; H, 5.72; N, 4.68; S, 10.71. Found: C, 52.57; H, 5.81; N, 4.85; S, 10.67.
		74–76 (lit.[33] 76–77)	($CHCl_3$), 1355 (s, br, $\nu_{AS}SO_2$), 1176 and 1150 (s, sharp, $\nu_S SO_2$)	($CDCl_3$), 4.11 (d, J = 6 Hz, 2 H, carbinol H)	
SO_2NMe_2	1.4602, 26	85–87 (0.13)	(film), 1360 (s, br, $\nu_{AS}SO_2$), 1171 (s, $\nu_S SO_2$)	3.85 (d, J = 6 Hz, 2 H, carbinol H), 2.83 (s, 6 H, NCH_3)	Anal. Calcd for $C_9H_{19}NO_3S$: C, 48.84; H, 8.65; N, 6.33; S, 14.49. Found: C, 49.33; H, 9.10; N, 6.56; S, 14.34. Straw-yellow oil
SOTol	1.5361, 21.5		(film), 1132 (s, νSO)	3.7 and 3.3 [AB, m, 2 H, $CH_2OS(=O)Ar$]	
CSSMe	1.5498, 21		(film), 1220 (s, br, νC=S), 1060 (s, νCO)	4.33 (d, J = 6 Hz, 2 H, carbinol H), 2.51 (s, 3 H, SCH_3)	Anal. Calcd for $C_9H_{16}OS_2$: C, 52.89; H, 7.89; S, 31.38. Found: C, 52.36; H, 7.80; S, 30.67.
COOMe	1.4467, 18		(film), 1750 (s, νC=O), 1260 (s, br, νCO)	3.85 (d, J = 6 Hz, 2 H, $-CH_2O-$), 3.70 (s, 3 H, $-OCH_3$)	Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.37. Found: C, 62.91; H, 9.67.
COOPh[a]	1.4994, 25		(film), 1765 (s, νC=O), 1250 (s, br, νCO)	7.15 (m, 5 H, ArH), 3.97 (d, J = 6 Hz, 2 H, $-CH_2O-$)	Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.90; H, 7.18.
$PO(OPh)_2$	1.5301, 25		(film), 1293 (s, νP=O), 1192 (s, POC_{aryl}), 1160 (m, sharp, νPO)	3.92 (d of d, J_{HH} = 6 Hz, J_{HP} = 15.5 Hz, $-CH_2OP$)	Anal. Calcd for $C_{19}H_{23}O_4P$: C, 65.89; H, 6.69; P, 8.94. Found: C, 65.52; H, 6.69; P, 9.18.
$PS(OMe)_2$	1.4845, 18		(film), 1185 (m, νPO), 1020 (s, br, νC—O)	3.79 (d of d, $-CH_2OP$) and 3.68 (d, J_{HP} = 14 Hz, $POCH_3$, total 8 H)	Anal. Calcd for $C_9H_{19}O_3PS$: C, 45.36; H, 8.04; P, 13.00; S, 13.46. Found: C, 45.10; H, 7.94; P, 12.38; S, 13.33.

[a] Registry no.: 62862-14-0.

t, $J_{CH_2CH=}$ = 6 Hz, $J_{HC=CF}$ = 22 Hz, 1 H, olefinic), 2.5–1.1 (m, 10 H, methylenes); IR (liquid film) 2920 (s), 2840 (s), 1695 (s, νHC=CF), 1446 (s), 1371 (s), 1220 (m), 1091 (s), 1065 (s), 1010 cm^{-1} (m).

l-2-Octyl Tosylate (11). A solution of 288.9 mg (1.02 mmol) of *l*-2-octyl tosylate (11) ($[\alpha]^{22}_D$ −8.255 ± 0.10° [cyclohexane][36]) in 8 mL of dry ether was stirred over 5.50 g of W-200-N-Dehydrated alumina at 25 °C for 2 days. Analysis by VPC (9 ft × ⅛ in., 5% SE-30 on Chromosorb G 100/140, using nonane as added, calibrated, internal standard) of the ether/methylene chloride extract showed 22% 1-octene, 12% *trans*-2-octene, 33% *cis*-2-octene, and <0.5% 2-octanol (molar percent yields, VPC comparison with known samples on two columns). No starting ester was recovered.

In a similar manner, a solution of 190.2 mg (0.67 mmol) of *l*-2-octyl tosylate (11) in 4.5 mL of dry ether was stirred over 3.73 g of W-200-N-Dehydrated alumina at 25 °C for 2 *h*. Filtering and rinsing the alumina with 45 mL of methylene chloride/ether/acetonitrile (1:1:1), followed by rotary evaporation (residue 28.2 mg) and preparative thin layer chromatography (silica gel), gave 8 mg of pure 2-octyl tosylate. Its optical rotation, $[\alpha]^{18}_D$ −8.27 ± 0.43° (cyclohexane), indicated no racemization of starting ester (100.2 ± 6.9% retention of configuration).

5,5-Dideuterio-6-undecyl Tosylate (12). A solution of 105.0 mg (0.32 mmol) of 5,5-dideuterio-6-undecyl tosylate[39] (12) in 3 mL of carbon tetrachloride was stirred over 2.56 g of W-200-N-Dehydrated alumina at 25 °C for 1 day. Filtering and washing the alumina with 30 mL of methylene chloride/ether (1:1), followed by removal of solvent by rotary evaporation, gave 40.6 mg (82%) of clear, colorless oil, 5-undecene (cis and/or trans; homogeneous by VPC, 10 ft × ⅛ in., 5% SE-30 on Chromosorb W 100/120). Mass spectral analysis showed *m/e* (peak height, average) 157 (12.4, M + 1 of $C_{11}H_{20}D_2^+$), 156 (82.0, M^+ of $C_{11}H_{20}D_2^+$ + M + 1 of $C_{11}H_{21}D^+$), 155 (4.13, M^+ of $C_{11}H_{21}D^+$ + M + 1 of $C_{11}H_{22}^+$), 154 (1.9, M^+ of $C_{11}H_{22}^+$). Correcting for the interference of isotope peaks (M + 1 of 5-undecenes measured in control experiment as 12.0% of parent peak), we find: 156 (77.0, $C_{11}H_{20}D_2^+$) and 155 (41.1, $C_{11}H_{21}D^+$), giving a value for k_H/k_D of 1.88.

In a similar experiment, run in ether solvent, a value for k_H/k_D of 1.94 was obtained.

2-Methyl-3-octyl Tosylate (13). A solution of 215.8 mg (0.72 mmol) of 2-methyl-3-octyl tosylate[40] (13) (n^{25}_D 1.4917) in 5 mL of dry ether was stirred over 3.36 g of W-200-N-Dehydrated alumina at 25 °C for 1 day. Analysis by VPC (9 ft × ⅛ in., 5% SE-30 on Chromosorb G 100/140) and NMR of the concentrated methylene chloride/ether (1:1) extract showed four components, identified as (relative percent yields by VPC and NMR): *cis*- and *trans*-2-methyl-3-octene (15, 8%), 2-methyl-2-octene (51%), and 2-methyl-1-octene (26%). No starting ester was recovered. Product mixture: NMR (CCl_4) δ 5.2–4.9 (m, olefinic C=CH), 4.60 (br s, terminal $=CH_2$), 2.2–1.7 (vinyl CH_2), 1.65 (m, vinyl CH_3), 1.53 (m, vinyl CH_3), 1.5–0.7 (m, methylenes and methyls). Integration was consistent with VPC.

2,2-Dimethyl-3-dodecyl Tosylate (14). A solution of 228.0 mg (0.62 mmol) of 2,2-dimethyl-3-dodecyl tosylate[41] (14) (n^{22}_D 1.4822) in 4 mL of dry ether was stirred over 4.29 g of W-200-N-Dehydrated alumina at 25 °C for 1.5 days. Filtering and rinsing the alumina with 50 mL of methylene chloride/ether/acetonitrile (1:1:1), followed by removal of solvent by rotary evaporation, yielded 111.8 mg of clear colorless liquid. Analysis by VPC (10 ft × ⅛ in., 5% SE-30 on Chromosorb W 100/120) showed (molar percent yields, products identified by NMR and IR of preparative VPC isolated materials): *trans*-2,2-dimethyl-3-dodecene [13%; NMR (CCl_4) δ 5.31 (m, 2 H, olefinic), 2.2–1.6 (m, 2 H, vinyl CH_2), 0.99 (s, *t*-Bu); IR (liquid film) 1665 (w, C=C), 968 cm^{-1} (m, sharp, *trans*-C=C)], *cis*-2,2-dimethyl-3-dodecene [7%; NMR (CCl_4) δ 5.19 (m, 2 H, olefinic), 2.2–1.6 (m, 2 H, vinyl CH_2), 1.09 (s, *t*-Bu); IR (liquid film) 1650 cm^{-1} (w, C=C)], 2,3-dimethyl-1-dodecene (27) [60%; NMR (CCl_4) δ 4.61 (m, 2 H, olefinic), 2.3–1.8 (m, 1 H, vinyl CH), 1.61 (m, 3 H, vinyl CH_3); IR (liquid film) 1641 (w, C=C), 885 cm^{-1} (s, sharp, $=CH_2$)], and 2,3-dimethyl-2-dodecene (28) [12%; NMR (CCl_4) δ 2.15–1.65 (m, 2 H, vinyl CH_2), 1.61 (s, 9 H, vinyl CH_3)].

Cyclohexanemethyl Tosylate (17). A solution of 156.9 mg (0.59 mmol) of cyclohexanemethyl tosylate (17) (mp 30–31 °C; lit.[42] mp

30–31 °C) and 25.8 mg of *trans*-2-octene (calibrated, internal standard) in 4.5 mL of carbon tetrachloride was stirred over 4.08 g of W-200-N-Dehydrated alumina doped with 4% w/w acetonitrile at 25 °C for 1 day. Analysis by VPC (10 ft × ⅛ in., 5% SE-30 on Chromosorb W 100/120) of the methylene chloride/ether/acetonitrile (1:1:1) extract showed (identified by VPC comparison with known samples on three columns) 61% methylenecyclohexane (**18**) and 8% 1-methylcyclohexene. Cyclohexanemethyl tosylate (27%) was also recovered.

Stability of Methylenecyclohexane over Alumina. A. With CCl_4 Solvent. A solution of 37.9 mg (0.39 mmol) of methylenecyclohexane (**18**) in 3 mL of carbon tetrachloride was stirred over 2.81 g of W-200-N-Dehydrated alumina at 25 °C for 1 day. Analysis by VPC (10 ft × ⅛ in., 5% SE-30 on Chromosorb W 100/120) of the ether extract showed (comparison with known samples) 99% 1-methylcyclohexene and a trace of methylenecyclohexane (**18**).

B. With Et_2O Solvent. A solution of 20–30 mg of impure methylenecyclohexane (containing about 20% 1-methylcyclohexene) in 2.5 mL of dry ether was stirred over 1.47 g of W-200-N-Dehydrated alumina at 25 °C for 1 day. Analysis by VPC (9 ft × ⅛ in., 5% SE-30 on Chromosorb G 100/140) of the ether filtrate showed no change in composition (methylenecyclohexane/1-methylcyclohexene, 5:1).

Cyclohexanemethyl 8-Quinolinesulfonate with Methanol-Doped Alumina. A solution of 103.0 mg (0.34 mmol) of cyclohexanemethyl 8-quinolinesulfonate [mp 74–76 °C (lit.[33] mp 76.0–77.0 °C)] and 21.9 mg of *trans*-2-octene (calibrated, internal standard) in 7 mL of carbon tetrachloride was stirred over 4.47 g of W-200-N-Dehydrated alumina doped with 3% w/w methanol (132.4 mg) at 25 °C for 1 day. Analysis by VPC (10 ft × ⅛ in., 5% SE-30 on Chromosorb W 100/120) of the methylene chloride/ether/acetonitrile (1:1:1) extract showed 10% methylenecyclohexane, <1% 1-methylcyclohexene and cycloheptene combined, a trace of cyclohexanemethanol, and 80–85% cyclohexanemethyl methyl ether (**19**) (identified by comparison with a known sample[43]): NMR δ 3.23 (s, 3 H, OCH_3), 3.09 (d, J = 6 Hz, 2 H, CH_2O), 2.0–0.8 (m, 11 H, cyclohexane ring); mass spectrum m/e 128 (M^+), 97 ($M^+ - OCH_3$).

10-Pinanyl Tosylate (21). A solution of 213.4 mg (0.69 mmol) of 10-pinanyl tosylate (**21**) [mp 74–76 °C (lit.[30b] mp 75.5–76 °C)] in 7.5 mL of carbon tetrachloride was stirred over 4.90 g of W-200-N-Dehydrated alumina doped with 4.5% acetonitrile at 25 °C for 1 day. Analysis by VPC (10 ft × ⅛ in., 5% SE-30 on Chromosorb W 100/120) of the methylene chloride/ether/acetonitrile (1:1:1) extract showed (absolute yields, identified by comparison with known samples on two columns): 67% β-pinene (**22**), 12% α-pinene (**23**), and 6% camphene (**24**) (plus two minor components in trace and 3% amounts). No starting tosylate was recovered.

Stability of Pinenes 22 and 23 on Alumina. A. With CCl_4 Solvent. A solution of 88.8 mg (0.65 mmol) of β-pinene (**22**) in 8 mL of carbon tetrachloride was added to 4.60 g of W-200-N-D alumina to which had been added 82.7 mg (0.44 mmol) of p-toluenesulfonic acid monohydrate. The mixture was stirred at 25 °C for 1 day, after which time the catalyst was filtered and rinsed with 23 mL of methylene chloride/ether (1:1). Analysis by VPC (10 ft × ⅛ in., 5% SE-30 on Chromosorb W 100/120) showed (relative percent yields) 54% camphene (**24**) and two unidentified isomers suspected (on the basis of relative retention times) to be terpinolene (38%) and fenchene (7%). No pinenes **22** and **23** were detected.

When α-pinene (**23**) was treated in this manner, the same three products were obtained in 55, 37, and 8% relative yields, respectively. When α-pinene was treated in this manner, save for the absence of p-toluenesulfonic acid monohydrate, the same three products were obtained in 57, 35, and 8% relative yields, respectively.

B. With Et_2O Solvent. A solution of 85.4 mg (0.63 mmol) of β-pinene (**22**) in 8.5 mL of dry ether was added to 4.52 g of W-200-N-Dehydrated alumina to which had been added 79.5 mg (0.42 mmol) of p-toluenesulfonic acid monohydrate. The mixture was stirred at 25 °C for 1 day, after which time the catalyst was filtered and rinsed with 25 mL of methylene chloride/ether (1:1). Analysis by VPC showed only unchanged β-pinene (**22**).

When α-pinene (**23**) was treated in this manner, only unchanged α-pinene was detected (by VPC).

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Registry No.—**3,** 53962-86-0; **4,** 56722-63-5; **5,** 28837-12-9; **6,** 62862-15-1; **9,** 53869-82-2; **10,** 2284-36-8; **19,** 19752-94-4; **21,** 62862-16-2; **22,** 127-91-3; **23,** 80-56-8; **27,** 62862-17-3; **28,** 62060-12-2; *trans*-4-*tert*-butylcyclohexyl tosylate, 7453-05-6; 4-*tert*-butylcyclohexene, 2228-98-0; *trans*-2,2,6-trimethylcyclohexyl tosylate, 62862-18-4; *cis*-2,2,6-trimethylcyclohexyl tosylate, 62862-19-5; *trans*-2-isopropenyl-1-methylcyclopentane, 62862-20-8; 1,5-cyclooctadiene, 111-78-4; 1,4-cyclooctadiene, 1073-07-0; 1,1-difluorocycloheptane, 27371-42-2; 1-fluorocycloheptene, 27415-45-8; *cis*-5-undecene, 764-96-5; *trans*-5-undecene, 764-97-6; *cis*-2-methyl-3-octene, 62862-21-9; *trans*-2-methyl-3-octene, 52937-36-7; 2-methyl-2-octene, 16993-86-5; *trans*-2,2-dimethyl-3-dodecene, 62862-22-0; *cis*-2,2-dimethyl-3-dodecene, 62862-23-1; methylenecyclohexane, 1192-37-6.

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Reductions of Conjugated Carbonyl Compounds with Copper Hydride—Preparative and Mechanistic Aspects

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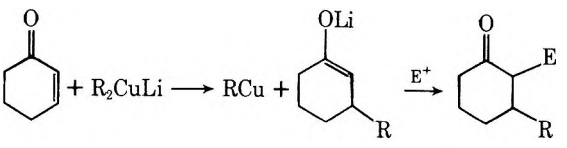
The reaction of lithium trimethoxyaluminum hydride with 0.5 molar equiv of cuprous bromide produces a heterogeneous mixture referred to as the Li complex, while sodium bis(2-methoxyethoxy)aluminum hydride with 1.0 molar equiv of cuprous bromide gives a similar mixture, the Na complex. Both reagents are effective in selective reduction of the olefin unit in conjugated ketones and esters, including two examples of acetylenic esters. The Li complex is more efficient with cyclohexenones, while the Na complex gives better yields in reduction of acyclic enones and enoates, especially in the presence of 2-butanol. Deuterium labeling experiments show that the hydrogen which is transferred to the β position of the conjugated carbonyl compound originates from the hydridocuprate reagent; the 2-butanol appears to serve as a weak acid, inhibiting polymerization. In the absence of 2-butanol, reduction of methyl cinnamate produces dimethyl *meso*-3,4-diphenyladipate as a major product, apparently the result of radical anion intermediates. Aldehyde, ketone, and halide functionality are reduced at rates comparable to the rate of enone reduction, but nitrile and ester units are inert.

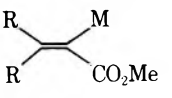
Organocopper reagents have been developed into powerful methods for carbon–carbon bond formation,[1,2] especially utilizing the remarkable preference for delivery of carbon units to the β position of α,β-unsaturated carbonyl compounds.[1] This general method of conjugate addition is selective not only for 1,4 instead of 1,2 addition, but also highly chemiselective: most nonacidic functional groups do not interfere. An added dimension in synthesis is the technique of "enolate trapping", where the product enolate anion from addition to the β position reacts with an electrophile in the α position.[3]



E = electrophilic species

Until recently, addition of hydrogen to the olefin unit in an α,β-unsaturated carbonyl compound was commonly achieved by catalytic hydrogenation[4] and dissolving metal reduction,[5] each method having characteristic technical advantages and conveniences in particular systems, and with shortcomings in chemiselectivity. Recently, hydride transfer reagents involving iron,[6,7] boron,[8] and aluminum[9] have been developed for 1,4 reduction; the boron reagent allows enolate trapping with carbon electrophiles.[8]

In analogy with the alkyl–copper chemistry, hydrido–copper reagents might provide selective conjugate addition of hydride, compatibility with most common functional groups, and would generate an enolate anion which could be trapped with protons (overall reduction of the olefin unit) or with electrophiles at the α position. We were particularly intrigued with the possibility of generation and trapping of α-metalloacrylate anion **1**, perhaps via conjugate addition of a hydrido–copper species to methyl propiolate. A few specific examples of organometal species closely related to **1** have been detected, through dialkyl cuprate addition to propiolate derivatives,[10] through halogen–metal exchange with α-bromo



1, M = metal

Li[H-Cu-R]

2, R = 1-pentynyl
3, R = $OC(CH_3)_3$
4, R = *n*-butyl

acrylates,[11] and through abstraction of the α-hydrogen from acrylates using strong base.[12] Since we began this project,[13] rapid development has occurred in the use of hydrido–copper reagents for organic reductions.

Early applications by Whitesides and coworkers in cleavage of alkyl-copper bonds provided a recipe for preparation of soluble hydrido(tri-*n*-butylphosphine)copper(I) using diisobutylaluminum hydride and cuprous bromide at low temperature.[14] The reaction of lithium trimethoxyaluminum hydride with cuprous iodide provides a heterogeneous mixture which cleaves carbon–halogen bonds efficiently. The required 2:1 stoichiometry of hydride–copper led to the suggestion that the effective reagent was lithium dihydridocopper(I), parallel with lithium dimethylcopper(I).[15] Conjugate addition of hydride to α,β-unsaturated ketones was reported by Boeckman and Michalak, using the "ate" complexes (**2, 3**) prepared by adding an anionic ligand to CuH (from diisobutylaluminum hydride and CuI at −50 °C, filtered).[16] Excellent selectivity for 1,4 addition was reported with a variety of cyclic and acyclic ketones.[16,17] Masamune[18] employed a similar reagent (**4**), prepared in the same way, and observed closely similar results; it is suggested that this homogeneous reagent (**4**) is more reproducible in cleavage of carbon–halogen bonds and enone reduction compared to the heterogeneous reagent[15] obtained under carefully specified conditions from lithium trimethoxyaluminum hydride–cuprous iodide. A simple mixture of lithium aluminum hydride and cuprous iodide in the ratio of 1:4 is successful in conjugate reduction of acyclic α,β-unsaturated ketones, but fails for 2-cyclohexenone derivatives, and no results were reported with unsaturated esters.[19] An intriguing feature of this work is that the results can be interpreted as reactions of H_2AlI or $HAlI_2$; no copper hydride need be invoked.[19]

From the experiments of House and DuBose,[20] and consistent with the stoichiometry generally used to prepare the active reagents, CuH itself does not add to conjugated ketones, but the "ate" complexes such as **2–4** are generally successful. The simplest such species, $LiCuH_2$, has been prepared and largely characterized by Ashby,[21] but no evidence of conjugate addition reactions was presented. Just as for the general reaction of organocuprates with unsaturated carbonyl compounds,[22] both electron transfer and nucleophilic addition mechanisms have been considered for the addition of hydride, but no direct experimental evidence has been presented.

Results

Using the general technique of earlier workers,[14,16] we have developed convenient preparations of copper-based reagents which provide efficient 1,4 reduction of both conjugated ketones and esters. The more generally efficient hydrido–copper species were prepared according to eq 1 and 2. The reagent involving the lithium cation (eq 1, here referred to as Li complex) was obtained as a brown-black suspension in tetrahydrofuran by simply mixing a solution of 2 molar equiv of lithium trimethoxyaluminum hydride with anhydrous cuprous bromide at 0 °C for 0.5 h. An equimolar mixture of sodium bis(2-methoxyethoxy)aluminum dihydride (Vitride,[23a] Red-al[23b]) and cuprous bromide in tetrahydrofuran at 0 °C for 0.5 h gives a similar suspension, here referred to as the Na complex. No attempt was made to purify the reactive species, but filtration at low temperature produced a filtrate which was not an active reducing agent.

$$2LiAlH(OCH_3)_3 + CuBr \xrightarrow[THF]{0\ ^\circ C} \text{"Li complex"} \quad (1)$$

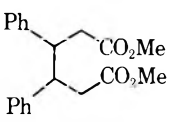
$$NaAlH_2(OCH_2CH_2OCH_2)_2 + CuBr \xrightarrow[THF]{0\ ^\circ C} \text{"Na complex"} \quad (2)$$

Reaction with Conjugated Ketones. Table I displays the results of reactions of 2-cyclohexenone and derivatives **5** and **6** with the Li complex and the Na complex. Simple aluminum hydride reagents give mainly 1,2 reduction (entry 16), but the hydrido–copper species give predominate 1,4 reduction under a variety of conditions. The Li complex tends to be superior in selectivity and yield; the results in entries 1, 10, and 14 are easily reproducible. Complete conversion requires more than 1 molar equiv of the Li complex and excess reagent seems not to be harmful. Cuprous iodide in place of cuprous bromide (entry 3) gives a much less selective reagent; similar effects are observed with (triphenylphosphine)cuprous iodide in preparation of an Na complex (entry 7). Other solvents such as toluene or ether (entry 8) used in place of tetrahydrofuran (both in complex formation and in reaction with the enone) lead to substantial amounts of 1,2 reduction or recovered enone. Reduction with the Li complex is quite fast, being about 90% complete after 20 min at −78 °C (entry 1). The addition of 2-butanol during the reaction of Na complex with the enone is not very beneficial (entries 9 and 13), in contrast to results below. The more highly substituted enones, 5,5-dimethyl-2-cyclohexenone (**5**) and 3,5,5-trimethylcyclohexenone (**6**), react more slowly than 2-cyclohexenone; at least 3 molar equiv of reducing agent are necessary for complete conversion (compare entries 10, 11, and 14).

Table II presents the results obtained with two acyclic ketones, 2,2,6,6-tetramethylhept-4-en-3-one (**7**) and chalcone (**8**). Conjugate reduction is again the preferred course of reaction; the Na complex is clearly superior, giving no trace of 1,2 reduction under a variety of conditions. The reduction is slow at −78 °C (entry 5), compared to the results with 2-cyclohexenone. Chalcone is a difficult case; the usual reduction conditions give mainly high molecular weight products. Added 2-butanol with the Na complex under carefully defined conditions produces moderate amounts of the 1,4 reduction product. The addition of 2-butanol seems to improve selectivity toward 1,4 reduction with the Li complex, but also destroys much of the reagent, resulting in only partial conversion (entry 2).

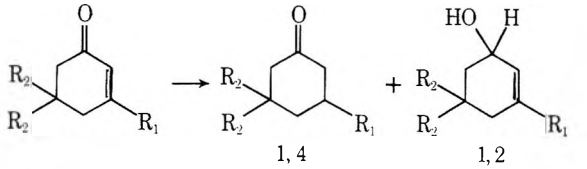
Reductions of methyl 2-butenoate (**9**) and methyl 3-methyl-2-butenoate (**10**) were successful with the Na complex (Table III). Reduction of the ester function was not a problem, but high molecular weight material accounted for most of the product from reaction with the Li complex. The presence of excess 2-butanol in the medium during reduction with the Na complex gave consistently higher yields (compare entries 2 and 4). With substrate **10**, good yields were obtained even without added alcohol, but the rate of reduction is slower compared to the rate for **9**; 4 h is required for complete conversion at −20 °C (entries 6–8).

The aryl-substituted acrylates were more difficult to reduce efficiently; methyl cinnamate was studied in detail to define optimum conditions (Table III). The Li complex led to high molecular weight products and only 5–8% of the saturated ester (entry 9). Added 2-butanol had no positive effect (entry 10). However, the Na complex gave moderate yields of the saturated ester under a variety of conditions; the best procedure (entry 13) involves an excess of the copper reagent and 2-butanol in the medium during reduction. From several reactions, a dimer has been isolated and characterized as dimethyl *meso*-3,4-diphenyladipate (**12**), the product of coupling at the β carbons. A preparative run with methyl 3,4,5-trimethoxycinnamate is detailed in the Experimental Section;



12

Table I. Reduction of 2-Cyclohexenones

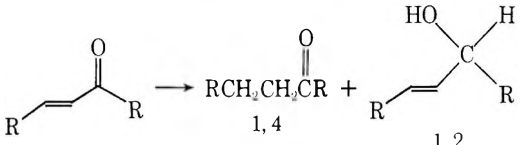


1,4 1,2

Entry[k]	Hydrido–copper species[a]	Ratio of copper–enone	Reaction conditions[b]	1,4 % yield[b]	1,2 % yield[b]	% conversion[b]
1. $R_1 = R_2 = H$	Li	1.6:1	−78 °C/20 min	64	10	90
2. $R_1 = R_2 = H$	Li	2:1	−20 °C/50 min	84	3	100
3. $R_1 = R_2 = H$	Li[c]	1.6:1	−20 °C/1.5 h	54	22	100
4. $R_1 = R_2 = H$	Na	1.6:1	−20 °C/1 h	60	5	97
5. $R_1 = R_2 = H$	Na	1.2:1	0 °C/ 0.5 h	62	0	100
6. $R_1 = R_2 = H$	Na[d]	2:1	−20 °C/2 h	10	3	55
7. $R_1 = R_2 = H$	Na[e]	1.6:1	−20 °C/1 h	64	18	100
8. $R_1 = R_2 = H$	Na[f]	1.6:1	0 °C/1 h	18	60	100
9. $R_1 = R_2 = H$	Na[g]	3:1	−20 °C/0.5 h	30	0	100
10. $R_1 = R_2 = H$	$LiCuH_2$[h]	2:1	−20 °C/0.5 h	21	64	100
11. $R_2 = CH_3$, $R_1 = H$	Li	3:1	−20 °C/1 h	98	1	100
12. $R_2 = CH_3$, $R_1 = H$	Li	2:1	−20 °C/1 h	84	1	85
13. $R_2 = CH_3$, $R_1 = H$	Na	3.5:1	−20 °C/10 min	17	0	81
14. $R_2 = CH_3$, $R_1 = H$	Na[i]	4:1	−20 °C/25 min	69	0	80
15. $R_1 = R_2 = CH_3$	Li	4:1	−20 °C/50 min	92	6	100
16. $R_1 = R_2 = CH_3$	Na	4:1	−20 °C/1 hr	61	13	100
17. $R_1 = R_2 = CH_3$	[j]	2:1	−20 °C/0.5 h	45	49	100
18. $R_1 = R_2 = CH_3$	$LiCuH_2$[h]	2:1	−20 °C/0.5 h	2	48	50

[a] Li refers to the Li complex, eq 1. Na refers to the Na complex, eq 2. [b] The yields were determined by quantitative GLC using an internal standard. [c] Cuprous iodide was used in place of cuprous bromide. [d] The molar ratio of sodium bis(2-methoxyethoxy)aluminum hydride to cuprous bromide was 1:2 instead of the usual 1:1. [e] Triphenylphosphinecuprous iodide was used in place of cuprous bromide. [f] Diethyl ether was used in place of tetrahydrofuran. [g] 8 molar equiv of 2-butanol was added (see procedure C, Experimental Section. [h] Prepared according to the procedure of Ashby (ref 21). [i] 11 molar equiv of 2-butanol was added (see procedure C, Experimental Section). [j] No cuprous halide was involved; lithium trimethoxyaluminum hydride in tetrahydrofuran was the reducing system. [k] Registry no.: $R_1 = R_2 = H$, 930-68-7; $R_2 = CH_3$, $R_1 = H$, 4694-17-1; $R_1 = R_2 = CH_3$, 78-59-1.

Table II. Reduction of Acyclic Ketones



1,4 1,2

7, R = *t*-Bu
8, R = Ph

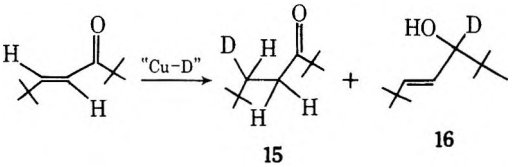
Entry[e] (compd)	Hydrido–copper species[a]	1,4 % yield	1,2 % yield	% conversion
1 (7)	Li	80	20	100
2 (7)	Li[b]	60	0	60
3 (7)	[b]	0	100	100
4 (7)	Na	98	1	100
5 (7)	Na[c]	32	0	32
6 (7)	Na[d]	98	0	100
7 (8)	Li	16	0	100
8 (8)	Na	32	0	100
9 (8)	Na[d]	54	0	85

[a] The hydride complex was prepared according to procedures A or B (Experimental Section). The conditions for reduction are −20 °C for 1 h in tetrahydrofuran with a 4:1 molar ratio of cuprous–species–enone. [b] No cuprous salt was used. Lithium trimethoxyaluminum hydride–tetrahydrofuran was the reducing system. [c] The reaction temperature was −78 °C instead of −20 °C. [d] 18 molar equiv of 2-butanol was added (procedure C, Experimental Section). [e] Registry no.: 7, 1653-94-7; 8, 94-41-7.

on a 5- or 10-mmol scale, the isolated yield of saturated ester was 85–90%.

Acetylenic esters show a still greater tendency to oligomerize. The simplest case, ethyl propynoate, gave no more than traces of ethyl acrylate and ethyl propionate. Two other cases, methyl 2-butynoate (**13**) and methyl 3-phenylpropynoate (**14**), were successful using the Na complex; partial reduction to a mixture of cis and trans β-substituted acrylates is the major pathway (Table IV). The rate of reduction is similar to that for acrylate esters; the yield decreases as time and temperature of the reduction increase beyond −20 °C for 0.5 h. Added alcohol has little effect on the distribution of products; the proportion of cis product is slightly increased.

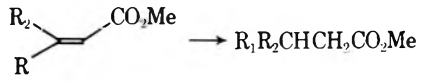
Deuterium Labeling Results. Using lithium trimethoxyaluminum deuteride, the Li complex was prepared with deuterium in place of hydrogen. Reaction of this reagent with 2,2,6,6-tetramethylhept-4-en-3-one for 1.0 h at −20 °C gave deuterium-labeled 2,2,6,6-tetramethylheptan-3-one (**15**) in 87% yield, accompanied by 12% of 2,2,6,6-tetramethylhept-4-en-3-ol (**16**). The ^1H NMR spectrum of **15** showed the characteristic triplet of triplets (J = 7.8, 1.0 Hz) for a $-CHDCH_2-$ arrangement, integrating for 1.13 ± 0.05 hydrogens, consistent with the 5-d_1 isomer (**15**). No significant deuterium was detected at C-4 in **15**. The 1,2-reduction product, **16**, also bears one deuterium, at C-2 (absence of signal at δ 6.28).



15 16

In the same way, methyl cinnamate was treated with deuterium-labeled Li complex; the yield of saturated ketone is low, but the methyl 3-phenylpropionate which can be isolated (15% yield) is selectively labeled at C-3; the lone proton at C-3

Table III. Reduction of Acrylate Derivatives



9, $R_1 = H$, $R_2 = CH_3$
10, $R_1 = R_2 = CH_3$
11, $R_1 = H$, $R_2 = Ph$

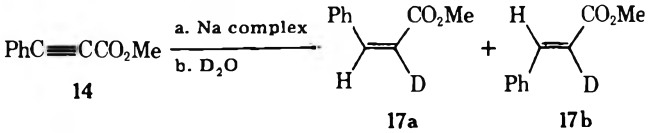
Entry[k] (compd)	Hydrido–copper species[a]	Saturated ester % yield	% conversion
1 (9)	Li	2	100
2 (9)	Na	60	100
3 (9)	Na[b]	62	73
4 (9)	Na[b,c]	84	100
5 (10)	Li	46	90
6 (10)	Na	17	24
7 (10)	Na[d]	60	77
8 (10)	Na[e]	92	100
9 (11)	Li	5	100
10 (11)	Li[f]	2	40
11 (11)	Na	28[g]	100
12 (11)	Na[f]	41	41
13 (11)	Na[f,h]	82	100
14 (11)	Na[h,i]	51	53
15 (11)	Na[h,j]	40	100

[a] The reaction conditions were −20 °C for 1 h, with 2:1 molar ratio of copper–ester unless otherwise noted. [b] 18 molar equiv of 2-butanol was present (procedure C, Experimental Section). [c] The molar ratio of copper reagent–ester was 4:1. [d] The reaction time was 2 h (−20 °C). [e] The reaction time was 4 h (−20 °C). [f] 10 molar equiv of 2-butanol was present (procedure C, Experimental Section). [g] The dimer 12 was isolated in 21% yield. [h] The molar ratio of copper reagent–ester was 8:1. [i] 11 molar equiv of methyl alcohol was added. [j] 11 molar equiv of 2-methyl-2-propanol was added (procedure C, Experimental Section). [k] Registry no.: 9, 18707-60-3; 10, 924-50-5.

appears as the characteristic triplet of triplets for a $-CHDCH_2-$ arrangement after $Eu(fod)_3$[24] is used to separate the chemical shift positions of aliphatic protons. The protons at C-2 appear as a simple doublet (J = 7 Hz).

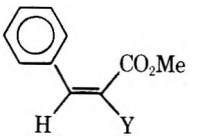
Using the Na complex in the presence of 2-butanol-2-*d*, methyl cinnamate was reduced to methyl 3-phenylpropionate in 81% yield; ^1H NMR analysis with the shift reagent as above indicated no deuterium incorporated in the product. A parallel experiment employing 2-butanol-O-*d* led to 3-phenylpropionate with 0% deuterium at C-3 and 24% deuterium (50% labeling of one H position) at C-2.

Addition of D_2O before the usual aqueous isolation procedure (after the reduction step is complete) generally gives about 50% deuterium in the α position, but no deuterium in the β position. For example, reduction of 2,2,6,6-tetramethylhept-4-en-3-one with the Li complex in THF at −20 °C for 1 h followed by addition of D_2O and then aqueous extraction procedures afforded 2,2,6,6-tetramethylheptan-3-one with 45% deuterium incorporation at C-4. Presumably, the aqueous isolation procedures led to partial exchange of protons for deuterium at C-4. When methyl 3-phenylpropynoate (14) is reduced with the Na complex (40 min/−20 °C) and excess D_2O is then added, the methyl *cis*- and *trans*-cinnamates bear deuterium to the extent of 98.5 ± 2% at C-2 (in 17).



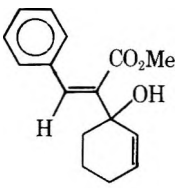
14 17a 17b

Trapping of the Intermediate Enolate with Carbon Electrophiles. As mentioned immediately above, reaction of methyl 3-phenylpropynoate with the Na complex followed by addition of D_2O gives efficient deuteration at C-2 (in 17). However, addition of alkyl halides (methyl iodide, allyl bromide) before aqueous isolation procedure gave no alkylation; only the usual mixture of *cis*- and *trans*-cinnamates was obtained. On the other hand, when the Na complex was allowed to react with methyl 3-phenylpropynoate at −20 °C for 0.5 h, and then benzaldehyde was added (−78 to −20 °C for 6 h), the adduct 18 was isolated as an oil in 47% yield. Treatment with benzoyl chloride afforded crystalline benzoate 19; the *Z* configuration is assigned based on ^1H NMR data (see Experimental Section). The *E* isomer is presumably also present in smaller amounts, but it was not isolated. A parallel reaction, except that the benzaldehyde was added at −78 °C and the reaction mixture was maintained at −78 °C for 19 h, produced no adduct 18; methyl cinnamates (*E*/*Z* mixture) were obtained as the main products.

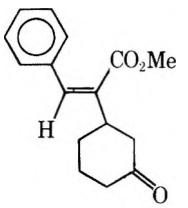


18, Y = PhCH(OH)
19, Y = PhCH(OCOPh)
20, Y = Li (or Cu, Al)

As a test of the 1,2 vs. 1,4 addition selectivity of intermediate 20, reaction with 2-cyclohexenone was studied. The intermediate was generated from the Na complex and methyl 3-phenylpropynoate as before (−20 °C/0.5 h), and allowed to react with a threefold excess of 2-cyclohexenone at −78 to −20 °C. Two major products were obtained, the 1,2 adduct, 21, and methyl cinnamate (cis). Extensive purification by preparative layer chromatography provided a pure sample of 21, but in only 14% yield. No evidence for the presence of a 1,4 adduct (i.e., 22) was obtained. When the reaction mixture with 2-cyclohexenone was maintained at −78 °C (19 h), the major product was methyl cinnamate (cis and trans).



21



22

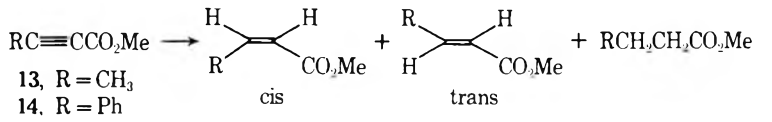
Discussion

The two complex metal hydride mixtures, the Li complex and Na complex, are prepared in a simple and convenient way. Both tend to react with α,β-unsaturated carbonyl compounds by 1,4 addition, but they differ in efficiency depending on the structure of the carbonyl substrate.

Derivatives of 2-cyclohexenone are best reduced by a threefold molar excess of the Li complex in THF at −20 °C. Reduction is slow at −78 °C, but complete within 1 h at −20 °C; β-alkyl substituents tend to slow the rate of reduction without affecting the selectivity for 1,4 over 1,2 addition. The Na complex reacts with 2-cyclohexenone at a similar rate and with high selectivity for 1,4 addition, but significant amounts of high molecular weight products appear (up to 35% from 2-cyclohexenone), perhaps due to condensation reactions of the enolate–metal species, which is presumed to be an important intermediate. Acyclic enones are reduced more efficiently by the Na complex (Table II), as are all of the alkenoate and alkynoate examples (Tables III and IV).

The composition of the reagents is not known. Both are heterogeneous mixtures in THF, and the reducing ability

Table IV. Reduction of Propynoate Ester Derivatives

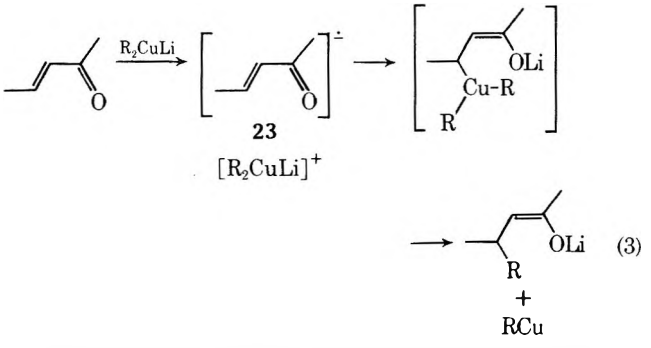


Entry[e] (compd)	Hydrido–copper species[a]	cis % yield	trans % yield	Saturated ester, % yield	% conversion
1 (13)	Li, 3:1, 35 min	9	8	2	100
2 (13)	Na, 6:1, 20 min	25	27	26	100
3 (13)	Na, 3:1, 4 h[b]	2	2	0	4
4 (13)	Na, 3:1, 20 min	21	31	5	73
5 (13)	Na, 3.5:1, 2 h[c]	29	25	18	96
6 (14)	Li, 3:1, 20 min	10	5	0	94
7 (14)	Na, 4:1, 15 min	56	21	6	100
8 (14)	Na, 3:1, 45 min[c]	61	14	4	83
9 (14)	Na, 4:1, 30 min	47	18	11	100
10 (14)	Na, 4:1, 30 min[d]	14	13	19	100
11 (14)	Na, 4:1, 1 h[b]	12	0	0	12

[a] This entry specifies which reducing species was used (Li or Na), the ratio of copper reagent–ester, and the reaction time at −20 °C. [b] The reaction was carried out at −78 °C. [c] 10 molar equiv of 2-butanol was added (procedure C, Experimental Section). [d] The reaction was carried out at 0 °C. [e] Registry no.: 13, 23326-27-4; 14, 4891-38-7.

resides in the solid, not in the solution. The effective stoichiometry is hydride units–cuprous bromide = 2:1, and is consistent with the presence of the cuprates, $LiCuH_2$ and $NaCuH_2$. However, we find that the reagent to which Ashby and co-workers[21] assign the composition $LiCuH_2$ does not parallel the Li complex in its pattern of reactivity (Table I, entries 10, 18). Addition to the carbonyl carbon (1,2 addition) is the major pathway of Ashby's $LiCuH_2$ with cyclohexenones. Consistent with earlier hydrido–copper species,[20] the reagent obtained from a 1:1 mole ratio of lithium trimethoxyaluminum hydride–cuprous bromide gives no reaction with enones. The pattern of reactivity for both the Li and Na complexes, especially the efficient reduction of 2-cyclohexenone derivatives, also suggests that simple haloaluminum hydrides are *not* the active ingredients, in contrast to the reagent prepared from lithium aluminum hydride and cuprous iodide.[19]

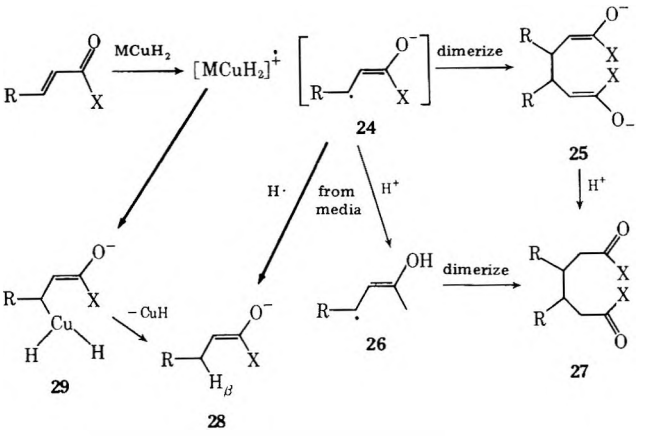
The isolation of dimethyl *meso*-3,4-diphenyladipate (**12**) from reaction of the Na complex and methyl cinnamate is particularly significant in considering a mechanism for the reduction. Reaction of dialkyl cuprates with unsaturated carbonyl compounds is thought[22] to proceed via electron transfer to give a transient radical anion (**23** in eq 3) followed



(3)

by a carbon–copper intermediate which can undergo reductive elimination (eq 3). However, the characteristic dimerization of such radical anions[25] has not been observed, even as a minor pathway, in the reaction of dialkyl cuprate with enones.

A parallel mechanism can be written for reduction with the hydrido–copper species, describing them as $MCuH_2$ for simplicity (eq 4). The radical anion (**24**) has several established pathways of reaction.[25] The dihydro dimer (**27** in eq 4) can arise through dimerization (to give the bisenolate **25**) followed by protonation (during isolation or from added alcohol) or through initial protonation (to give **26**; proton from the medium) followed by dimerization of the enol radical **26**. The reduction product enolate (**28**) is formed either from coupling of the radical anion (**24**) with the $MCuH_2$ radical cation (to give transient complex **29**) and reductive elimination of CuH or from hydrogen atom abstraction from the medium (to give **28** directly).



Clearly, during the reduction of methyl cinnamate in the absence of 2-butanol, dimerization to form the species **25** is favorable, presumably because the extended conjugation with the phenyl substituent allows a longer lived radical anion (**24**, R = Ph). Less substituted acrylate and propiolate derivatives also require careful control of reaction conditions in order to minimize oligomerization. Hydrodimerization products (i.e., **27**) have not been observed in these cases; condensation polymerization may be the major side reaction. The hydrogen added to the β carbon (i.e., H_β in **28**) is clearly derived from the hydrido–cuprate reagent as shown by efficient deuterium (mono) labeling of the β position during reduction of 2,2,6,6-tetramethylhept-4-en-3-one and of methyl cinnamate with the Li complex bearing deuterium. It does not arise from hydrogen atom abstraction from the THF solvent, as shown by carrying out a reduction of methyl cinnamate with the Na complex in THF-d_8.

The addition of alcohols to the medium before reduction tends to minimize oligomerization and completely inhibits hydrodimerization of methyl cinnamate. Among the alcohols tested, 2-butanol offers the best balance between destruction of the hydrido–copper agent and optimum yields of reduction

Table V. Reduction of Other Functional Groups

Entry, compd[a]	Registry no.	Product (% yield)[b]	% conversion
1. $Ph(CH_2)_4CN$	7726-45-6	No reaction	0
2. $PhCH_2CH_2Br$	103-63-9	$PhCH_2CH_3$ (68)	100
3. p-$CH_3OC_6H_4Br$	104-92-7	$CH_3OC_6H_5$ (33)	33
4. $PhCH_2CHO$	122-78-1	$PhCH_2CH_2OH$ (100)	100
5. Cyclohexanone	108-94-1	Cyclohexanol (69)	100

[a] In each case, the compound was added to a fourfold molar excess of the Na complex in THF at −78 °C and allowed to stir at −20 °C/2 h. [b] Product yields and recovery of starting material were determined by quantitative GLC, ^1H NMR spectroscopy, or both.

product. Methyl alcohol reacts too rapidly with the Na complex and 2-methyl-2-propanol is ineffective in avoiding oligomerization. Presumably, the alcohol acts as a proton donor to speed formation of the key carbon–copper intermediate (**29**, eq 4) relative to dimerization, but the detailed role of the alcohol is not clear.[26] Hydrogen atom transfer from position C-2 in 2-butanol is known to be favorable,[27] but the experiment with 2-butanol-2-*d* shows clearly that in the reduction of methyl cinnamate with the Na complex, the added alcohol does *not* deliver deuterium from C-2 to the β position of the product, 2-phenylpropionate. Similarly, 2-butanol-*O*-*d* does *not* contribute a deuterium to the β position; the α position is found to be partially labeled. This observation contrasts with the results from generation of enone radical anions (using sodium metal) in the presence of 2-methyl-2-propanol-*O*-*d*, where the β carbon does receive the deuterium.[25]

Vinyl–metal species such as **20** are clearly intermediates in the reduction of acetylenic esters. They are not particularly stable, suffering inversion of configuration and polymerization on standing in solution at 0 °C. No information is available from our studies bearing on the questions of whether the metal is carbon or oxygen bound,[28] or whether the metal is lithium, copper, or aluminum. The intermediate does parallel the related compounds studied by Marino and co-workers, in adding to the carbonyl group of 2-cyclohexenone. By adding the carbonyl trapping agent immediately after reduction at −20 °C, the cis configuration is obtained preferentially.

The reactivity of the Na complex toward common functional groups will limit its applicability for reduction of conjugated carbonyl units in polyfunctional molecules. As summarized in Table V, saturated ketones and aldehydes, alkyl bromides react with the Na complex approximately as rapidly as a typical conjugated ketone. Nitrile and ester units are inert under these conditions. The yield of alcohol from the saturated ketone is only 69%; the remainder is high molecular weight material. The reduction of organic halides has been observed with other hydrido–copper reagents, but relative rate information was not available.[15,29]

Experimental Section

General. Tetryhydrofuran (THF) and ether were freshly distilled from sodium–benzophenone ketyl under argon immediately before use. All other solvents were ACS reagent grade and were not further purified unless otherwise noted. All reactions involving hydride reagents were carried out under an atmosphere of argon achieved by alternately evacuating and filling the reaction vessel three times with argon. All organic extracts were dried over anhydrous magnesium sulfate. Cyclohex-2-enone, isophorone, 5,5-dimethylcyclohex-2-enone, methyl crotonate, chalcone, *trans*-cinnamic acid, 3-methylbut-2-enoic acid, 3-phenylpropionic acid, and pinacolone were purchased from Aldrich Chemical Co. Methyl 3-methylpropynoate was purchased from Farchan Research Laboratories. 2-Butanol and Vitride were purchased from Eastman Organic Chemicals. Methyl esters of *trans*-cinnamic acid, 3-methylbut-2-enoic acid, and 3-phenylpropionic acid were prepared by dissolving the acid in methyl alcohol, adding 3–4 mL of thionyl chloride, and heating at reflux for 12–18 h. Methyllithium in ether, lithium aluminum hydride (granular and in ether solution), and cuprous bromide were purchased from Alfa Inorganics (Ventron), or prepared according to the procedure of Keller and Wycott.[30a] Cuprous iodide was purchased from ROC/RIC. Colored impurities from the Cu(I) halides were removed from these salts by dissolution in a saturated aqueous solution of the appropriate potassium halide followed by treatment with charcoal, filtration, and dilution with water to reprecipitate the Cu(I) halide.[30b] The purified Cu(I) halide was dried for 24 h under vacuum (0.001 Torr). Lithium aluminum deuteride was purchased from ICN Corp. and was stated to contain 99 atom % deuterium. Following the method of House and co-workers,[25] 2,2,6,6-tetramethylhept-4-en-3-one was prepared.

Lithium Trimethoxyaluminum Deuteride. Exactly parallel with the procedure for preparation of lithium trimethoxyaluminum hydride,[31] lithium aluminum deuteride and methyl alcohol-*O*-*d* were combined in THF and filtered, and the filtrate used as a solution of lithium trimethoxyaluminum deuteride.

2-Butanol-2-*d*. Lithium aluminum deuteride (1.0 g, 24 mmol) was dissolved in 70 mL of ether and cooled to 0 °C. Methyl ethyl ketone (5.2 g, 72 mmol) was added dropwise over a 45-min period. After the reaction mixture was stirred for 3.5 h at 25 °C, 1.0 mL of water, 1.0 mL of 15% aqueous sodium hydroxide solution, and 3 mL of water were added sequentially. The mixture was filtered, and the filtrate was washed several times with saturated salt solution, dried, and fractionally distilled using *n*-butylbenzene as a "chaser". At bp 95–100 °C, 2-butanol-2-*d* was obtained which showed ^1H NMR ($CDCl_3$) δ 1.42 (m, $-CH_2-$), 0.78–1.2 (m, $-CH_3$), 3.67 (s, $-OH$). No signal due to hydrogen at C-2 was visible (<2%), expected at δ 3.68. The sample was stored over Linde Type 4A molecular sieves.

Preparation of 2-Butanol-*O*-*d*. All glassware was rinsed with D_2O and dried. Freshly distilled 2-butanol (7 g) was dissolved in 15 mL of dichloromethane and treated four times with batches of D_2O (99.5%) containing a small amount of NaOD. Using *n*-butylbenzene as chaser, fractional distillation produced a fraction of bp 95–100 °C which was 2-butanol with 96 atom % deuterium, as determined by ^1H NMR spectroscopy. The sample was stored over Linde Type 4A molecular sieves.

Procedure A. Preparation and Reactions of the Li Complex. The following procedure is typical of the techniques used to obtain the data involving the Li complex. Lithium trimethoxyaluminum hydride (0.79 M, 5.3 mL, 4.2 mmol) was added dropwise to a suspension of cuprous bromide (315 mg, 2,2 mmol) in 8 mL of THF maintained at 0 to −5 °C. After 30 min, the resulting dark brown suspension was cooled to −78 °C. Cyclohex-2-enone (110 mg, 1.15 mmol) was added rapidly via syringe and after 10 min, the mixture was placed in a bath at −20 °C and stirred for 50 min. Then methyl alcohol (5 mL) was added and the mixture poured into 25 mL of saturated aqueous ammonium chloride solution. Ether was added and the mixture was shaken in a separatory funnel. The blue (copper) layer was separated. The other layer was washed with water, dried, and analyzed by quantitative GLC with an internal standard (*n*-butylbenzene) added at this point. Using a 6 ft × 0.125 in. column packed with 3% Carbowax 20 M on Chromosorb P at 110 °C, quantitative analysis was carried out for unreacted cyclohex-2-enone (retention time: 5.9 min), cyclohexanone (5.0 min), *n*-butylbenzene (5.5 min), cyclohexanol (7.0 min), and 2-cyclohexenol (10.2 min). The identity of the products was assigned based on GLC retention time comparisons with samples of established identity (two columns) and by GCMS, using a Finnegan 3300 instrument. In this example, the yields were: cyclohexanone, 84 ± 2%; 2-cyclohexenol, 3 ± 2%; and cyclohexanol, ≤1%. For a survey of other conditions, see Table I. For reactions under similar conditions with other conjugated carbonyl substrates, see Tables II–IV.

Procedure B. Preparation and Reactions of the Na Complex. A solution of sodium bis(2-methoxyethoxy)aluminum hydride in benzene (Vitride[23a] or Red-Al,[23b] 70% solution, 0.56 mL, 2.0 mmol, 4.0 hydride equiv) was added dropwise to a suspension of cuprous bromide in 4 mL of THF at 0 to −5 °C under argon. The resulting brown-black suspension was allowed to stir at 0 °C for 0.5 h, then it was cooled to −78 °C. To this mixture at −78 °C was added via syringe a solution of 2,2,6,6-tetramethylhept-4-en-3-one (84 mg, 0.5 mmol) in 3 mL of THF. After 10 min, the solution was stirred at −20 °C for 1 h, quenched by addition of water (4 mol), and poured into 25 mL of saturated aqueous ammonium chloride solution. Ether was added, the blue (copper) aqueous solution was separated, the ether solution was washed with water and then dried, and finally the ether solution was analyzed by GLC. Ethylbenzene was added as internal standard.

Using a 6 ft × 0.125 in. column packed with 3% Carbowax 20 M on Chromosorb P at 120 °C the following retention times/yields were observed: ethylbenzene, 2.0 min; 2,2,6,6-tetramethylheptan-3-one, 3.75 min, 98 ± 2%; 2,2,6,6-tetramethylhept-4-en-3-one, 4.5 min, <1%; 2,2,6,6-tetramethylhept-4-en-3-ol, 7.0 min, <1%. The identity of the products was assigned based on GLC retention time comparisons with samples of established identity and by GC/MS, using a Finnegan 3300 instrument. For a survey of other conditions, see Table I. For reactions of the Na complex with other conjugated carbonyl substrates, see Tables I–IV.

Procedure C. Reductions Using the Na Complex with 2-Butanol Present. Exactly as above, the Na complex was prepared under argon from cuprous bromide (686 mg, 4.8 mmol) and Vitride (1.34 mL, 9.6 equiv of hydride) in 12 mL of THF and cooled to −78 °C. Then 2-butanol (2.0 mL, 1.6 g, 18 mmol) was added all at once, followed within 5 min by a solution of 2,2,6,6-tetramethylhept-4-en-3-one (200 mg, 1.2 mmol) in 4.0 mL of THF. After 10 min at −78 °C, the mixture was stirred at −20 °C for 1.0 h. After the usual isolation procedure, quantitative GLC analysis showed the presence of 2,2,6,6-tetramethylhept-4-en-3-one in 98% yield. Collection of this material by preparative GLC followed by ^{1}H NMR analysis confirmed the identity of the product.

Characterization of Products in Tables I–IV. (a) From Isophorone. Reduction of isophorone according to procedure A gave 3,3,5-trimethylcyclohexanone and 3,5,5-trimethylcyclohex-2-enol which were separated by preparative GLC (5% FFAP at 165 °C). The ketone was identified from comparison of ^{1}H NMR[32] data, mass spectral molecular weight (found, parent at *m/e* 140; calcd for $C_9H_{16}O$, 140), and by IR (neat): 1710 cm^{-1}. The alcohol was prepared by reduction of isophorone with lithium aluminum hydride[33] and compared with the sample from preparative GLC in ^{1}H NMR and mass spectral properties. The mass spectrum has been published.[34]

(b) From 5,5-Dimethylcyclohex-2-enone. Reduction according to procedure A gave 3,3-dimethylcyclohexanone and 5,5-dimethylcyclohex-2-enol, which were separated by preparative GLC. The ketone was identified by comparison of ^{1}H NMR data,[35] mass spectral data (found, parent at *m/e* 126; calcd for $C_8H_{14}O$, 126), and IR (neat): 1710 cm^{-1}. The alcohol was prepared by reduction of 5,5-dimethylcyclohex-2-enone with lithium aluminum hydride[36] and compared with the sample from preparative GLC in ^{1}H NMR and mass spectral properties.

(c) From Chalcone. Reduction according to procedure C. The ether extract, after analysis by GLC, was concentrated and the residue was separated into three fractions by preparative layer chromatography (10% ethyl acetate–benzene, silica gel). Fraction 1 (R_f ~0.6) was identified as 1,3-diphenylpropan-1-one by comparison of GLC retention time, ^{1}H NMR data, and melting point (67–69 °C) with corresponding data from a commercial sample (Eastman Organic Chemicals). Fraction 2 (R_f 0.5) was unreacted chalcone, while the slower moving material consisted of a nondistillable mixture which was not further characterized.

(d) From Methyl Crotonate. Reduction according to procedure C produced a single product detectable by GLC which was shown to be methyl butanoate by comparison of GLC retention time and mass spectral properties with corresponding data from a commercial sample (Aldrich Chemical Co.).

(e) From Methyl 3-Methylbut-2-enoate. Reduction according to procedure C produced a single product detectable by GLC which was shown to be methyl 3-methylbutanoate by comparison of GLC retention time and mass spectral properties with corresponding data from a commercial sample (Aldrich Chemical Co.).

(f) From Methyl Cinnamate. Reduction according to procedure B produced an ether solution which was concentrated at reduced pressure. Short-path distillation (up to 50 °C (0.01 Torr)] afforded a colorless liquid distillate which was shown to be a single compound by GLC and TLC, and was identified as methyl 3-phenylpropionate by comparison of ^{1}H NMR and mass spectral data with corresponding data from a commercial sample (Aldrich Chemical Co.). The residue was applied to a preparative layer chromatography plate (silica gel) and eluted with 10% ethyl acetate–benzene. The main component was recovered from the plate, mp 174–175 °C. It was identified as dimethyl *meso*-2,3-diphenyladipate (12) by comparison of melting point (lit.[37] 174–175 °C): ^{1}H NMR ($CDCl_3$) δ 6.22 (s, 5 H, ArH), 3.32 (s, 4 H, $-OCH_3$ and $-CHAr$), 2.38 (m, 2 H, $-CH_2CO_2-$); IR (KBr)1710 cm^{-1}; mass spectrum *m/e* 326 (parent), 296, 253, 252, 220, 163, 121 (base), 104, 91; calcd for $C_{20}H_{22}O_4$, mol wt 326.

(g) From Methyl 3-Methylpropiolate. Reduction according to procedure B produced an ether solution which was analyzed by GLC using a 12 ft × 0.125, in. column packed with 5% Carbowax 20M on Chromosorb P at 70 °C; ethylbenzene was added as internal calibration standard. Peaks observed were attributed to: methyl propionate (25 min, 26%), methyl *cis*-crotonate (4.0 min, 25%), methyl *trans*-crotonate (5.5 min, 27%), ethylbenzene (6.5 min), and methyl 3-methylpropynoate (7.0 min, <1%). The crotonate isomers were identified by comparison of GC retention times and mass spectral data with corresponding data from commercial or independently synthesized material.

(h) From Methyl 3-Phenylpropynoate. Reduction according to procedure B produced an ether solution which was concentrated. Short-path distillation of the residue [50–60 °C (0.01 Torr)] afforded a colorless distillate. Quantitative ^{1}H NMR analysis on the distillate using toluene as internal standard indicated the presence of three major components: methyl *cis*-cinnamate (47% yield, integration of olefinic H doublet centered at δ 5.90),[38] methyl *trans*-cinnamate (18%, integration of olefinic H doublet centered at δ 6.38),[38] and methyl 3-phenylpropionate (11%, integration of $-OCH_3$ at δ 3.75). The components were prepared independently or purchased, and were compared in GLC retention times, mass spectral data, and ^{1}H NMR data with the reaction product mixture.

Reductions with Ashby's $LiCuH_2$. Lithium dihydridocuprate was prepared[21] by adding methyllithium (1.55 M in ether, 3.87 mL, 6.0 mmol) to a suspension of cuprous iodide (571 mg, 3.0 mmol) in 25 ml of ether at −78° under argon. The colorless solution of lithium dimethylcuprate was allowed to stir at −78 °C for ca. 45 min, at which time lithium aluminum hydride (1.44 M in ether, 2.08 mL, 3.0 mmol) was added all at once. The colorless solution changed immediately to yellow and a yellow solid precipitated as the temperature was allowed to rise to 25 °C. The solid was filtered under argon and washed two to three times with 2–3-mL portions of ether. Then to a suspension of the yellow solid in 16 mL of ether stirred at −78 °C under argon was added 154 mg (1.0 mmol) of 2-cyclohexenone via syringe. The color changed to brown immediately. After being stirred at −78 °C for 20 min and at −20 °C for 30 min, the mixture was quenched by cooling to −78 °C and adding 15–20 ml of saturated aqueous ammonium chloride solution. The ether layer was washed with water, dried, and analyzed by GLC as in procedure A above. Present were: cyclohexanone (21%, 5.0 min), cyclohexanol (~3%, 7.5 min), and cyclohex-2-enol (64%, 10.5 min). The products were identified by comparison of retention times with commercial samples. A similar experiment with isophorone gave parallel results; the ratio of 1,4 reduction–1,2 reduction was 1:30.

Reduction of 2,2,6,6-Tetramethylhept-4-en-3-one in the Presence of 2-Butanol-*2-d*. According to procedure C, using 2-butanol-2-*d* in place of 2-butanol, 2,2,6,6-tetramethylheptan-3-one was detected by GLC (98% yield). Following preparative GLC, the deuterium incorporation was assayed by repeated integration of the signals due to the $-CH_2-$ units (δ 2.46 and 1.50) relative to the signals due to the *tert*-butyl units (δ 1.15 and 0.90). No deuterium incorporation into either $-CH_2-$ unit (<5%) was observed.

Reduction of 2,2,6,6-Tetramethylhept-4-en-3-one in the Presence of 2-Butanol-*O-d*. The experiment exactly parallelled that immediately above, except 2-butanol-*O*-*d* was used in place of 2-butanol-*1*-*d*. Quantitative GLC analysis indicated the presence of 2,2,6,6-tetramethylheptan-3-one, 99% yield. Isolation by preparative GLC as above gave material with the following properties: ^{1}H NMR ($CDCl_3$) δ 2.46 (m, 1.51 H), 1.50 (m, 2.0 H), 1.15 (s, 8.95 H), 1.00 (s, 9.02 H). These data indicate the incorporation of 24 ± 2 atom % deuterium at the position C-4, corresponding to the signal at δ 2.46.

Reduction of 2,2,6,6-Tetramethylhept-4-en-3-one with the Li Complex Prepared from Lithium Trimethoxyaluminum Deuteride. According to procedure A, but using lithium trimethoxyaluminum deuteride, 2,2,6,6-tetramethylheptan-3-one was reduced. Preparative GLC afforded the ketone **15** and the alcohol **16**. The ketone **15**: ^{1}H NMR ($CDCl_3$) δ 1.18 (s, 9.1 H), 0.92 (s, 9.0 H), 1.40 (t of t, 1.13 H, $J_{1,2}$ = 7.8, $J_{1,0}$ = 2.3 Hz), 2.45 (d of t, 2.0 H, $J_{2,0}$ = 1.0, $J_{1,2}$ = 7.8 Hz). The alcohol **16**: ^{1}H NMR ($CDCl_3$) δ 3.5–4 (m, 2 H), 1.45 (s, 1 H, OH, exchangeable with D_2O), 1.01 (s, 9.0 H), 0.91 (s, 9.0 H). Less than 0.1 relative H units was observed by integration over the position at δ 3.72, where the methine hydrogen (D in **16**) appears in the ^{1}H NMR spectrum of the unlabeled material.

Reduction of Methyl Cinnamate with the Li Complex Prepared from Lithium Trimethoxyaluminum Deuteride. According to procedure A, except using lithium trimethoxyaluminum deuteride, methyl cinnamate was reduced. The organic product was distilled in a short-path apparatus (50 °C (0.001 Torr)] to afford a colorless distillate (25 mg, 15% yield): ^{1}H NMR ($CDCl_3$) δ 7.25 (s, 5.1 H, ArH), 3.68 (s, 3.0 H, $-OCH_3$), 2.5–2.9 (m, ~3 H, $-CH_2-$, $-CHD-$). Addition of ^{1}H NMR shift reagent, Eu(fod)$_3$,[24] to the ^{1}H NMR sample tube caused the multiplet at ca. δ 2.7 to become a singlet. Additional Eu(fod)$_2$ provided separation of the signals due to the C-1 and C-2 protons in

the methyl 3-phenylpropionate product (**31**). With 43 mg of $Eu(fod)_2$ added to the solution, a multiplet (t of t, 1 H, $J_{1,2}$ = 7, $J_{1,0}$ = 3 Hz) assigned to H-1 appeared upfield of a second multiplet (br d, ~2 H, $J_{1,2}$ = 7 Hz).

Reduction of Methyl Cinnamate with the Na Complex in the Presence of 2-Butanol-*2-d*. Reduction of methyl cinnamate (162 mg, 1.0 mmol) exactly according to procedure C except using 2-butanol-*2-d* in place of 2-butanol produced an ether solution which was concentrated by rotary evaporation. The residue was distilled in a short-path apparatus [50 °C (0.001 torr)] to give a colorless distillate, 132 mg, which was identified as methyl 3-phenylpropionate by comparison with a commercial sample.

Reduction of Methyl 3-Phenylpropiolate with the Na Complex with Quenching by Deuterium Oxide. Reduction of methyl 3-phenylpropynoate (147 mg, 0.92 mmol) according to procedure B, except that deuterium oxide (4.0 mL, 99.8 atom % D) was added after reduction was complete, produced an ether solution which was analyzed by quantitative GLC as before. From retention time and mass spectral data comparisons, the following components were determined (5 ft × 0.125 in. 5% Carbowax 20M on Chromosorb P, 170 °C): methyl *cis*-cinnamate (retention time 12 min, 32%), methyl *trans*-cinnamate (18 min, 18%), methyl 3-phenylpropionate (8 min, 18%). The solution was concentrated by rotary evaporation and the residue was distilled in a short-path apparatus [50 °C (0.01 Torr)] to give a colorless distillate (91 mg) which was analyzed by quantitative ^1H NMR. The signal from methyl *cis*-cinnamate, which appears in the unlabeled compound at δ 6.88 (d, β-H, $J_{\alpha,\beta}$ = 13 Hz), appeared as a triplet with J = 1 Hz; the signal which appears in the unlabeled compound at δ 5.90 (d, α-H, $J_{\alpha,\beta}$ = 13 Hz) was absent (<0.05 relative proton area) during scanning of the spectrum at high sensitivity (>95 atom % deuterium at α-H in **17a**). The signal from methyl *trans*-cinnamate which appears in the unlabeled compound at δ 6.38 was absent (<0.05 relative proton area, >95 atom % deuterium at α-H). The mass spectra (GC/MS, electron impact) for both the cis and trans methyl cinnamate product showed the base peak at *m/e* 163, with no peak at *m/e* 162 (<5% unlabeled). Calcd for $C_{10}H_9DO_2$: mol wt 163.

Preparative Scale Reduction of Methyl 3,4,5-Trimethoxycinnamate. A solution of sodium bis(2-methoxyethoxy)aluminum hydride (Vitride, 70% solution in benzene, 11.2 mL, 40 mmol, 80 mmol of hydride) was added dropwise to a suspension of cuprous bromide (5.70 g, 40 mmol) in 75 mL of THF maintained at −5 to 0 °C (bath temperature) under argon. After 30 min at 0 °C, the mixture was cooled to −78 °C and 2-butanol (8.0 mL, 90 mmol) was added rapidly. Within 10 min, a solution of methyl 3,4,5-trimethoxycinnamate (1.26 g, 5.0 mmol) in 10 mL of THF was added rapidly. After 15 min at −78 °C, the reaction mixture was stirred at −20 °C for 2 h. Then water (10 mL) was added and the mixture was poured in a saturated aqueous solution of ammonium chloride. The ether layer was washed with water and concentrated by rotary evaporation, and the residue was distilled in a short-path apparatus. The colorless distillate (1.23 g, 96.8% yield) was pure methyl 3-(3,4,5-trimethoxyphenyl)propionate:[39] ^1H NMR ($CDCl_3$) δ 6.42 (s, 2 H, Ar**H**), 3.80 (s, 9 H, $-OCH_3$), 2.4–3.1 (m, 4 H, $-CH_2CH_2-$); IR (neat) 1740 cm^{-1}; mass spectrum parent at 254.1154, calcd for $C_{13}H_{18}O_5$, 254.1167.

Reduction of Methyl 3-Phenylpropynoate with the Na Complex Followed by Trapping of the Organometal Intermediate. (a) With Benzaldehyde. A solution of sodium bis(2-methoxyethoxy)aluminum hydride (Vitride, 70% solution in benzene, 2.24 mL, 8 mmol, 16 mmol of hydride units) was added dropwise to a suspension of cuprous bromide in 25 mL of THF maintained at −5 to 0 °C. After 30 min at 0 °C, the mixture was cooled to −78 °C and a solution of methyl 3-phenylpropynoate (386 mg, 2.4 mmol) in 5.0 mL of THF was added rapidly. The mixture was stirred at −78 °C for 30 min, then at −20 °C for 30 min, and then it was cooled to −78 °C. Benzaldehyde (848 mg, 8.0 mmol) was added rapidly and the mixture was allowed to stir for 2 h at −78 °C and slowly warmed to −20 °C over 6 h. Then water (5 mL) was added and the mixture was poured into saturated aqueous ammonium chloride solution. Ether was added, the mixture was shaken, and the organic layer was washed with water, dried, and concentrated by rotary evaporation. TLC analysis (ether–hexane–methanol in the ratio 6:14:1 by volume, on silica gel) indicated a major component of R_f 0.24. Preparative layer chromatography (ether–hexane, 3:7; silica gel; develop eight times) afforded 300 mg of an oil; 47% yield based on methyl cinnamate: IR (neat) 3550 (s), 1730 (m) cm^{-1}; ^1H NMR ($CDCl_3$–D_2O) δ 7.2 (br s, 10 H, Ar**H**), 6.82 (s, 1 H, vinyl H), 5.50 (s, 1 H, $-OCHAr$), 4.50 (s, 3 H, $-OCH_3$), 3.44 (s, 3 H, $-OCH_3$). The compound (**18**) was characterized by benzoylation (benzoyl chloride–pyridine, 25 °C, 15 h) to give **19**, mp 76–78 °C dec (crystals from isopropyl ether–hexane): IR (CCl_4) 1735 (s), 1605 (m), 1590 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8–8.3 (m, 2 H, benzoyl ortho H), 7.3–7.7 (m, 13 H, Ar**H**), 6.95 (d, 1 H, vinyl **H**, J = 1 Hz), 6.85 (d, 1 H, $-OCHAr$, J = 1 Hz), 3.55 (s, 3 H, OCH_3); mass spectrum, parent at *m/e* 372, fragments at 267, 235, 191.

Anal. Calcd for $C_{24}H_{20}O_4$: C, 77.40; H, 5.41. Found: C, 77.39; H, 5.46.

(b) With 2-Cyclohexenone. Reduction of methyl 3-phenylpropynoate with the Na complex was carried exactly as in (a) above. In place of benzaldehyde, 2-cyclohexenone (769 mg, 8.0 mmol) was added rapidly to the reduction product mixture at −78 °C. After 2 h at −78 °C, the bath temperature was allowed to rise slowly to −20 °C over 6 h. Then, after 30 min at −20 °C, water (5 ml) was added, and the mixture was poured into saturated aqueous ammonium chloride solution. Ether was added, the mixture was shaken, and the ether layer was washed with water, dried, and concentrated by rotary evaporation. Analytical TLC indicated a major component of R_f 0.24 (ether–hexane–methanol in the ratio 6:14:1 by volume; silica gel). Purification by preparative layer chromatography (multiple elution with benzene–hexane–methanol in the ratio 6:6:1; silica gel; repeating on three plates) afforded material which showed a single spot on analytical TLC. The product (87 mg, 14% yield based on methyl 3-phenylpropynoate) showed: IR (mull) 3560 (w), 3000 (s), 1750 (m), 1460 (m), 748 (w), 690 (w); ^1H NMR ($CDCl_3$) δ 7.12 (br s, 5 H, Ar**H**), 6.59 (s, 1 H, vinyl H), 5.4–6.0 (br AB q, 2 H, vinyl H), 3.50 (s, 3 H, $-OCH_3$), 2.5 (br s, 1 H, –OH), 1.5–2.2 (br m, 6 H, $-CH_2-$); mass spectrum (electron impact) *m/e* 258 (34%), 240 (76%), $-H_2O$), 226 (73%), 199 (100%). Recrystallization from hexane afforded colorless needles, mp 77.5–78 °C.

Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.38; H, 7.02. Found: C, 74.32; H, 7.12.

Registry No.—**12**, 61883-07-6; **15**, 62862-24-2; **16**, 62862-25-3; (*E*)-**18**, 62862-26-4; (*Z*)-**18**, 62862-27-5; (*E*)-**19**, 62862-28-6; (*Z*)-**19**, 62862-29-7; **21**, 62862-30-0; **31**, 62862-31-1; methyl ethyl ketone, 78-93-3; 2-butanol-*2-d*, 19403-02-2; 2-butanol, 78-92-2; lithium trimethyoxyaluminum hydride, 12076-93-6; cuprous bromide, 7787-70-4; sodium bis(2-methoxyethoxy)aluminum hydride, 22722-98-1; 3,3,5-trimethylcyclohexanone, 873-94-9; 3,3-dimethylcyclohexanone, 2979-19-3; lithium dihydridocopper, 53201-99-3; lithium trimethoxyaluminum deuteride, 62905-96-8; methyl *cis*-cinnamate, 19713-73-6; methyl *trans*-cinnamate, 1754-62-7; methyl 3,4,5-trimethoxycinnamate 7560-49-8; methyl 3-(3,4,5-trimethoxyphenyl)-propionate, 53560-25-1; cuprous iodide, 7681-65-4; triphenylphosphinecuprous iodide, 47107-74-4.

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Notes

Molecular Geometry Studies. The Crystal and Molecular Structure of a 7-Spirocyclopentylbicyclo[2.2.1]heptene Anhydride[1]

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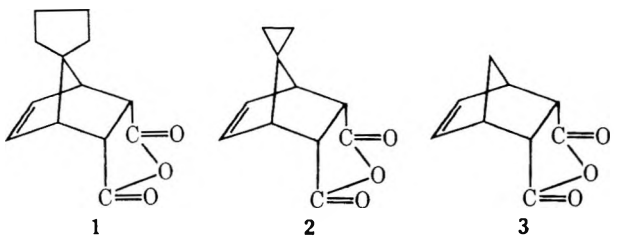
The conformation of the rigid bicyclo[2.2.1]heptane nucleus in various bifunctional derivatives (anhydrides, diacids, diesters) is essential to our study relating the molecular geometry in the solid state to the molecular geometry as determined in solution via NMR–LIS measurements.[3-5] Compound 1, which represents only the second bicyclo[2.2.1]heptane system containing a 7-spiro hydrocarbon substituent that has been reported, is one of the model compounds used in conformational equilibria determinations in the *cis*-1,2,3,6-tetrahydrophthalic anhydride series.[5]

In addition, compound 1 has been included in a series of kinetic studies on the mechanism of the endo–exo transformation.[3] Because compound 1 was the only endo compound



1 2 3

in the series which did not thermally rearrange to the corresponding exo isomer, a knowledge of its molecular geometry in the solid state would indicate if steric requirements were too stringent to allow the reverse Diels–Alder reaction to proceed.

In anhydrides 2 and 3 of the series, long carbon–carbon bonds (C_1–C_2, C_3–C_4) peculiar to some Diels–Alder adducts[6] occurred; hence we desired to further investigate this molecular asymmetry in compound 1.

Experimental Section

[3′aβ,4′α,7′α,7′aβ]-3′a,4′,7′,7′a-Tetrahydrospiro[cyclopentane-1,-8′-[4,7]methanoisobenzofuran]-1′,3′-dione (1) was synthesized as previously described.[7] Colorless crystals with well-defined faces were obtained by recrystallization from solution in benzene by vapor diffusion of 60–110 °C petroleum ether into the benzene solution. Preliminary Weissenberg and precession photographs of a small crystal (ca. 0.21 × 0.24 × 0.24 mm) indicated an orthorhombic space group with systematic absences of $0kl$, $l \neq 2n$, and $h0l$, $h \neq 2n$. The choice of space group $Pca2_1$ with $Z = 4$ was confirmed by the eventual solution of the structure. Unit cell dimensions of $a = 12.3397$ (10), $b = 8.3315$ (5), and $c = 10.5058$ (11) Å were provided by least-squares refinement of 14 independent 2θ values obtained by automatic centering routines on a G.E. XRD-490 diffractometer with a scintillation counter detector using Ni filtered Cu Kα radiation. Intensity data were collected out to 120° 2θ using θ–2θ step scans with a 2° 2θ scan range for each reflection; backgrounds were counted at both extremes of each scan. Of the 854 reflections measured, 780 were considered observed by the criteria $I > 3\sigma(I)$ and were used for structure refinement. Lorentz and polarization factors were applied,[8] and the data were corrected for absorption by the method of Tompa[9] ($\rho_c = 1.342$ g cm^{-3}, μ(Cu Kα) = 7.848 cm^{-1}, transmission factor range 0.903–0.938). Weights were calculated by the method of Stout and Jensen,[10] $w(F) = [(k/4LpI)(\sigma^2(I) + (0.03I)^2)]^{-1}$. Scattering factors for nonhydrogen atoms were taken from Cromer and Mann;[11] the scattering factor curve for hydrogen was that of Stewart, Davidson, and Simpson.[12] No correction was made for extinction.

The structure was solved by direct methods using the program MULTAN.[8] Using phases chosen by the program for 80 reflections, an E map revealed the positions of 15 of the 16 nonhydrogen atoms in the asymmetric unit. These positions were refined isotropically by full-matrix least squares minimizing $\Sigma w\Delta F^2$, and a subsequent Fourier map revealed the remaining nonhydrogen atom. The structure was refined isotropically to an R factor of 10.7% ($R = \Sigma||F_o| - F_c||/\Sigma F_o$); further refinement, treating the vibration of all atoms anisotropically, reduced the R to 8.0%. A difference Fourier was calculated which revealed the positions of all hydrogen atoms. Hydrogen atoms were assigned the refined isotropic temperature factors of the atoms to which they were attached, and subsequent refinement of all positional parameters and anisotropic thermal parameters for nonhydrogen atoms reduced the R factor to 4.6%. The R for all data, including unobserved reflections, was 5.2%; the weighted R_w was 6.7% ($R_w = [\Sigma w\Delta F^2]^{1/2}/[\Sigma wF_o^2]^{1/2}$). The largest shift divided by the standard deviation was 0.3 for the last refinement cycle, and a final difference Fourier showed no areas higher than ±0.3 e Å^{-3}. A normal probability plot[13] was calculated which was essentially linear with a slope of 1.42 and an intercept of 0.06.

Results and Discussion

Figure 1 shows an ORTEP drawing of compound 1 with atom designations. Bond distances and bond angles for all atoms are given in Tables I and II, respectively. Characteristic bond lengths and bond angles are observed. Two important features of the data should be noted.

The long carbon–carbon bonds (C_1–C_2, C_3–C_4) typical of

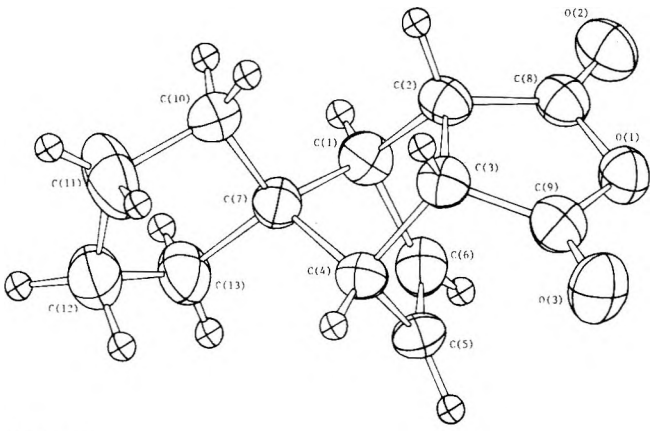


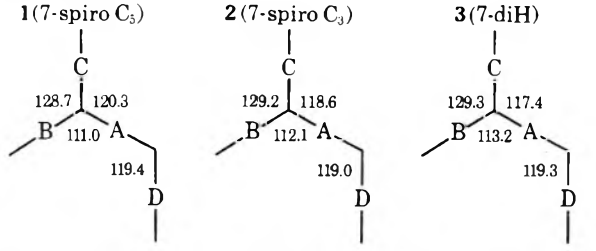
Figure 1.

Table I. Bond Distances in Å with Standard Deviations in Parentheses

C(1)–C(2)	1.568 (6)	C(8)–O(1)	1.405 (6)
C(1)–C(6)	1.509 (7)	C(8)–O(2)	1.184 (5)
C(1)–C(7)	1.551 (6)	C(9)–O(1)	1.404 (5)
C(1)–H1	0.86 (5)	C(9)–O(3)	1.187 (7)
C(2)–C(3)	1.538 (6)	C(10)–C(11)	1.511 (8)
C(2)–C(8)	1.500 (6)	C(10)–H10(1)	0.82 (5)
C(2)–H2	1.04 (4)	C(10)–H10(2)	0.94 (4)
C(3)–C(4)	1.570 (6)	C(11)–C(12)	1.505 (9)
C(3)–C(9)	1.499 (7)	C(11)–H11(1)	0.91 (6)
C(3)–H3	0.96 (4)	C(11)–H11(2)	1.27 (6)
C(4)–C(5)	1.510 (7)	C(12)–C(13)	1.500 (8)
C(4)–C(7)	1.555 (7)	C(12)–H12(1)	1.03 (5)
C(4)–H4	1.00 (4)	C(12)–H12(2)	1.05 (5)
C(5)–C(6)	1.318 (7)	C(13)–H13(1)	0.97 (5)
C(5)–H5	0.96 (5)	C(13)–H13(2)	0.81 (5)
C(6)–H6	0.99 (5)		
C(7)–C(10)	1.532 (7)		
C(7)–C(13)	1.543 (6)		

similar Diels–Alder adducts are present *but* in this case the two bonds are equivalent. This observation is in accord with chemical and spectroscopic properties. We suggest that the nonequivalence of the long bonds found in x-ray structure determination of similar adducts is artifact.[4,6]

The five-membered spiro ring imposes, by its bulk, subtle but consistent changes in the molecular architecture of **1** as compared to the unsubstituted and spirocyclopropyl substituted adducts. The dihedral angular relationships of several prominent atomic planes in the three adducts are shown below. In each case the planes are A = $C_1C_2C_3C_4$, B = $C_1C_4C_5C_6$, C = $C_1C_4C_7$, and D = $C_2C_3C_8C_9O_1$. The data for **2** are the averaged values for the two molecules of the asymmetric unit[4] and the values for **3** are due to Simonetta and co-workers.[6]



Larger substituents at C_7 appear to cause only the A–C angle to become larger at the expense of the A–B angle. This certainly suggests that the π-bond/anhydride ring portion of the adducts are less repulsive/more compressible than the π-bond/bridge substituent or the bridge substituent/exo hydrogen portions. It is surprising that the A–D angle is essentially constant indicating no differential steric effects on the anhydride ring in any of the adducts.

Table II. Bond Angles with Standard Deviations in Parentheses

C(2)–C(1)–C(6)	105.6 (4)	C(4)–C(7)–C(13)	113.6 (4)
C(2)–C(1)–C(7)	100.1 (3)	C(10)–C(7)–C(13)	102.8 (4)
C(2)–C(1)–H1	114 (3)	C(2)–C(8)–O(1)	110.3 (4)
C(6)–C(1)–C(7)	101.1 (4)	C(2)–C(8)–O(2)	130.8 (4)
C(6)–C(1)–H1	120 (3)	O(1)–C(8)–O(2)	119.0 (4)
C(7)–C(1)–H1	113 (3)	C(3)–C(9)–O(1)	109.5 (4)
C(1)–C(2)–C(3)	103.1 (3)	C(3)–C(9)–O(3)	131.6 (5)
C(1)–C(2)–C(8)	113.8 (4)	O(1)–C(9)–O(3)	118.9 (4)
C(1)–C(2)–H2	111 (2)	C(7)–C(10)–C(11)	105.5 (4)
C(3)–C(2)–C(8)	104.3 (4)	C(7)–C(10)–H10(1)	112 (3)
C(3)–C(2)–H2	109 (2)	C(7)–C(10)–H10(2)	123 (3)
C(8)–C(2)–H2	114 (2)	C(11)–C(10)–H10(1)	115 (3)
C(2)–C(3)–C(4)	102.9 (3)	C(11)–C(10)–H10(2)	113 (3)
C(2)–C(3)–C(9)	105.5 (4)	H10(1)–C(10)–H10(2)	88 (4)
C(2)–C(3)–H3	114 (2)	C(10)–C(11)–C(12)	107.7 (5)
C(4)–C(3)–C(9)	113.0 (4)	C(10)–C(11)–H11(1)	130 (4)
C(4)–C(3)–H3	113 (2)	C(10)–C(11)–H11(2)	99 (3)
C(9)–C(3)–H3	109 (2)	C(12)–C(11)–H11(1)	116 (4)
C(3)–C(4)–C(5)	105.0 (4)	C(12)–C(11)–H11(2)	112 (3)
C(3)–C(4)–C(7)	100.3 (3)	H11(1)–C(11)–H11(2)	86 (5)
C(3)–C(4)–H4	114 (2)	C(11)–C(12)–C(13)	107.0 (5)
C(5)–C(4)–C(7)	100.9 (4)	C(11)–C(12)–H12(1)	115 (3)
C(5)–C(4)–H4	116 (2)	C(11)–C(12)–H12(2)	105 (3)
C(7)–C(4)–H4	118 (2)	C(13)–C(12)–H12(1)	114 (3)
C(4)–C(5)–C(6)	107.9 (4)	C(13)–C(12)–H12(2)	99 (3)
C(4)–C(5)–H5	126 (3)	H12(1)–C(12)–H12(2)	114 (4)
C(6)–C(5)–H5	126 (3)	C(7)–C(13)–C(12)	105.3 (4)
C(1)–C(6)–C(5)	107.8 (4)	C(7)–C(13)–H13(1)	104 (3)
C(1)–C(6)–H6	135 (3)	C(7)–C(13)–H13(2)	109 (3)
C(5)–C(6)–H6	117 (3)	C(12)–C(13)–H13(1)	110 (3)
C(1)–C(7)–C(4)	92.4 (3)	C(12)–C(13)–H13(2)	117 (3)
C(1)–C(7)–C(10)	117.7 (4)	H13(1)–C(13)–H13(2)	111 (4)
C(1)–C(7)–C(13)	115.7 (4)	C(8)–O(1)–C(9)	110.4 (4)
C(4)–C(7)–C(10)	115.2 (4)		

However, since the molecular geometries of the three adducts are very similar and whatever differences there are vary systematically from **3** to **2** to **1**, relatively faster endo → exo isomerization of **2** and the absence of isomerization in **1** cannot be rationalized by ground state geometrical differences.

Prior comparison via the program PDIGM[14,15] of experimental LIS and LIS calculated from partially idealized atomic coordinates for the anhydride **1** clearly showed that $Eu(fod)_3$ complexed at the carbonyl oxygen rather than the ether oxygen of the anhydride.[3]

Use of the actual x-ray determined coordinates confirmed this preference. The agreement factor, R, decreased by a factor of 2 (from 0.7 to 0.37) for the best fit at carbonyl oxygen, although in this case the best fit distance remained near 2.8 Å and the agreement factor contour was not as steep as in the spirocyclopropyl anhydride **2**.[4] The agreement factor for the best fit at ether oxygen remained an order of magnitude higher than that for the carbonyl oxygen fit.

Because the calculated/observed LIS data are in such good

agreement and because the choice of coordination sites is so clear-cut for rigid bifunctional molecules, whose solution geometry must be nearly identical with their crystal geometry, we are convinced that assessment of solution geometry for conformationally flexible molecules by the analysis of LIS data is a fairly sensitive and, when applied with due caution, an appropriate procedure.

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Registry No.—1, 56587-28-1.

Supplementary Material Available. Table III, torsion angles excluding atoms C(8), C(9), O(1), O(2), O(3); Table IV, equations of planes and dihedral angles; Table V, crystal data for $C_{13}H_{14}O_3$; and Table VI, positional and thermal parameters and standard deviations for the structure of 1 (3 pages). Ordering information is given on any current masthead page.

References and Notes

(1) The *Chemical Abstracts* nomenclature for compound **1** is [3′aβ,4′α,-7′α,7′aβ]-3′a,4′,7′,7′a-tetrahydrospiro[cyclopentane-1,8′-[4,7]methanoisobenzofuran]-1′,3′-dione.
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Total Synthesis of (±)-Discretamine and (±)-Stepholidine

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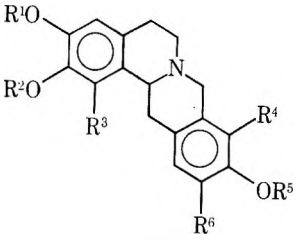
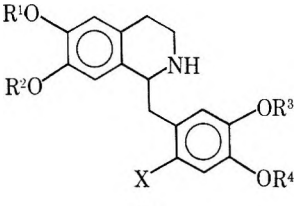
Discretamine, a tetrahydroprotoberberine alkaloid, was isolated in 1959 by Schmutz[1b] from *Xylopia discreta*. Elemental analysis gave the empirical formula $C_{19}H_{21}NO_4$ indicating the presence of two hydroxyl and two methoxyl groups in the cyclic moiety. Methylation with diazomethane gave (−)-tetrahydropalmatine (**1**), establishing absolute configuration and a 2,3,9,10-tetraoxygenated substitution pattern. Recently, structure **2** was proposed for discretamine based on mass spectroscopic evidence.[2]

Another diphenolic tetrahydroprotoberberine alkaloid, stepholidine, was isolated from *Stephania glabra* in 1968 and assigned structure **3** based on degradative evidence.[3] In 1975 stepholidine was discovered in opium[4] which also contains a third isomer, namely, scoulerine (**4**).[5] Neither discretamine nor stepholidine has been previously synthesized. The purpose of the investigation reported in the present communication was to confirm the structures of discretamine and stepholidine by synthesis, and to prepare these alkaloids in sufficient quantities for later use as cold carriers in biosynthetic studies.

Many approaches have been described for synthesis of protoberberines.[6,7] The oldest method which is still widely used is based on intramolecular Mannich condensation of an appropriately substituted 1-benzyltetrahydroisoquinoline with formaldehyde.[8,9] If the benzyltetrahydroisoquinoline carries a 3-hydroxy substituent in the benzyl moiety, cyclization occurs ortho and para to the phenolic hydroxyl group to afford a mixture of a tetrahydroprotoberberine and a tetrahydropseudoberberine, their relative proportion depending on steric factors and on reaction conditions such as pH and temperature. Applying this method to norreticuline (**9a**) at pH 6.3 and room temperature, Battersby et al.[10] obtained a mixture of scoulerine (**4**) and coreximine (**5**) in a ratio of approximately 2:1. When norreticuline was heated with formaldehyde in ethanol or in formic acid, Kametani et al.[11,12] and Tomita et al.[13] could isolate only coreximine. However, by blocking the para position with bromine (as in **9b**) ortho cyclization proceeded cleanly and debromination gave the 9,10-substituted tetrahydroprotoberberine.[14,15] With methoxy or benzyloxy groups in 3 and 4 positions of the benzyl moiety, only 10,11-substituted products could be obtained.[9,12,13,16,17]



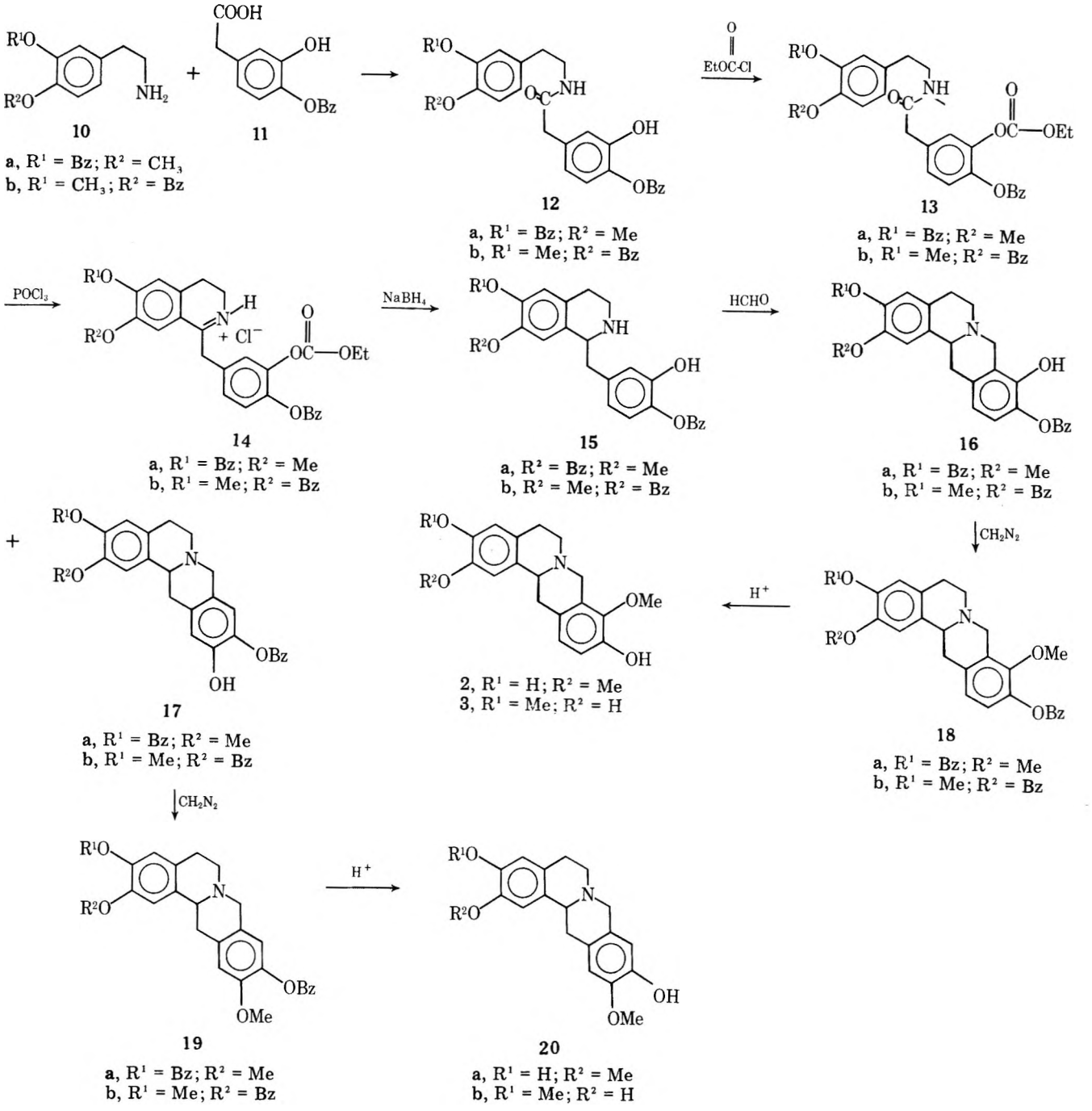
1, $R^1 = R^2 = R^5 = Me$; $R^3 = R^6 = H$; $R^4 = OMe$
2, $R^1 = R^3 = R^5 = R^6 = H$; $R^2 = Me$; $R^4 = OMe$
3, $R^1 = Me$; $R^2 = R^3 = R^5 = R^6 = H$; $R^4 = OMe$
4, $R^1 = R^5 = Me$; $R^2 = R^3 = R^6 = H$; $R^4 = OH$
5, $R^1 = R^5 = Me$; $R^2 = R^3 = R^4 = H$; $R^6 = OH$
6, $R^1 = R^2 = Me$; $R^3 = R^5 = R^6 = H$; $R^4 = OMe$
7, $R^1 = R^2 = Me$; $R^3 = OH$; $R^4 = OMe$; $R^5 = R^6 = H$
8, $R^1 = R^2 = R^5 = Me$; $R^3 = R^4 = H$; $R^6 = OMe$



9

a, $R^1 = R^4 = Me$; $R^2 = R^3 = X = H$
b, $R^1 = R^4 = Me$; $R^2 = R^3 = H$; X = Br

Scheme I



Kikemanine (**6**) and capaurimine (**7**), which are 10-hydroxy-9-methoxy substituted protoberberines, were also synthesized by the Mannich reaction.[18,19] This method, which is illustrated in Scheme I, was chosen for the synthesis of discretamine and stepholidine, particularly because the tetrahydropseudoberberines (**17a** and **17b**), which could be expected as byproducts, would be needed for structural studies in progress. According to a recent report, the L isomer of **20b** has been isolated from *Corydalis govaniana*.[20] Fusion of 3-benzyloxy-4-methoxyphenethylamine[21] (**10a**) with 4-benzyloxy-3-hydroxyphenylacetic acid (**11**), obtained from 4-benzyloxy-3-tosyloxybenzyl cyanide,[22] gave the amide (**12a**) which was converted by ethoxycarbonylation to the nonphenolic amide (**13a**). Bischler–Napieralski cyclization with phosphorus oxychloride in dry toluene to **14a** was followed by reduction with sodium borohydride and hydrolysis of the ester group to **15a**. Intramolecular Mannich reaction of the 1-benzyltetrahydroisoquinoline (**15a**) with formaldehyde at pH 6.3 and room temperature resulted in a mixture of the protoberberines **16a** and **17a** which was separated by column chromatography on silica gel. 3,10-Benzyloxy-9-hydroxy-2-methoxytetrahydroprotoberberine (**16a**) was methylated with diazomethane to the nonphenolic base **18a** [(±)-*O*,*O*-dibenzyldiscretamine]. Debenzylation of **18a** with ethanolic hydrochloric acid gave the diphenolic base **2**. Elemental analysis showed a $C_{19}H_{21}NO_4$ composition. The mass spectrum was identical with that of natural discretamine[2] and showed the presence of a 9-methoxy group.[23] Methylation of **2** with diazomethane gave (±)-tetrahydropalmatine (**1**) which was spectroscopically identical with an authentic sample of (−)-tetrahydropalmatine.[24]

(±)-Stepholidine was synthesized from 4-benzyloxy-3-methoxyphenethylamine (**10b**) and 4-benzyloxy-3-hydroxyphenylacetic acid (**11**) by the same method outlined for (±) discretamine. The synthetic product (**3**) was spectroscopically identical with natural stepholidine.[3,4,23] Methylation with

Table I. Melting Points and Spectroscopic Data

Registry no.	Compd	Mp, °C	NMR ($CDCl_3$), ppm	MS (EI), *m/e* (rel intensity)	MS (CI)	Accurate mass $(M + 1)^+$
42522-12-3	**12a**	128–131	3.40 (s, $COCH_2Ar$) 3.84 (s, OMe) 5.07 (s, OCH_2Ph) 5.09 (s, OCH_2Ph)		498	
62744-12-1	**12b**	122–125	3.42 (s, $COCH_2Ar$) 3.83 (s, OMe) 5.09 (s, OCH_2Ph) 5.11 (s, OCH_2Ph)		498	
42522-13-4	**13a**	81–83	1.31 (t, J = 7.0 Hz, OCH_2CH_3) 3.41 (s, $COCH_2Ar$) 3.84 (s, OMe) 4.26 (q, J = 7.0 Hz, OCH_2CH_3) 5.09 (s, 2 OCH_2Ph)		570	
62744-13-2	**13b**	68–71	1.30 (t, J = 7.0 Hz, OCH_2CH_3) 3.41 (s, $COCH_2Ar$) 3.83 (s, OMe) 4.26 (q, J = 7.0 Hz, OCH_2CH_3) 5.10 (s, 2 OCH_2Ph)		570	
	14a	Oil (not purified)				
62744-14-3	**14b**	188–190				
42522-14-5	**15a**	134–136	3.79 (s, OMe) 5.07 (s, 2 OCH_2Ph)		482	482.2345 ± 0.002
62744-15-4	**15b**	159–161	3.83 (s, OMe) 5.05 (s, 2 OCH_2Ph)		482	482.2338 ± 0.002
50796-02-6	**16a**	109–112 dec	3.89 (s, OMe) 5.10 (s, OCH_2Ph) 5.13 (s, OCH_2Ph) 6.66 (1 H, s, ArH) 6.69 (1 H, s, ArH) 6.77 (2 H, s, ArH)	493 (12.1) (M^+) 403 (34.6) 402 (100) 311 (9.1) 268 (16.3) 176 (26.2) 135 (25.0) 91 (90.3)		
62744-16-5	**16b**	85–88 dec	3.87 (s, OMe) 5.09 (s, OCH_2Ph) 5.13 (s, OCH_2Ph) 6.64 (2 H, s, ArH) 6.75 (2 H, s, ArH)	493 (12.5) (M^+) 403 (32.1) 402 (100) 311 (4.6) 268 (21.7) 176 (12.9) 135 (28.9) 91 (63.4)		
50796-03-7	**17a**	87–90	3.89 (s, OMe) 5.09 (s, OCH_2Ph) 5.13 (s, OCH_2Ph) 6.65 (2 H, s, ArH) 6.76 (2 H, s, ArH)	493 (15.5) (M^+) 402 (100) 268 (15.7) 176 (24.2) 135 (22.6) 91 (83.7)		494.2315 ± 0.002
62744-17-6	**17b**	78–80	3.88 (s, OMe) 5.09 (s, OCH_2Ph) 5.14 (s, OCH_2Ph) 6.64 (2 H, s, ArH) 6.75 (2 H, s, ArH)	493 (13.5) (M^+) 402 (100) 268 (23.9) 176 (13.4) 135 (28.9) 91 (85.3)		494.2315 ± 0.002
62744-18-7	**18a**	139–141	3.89 (s, OMe) 3.90 (s, OMe) 5.10 (s, OCH_2Ph) 5.13 (s, OCH_2Ph) 6.64 (1 H, s, ArH) 6.74 (1 H, s, ArH) 6.83 (2 H, s, ArH)	507 (28.4) (M^+) 417 (32.5) 416 (100) 414 (5.1) 178 (10.0) 176 (11.6) 150 (12.5) 149 (60.5) 121 (17.5) 91 (66.1)		
62744-18-7	**18b**	100–102	3.87 (s, OMe) 3.89 (s, OMe) 5.10 (s, OCH_2Ph) 5.13 (s, OCH_2Ph) 6.64 (1 H, s, ArH) 6.74 (1 H, S, ArH) 6.80 (2 H, s, ArH)	507 (21.3) (M^+) 416 (100) 414 (10.2) 150 (9.9) 149 (77.3) 121 (15.0) 91 (63.9)		

Table I (*Continued*)

Registry no.	Compd	Mp, °C	NMR ($CDCl_3$), ppm	MS (EI), *m/e* (rel intensity)	MS (CI)	Accurate mass $(M + 1)^+$
55934-50-4	**2**	208–212 dec	3.82 (s, OMe) 3.90 (s, OMe) 6.68 (1 H, s, ArH) 6.70 (1 H, s, ArH) 6.82 (2 H, s, ArH)	327 (62.6) (M^+) 326 (34.9) 296 (9.1) 178 (100) 176 (27.1) 150 (35.3) 149 (17.8) 135 (29.9)		
16562-14-4	**3**	136–140 dec	3.82 (s, OMe) 3.88 (s, OMe) 6.60 (1 H, s, ArH) 6.82 (3 H, s, ArH)	327 (59.4) (M^+) 326 (39.1) 296 (10.2) 178 (100) 176 (23.3) 150 (25.9) 149 (23.6) 135 (22.5)		
55934-51-5	**19a**	134–136	3.86 (s, OMe) 3.89 (s, OMe) 5.12 (s, 2 OCH_2Ph) 6.60 (1 H, s, ArH) 6.65 (1 H, s, ArH) 6.69 (1 H, s, ArH) 6.77 (1 H, s, ArH)	507 (20.4) 417 (19.4) 416 (54.7) 241 (10.2) 240 (13.7) 150 (15.9) 91 (100)		508.2472 ± 0.002
60342-44-1	**19b**	130–132	3.87 (s, 2 OMe) 5.11 (s, OCH_2Ph) 5.13 (s, OCH_2Ph) 6.58 (1 H, s, ArH) 6.64 (2 H, s, ArH) 6.76 (1 H, s, ArH)	507 (20.3) (M^+) 417 (24.5) 416 (77.6) 241 (12.9) 240 (15.4) 150 (12.4) 91 (100)		508.2500 ± 0.002
62744-19-8	**20a**	218–220	3.87 (s, OMe) 3.90 (s, OMe) 6.64 (2 H, s, ArH) 6.68 (1 H, s, ArH) 6.71 (1 H, s, ArH)	327 (65.4) (M^+) 326 (27.6) 178 (100) 176 (35.7) 151 (33.7) 150 (93.8) 135 (15.3)		
60383-78-0	**20b**	222–225	3.87 (s, OMe) 3.88 (s, OMe) 6.60 (1 H, s, ArH) 6.63 (2 H, s, ArH) 6.82 (1 H, s, ArH)	327 (55.7) (M^+) 326 (24.9) 178 (100) 176 (25.6) 151 (31.1) 150 (87.5) 135 (14.4)		

diazomethane gave (±)-tetrahydropalmatine, identical with authentic material. Thus, the structures proposed for discretamine and stepholidine were confirmed.

The products of para cyclization (**17a, 17b**) were methylated with diazomethane to **19a** and **19b,** respectively, and debenzylated to afford 3,10-dihydroxy-2,11-dimethoxytetrahydropseudoberberine (**20a**) and 2,10-dihydroxy-3,11-dimethoxytetrahydropseudoberberine (**20b**). When the hydrochlorides of **15a** and **15b** were reacted with formaldehyde under reflux without pH adjustment the products of para cyclization were the only products which could be isolated. Methylation of **20a** and **20b** with diazomethane gave (±)-xylopinine (**8**) [= (±)-norcoralydine], spectroscopically identical with (−)-xylopinine.[25] Compounds **20a** and **20b** were synthesized earlier by Tomita et al.[26] and by Kametani et al.[16] using a different approach.

Experimental Section

General. Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Infrared (IR) spectra were obtained in potassium bromide on a Perkin-Elmer 337 spectrometer. ^1H NMR spectra were obtained in deuteriochloroform with tetramethylsilane as an internal reference at a field strength of 100 MHz on a Varian XL-100 spectrometer equipped with a Nicolet Technology Corp. Fourier transform accessory. Electron impact (EI) mass spectra were taken on a AEI MS-12 mass spectrometer interfaced to a PDP 8/I computer using the DS-30 software. High-resolution and chemical ionization (CI) mass spectra were taken on an AEI MS-9 spectrometer with a specially modified source for chemical ionization using isobutane as the reagent gas. The analytical samples were vacuum dried (0.1 mmHg) at 56.5 °C (boiling acetone). Elemental analyses were carried out at the Department of Chemistry, National Taiwan University, and the Microanalytical Department, University of California at Berkeley. The syntheses were carried out as described by Kametani et al.[18] for the synthesis of (±)-kikemanine. The results of the combustion analyses for carbon, hydrogen, and nitrogen were within 0.4% of the calculated values. The melting points, NMR, and MS data are recorded in Table I.

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A Convenient Synthesis of Allylic Hydroperoxides

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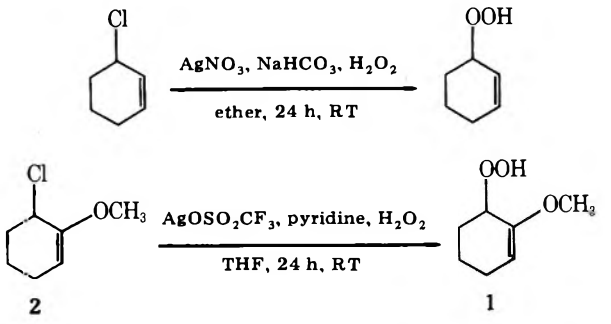
Because of our recent investigation of the singlet oxygen "ene" reaction of 1-methoxycyclohexene,[2] we were interested in preparing the enol ether allylic hydroperoxide, 3-hydroperoxy-2-methoxycyclohexene (**1**). Allylic hydroperoxides have been synthesized by various methods:[3] (a) from the free-radical autoxidation of olefins, initiated thermally or photolytically; (b) from the autoxidation of organometallic compounds, particularly Grignard reagents; (c) from the reaction of olefins with singlet oxygen; (d) from the solvolysis of alkenyl sulfates (prepared in situ from equimolar quantities of alcohol and sulfuric acid) in hydrogen peroxide; (e) from the solvolysis of allylic mesylates and other sulfonate esters in basic hydrogen peroxide; and (f) from the nucleophilic displacement of allyl halides with basic hydrogen peroxide.

Methods a and c are often problematic since they yield a multiplicity of products. Isolation and purification is a serious problem with hydroperoxides in general and alkenyl hydroperoxides in particular.[2b] Because hydroperoxide **1**, in addition to being allylic, is at the same time an enol ether, methods involving acidic hydrogen peroxide or acidic workups are to be avoided (method d).[4] Nor could a Grignard path (method b) be used since enol ethers react with Grignard reagents at the double bond site.[4]

We would like to report a convenient synthesis of allylic hydroperoxides via the silver ion assisted reaction of the corresponding allylic halide and hydrogen peroxide. In particular, an ether solution of 3-chlorocyclohexene,[5] silver nitrate,[6] $NaHCO_3$ (in a 1:1:2 molar ratio), and a tenfold excess of 98% H_2O_2 was stirred for 24 h at room temperature in the dark under argon.[7] Filtration and evaporation of the solvent under reduced pressure gave an almost quantitative yield of 3-hydroperoxycyclohexene.



Similarly, a THF solution of 3-chloro-2-methoxycyclohexene (**2**) was stirred for 1 day in the dark under argon[7] with 1 equiv of pyridine,[8] 2 equiv of silver triflate, and 15 equiv of 98% H_2O_2. Filtration and evaporation of the solvent and pyridine under high vacuum gave the desired hydroperoxide in an 80% yield.

At this juncture we would like to note that when **2** was allowed to react with H_2O_2 in the presence of silver nitrate, the yet unknown[9] 2-methoxy-2-cyclohexen-1-yl nitrate (**3**) was obtained, in approximately 50% yield, in addition to the allylic hydroperoxide **1**. The unstable nitrate was isolated by high vacuum distillation and identified by its spectral data (see Experimental Section).

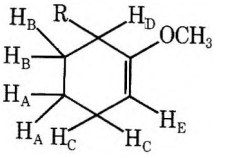
The starting allylic chloride **2**[11] could not by synthesized from 1-methoxycyclohexene and *N*-chloro amides since enol ethers react via a polar, not free-radical, mechanism with these chlorinating agents.[4] Nor could it be prepared conveniently by the action of Ph_3P–CCl_4 on 3-hydroxy-2-methoxycyclohexene (**4**).[13] In contrast to 3-hydroxycyclohexene, which in the presence of Ph_3P–CCl_4 proceeded smoothly and quantitatively to the corresponding chloride, **4** yielded only 25% **2**. Surprisingly, the major product was 2-methoxycyclohexanone (**5**), which was readily synthesized by reducing 2-methoxy-2-cyclohexen-1-one (**6**) with hydrogen and palladium.

Chloride **2** was successfully prepared as follows. Epoxidation of commercially available (Aldrich Chemical Co.) 2-cyclohexen-1-one (**8**) with either alkaline hydrogen peroxide[14] or *tert*-butyl hydroperoxide[15] affords 2,3-epoxycyclohexanone (**7**). The latter method is the procedure of choice since it gives the desired product in approximately 80% yield while the former gives it in 30% yield. Treatment of the epoxide with methoxide in methanol followed by neutralization and distillation gives 26–34% yield of ketone **6**.[16] Reduction of **6** with diisobutylaluminum hydride (DIBAL),[17] neutralization with methanol, and distillation give alcohol **4** in 88% yield.[18] The corresponding mesylate **9** was conveniently prepared in situ according to the procedure of Crossland and Servis.[19] Displacement of the mesylate group with chloride ion, workup, and distillation gave the desired product in 75% yield.[20,21]

Both 3-hydroperoxycyclohexene and its 2-methoxy analogue (**1**) are readily reduced by triphenylphosphine to yield the corresponding alcohols. Thermolysis of these two hydroperoxides in the VPC injection port produced both the corresponding alcohol and ketone. The mechanism of such a thermal cleavage is discussed by Walsh[22] and Frank.[23,24]

Throughout this work most spectra were recorded using deuteriochloroform as solvent. In many cases, it was convenient to follow the progress of the reaction by NMR particularly by studying the growth and disappearance of methoxy group absorptions which show up as sharp singlets. As can be seen from Table I, however, the methoxy absorptions in $CDCl_3$

Table I. ^{1}H NMR Absorption (δ, ppm Me_4Si) of 3-Substituted 2-Methoxycyclohexenes



Registry no.	Compd	Solvent	R =	H_A	H_B	H_C	$-OCH_3$	H_D [c]	H_E [b]	Misc
931-57-7		$CDCl_3$	H	1.57	1.57	2.00	3.40	2.00	3.51	
23740-37-6	6		=O	2.00	2.43	2.43	3.58		5.90	
62796-20-7	4		OH	1.73	1.73	2.01	3.53	4.13	4.73	HO −3.10
59892-15-8	2		Cl	1.70	2.05	2.05	3.55	4.43	4.82	
62796-21-8	3		ONO_2	1.90	1.90	1.90	3.53	5.45	5.05	
62796-22-9	1		OOH	1.60	1.60	2.03	3.53	4.43	4.92	HOO ~9.17[a]
7429-44-9	5		=O[d]	1.81	2.33	1.81	3.38		1.81	CH_3OCH — 3.72
1728-36-5	2'		Br	1.75	2.13	2.13	3.54	4.62	4.85	
	6	C_6H_6	=O	1.62	2.13	2.13	3.32		5.53	
	4		OH	1.83	1.83	1.83	3.24	4.20	4.50	HO −2.98
	2		Cl	1.85	1.85	1.85	3.22	4.40	4.40	
	3		ONO_2	1.60	1.60	1.60	3.15	5.37	4.64	
	1		OOH	1.60	1.60	1.90	3.27	4.65	4.65	HOO ~9.33[a]

[a] Usually very broad and variable. [b] H_E generally comes as a clearly defined triplet. [c] H_D usually comes as a broad peak with hyperfine splitting, sometimes as a triplet. [d] Compound 6 with saturated double bond.

for many of the 3-substituted 2-methoxycyclohexenes are very close together if not identical. Benzene, as shown in Table I, has a dramatic effect on these absorptions and was often used as the NMR solvent of choice.

Experimental Section

NMR spectra were obtained on Varian A-60 and T-60 spectrometers. Infrared spectra were taken with a Perkin-Elmer Model 137 spectrometer. Mass spectra were run on an Associated Electrical Industries, Ltd., Model MS-9 mass spectrometer.

Analyses of compounds were obtained from Anacon Associates, Chelmsford, Mass. Vapor phase chromatograms were run with a Hewlett-Packard F and M Model 700, Varian Aerograph Models 90-P3, and Autoprep Model A-700 chromatographs. Peak areas were measured by disk integration and triangulation.

The 98% H_2O_2 was obtained from FMC Corp. All reactions involving 98% H_2O_2 were run with the necessary safety precautions. All operations were carried out behind a shield and in a hood with the hood cover as far down as possible. The experimentor wore safety glasses, a face shield, and thick neoprene gloves. To prevent contamination of the H_2O_2 bottle, H_2O_2 samples were poured into a graduated cylinder rather than removing them from the bottle with a pipet.

2-Methoxy-2-cyclohexen-1-ol (4). A 2-L three-necked round-bottom flask fitted with a reflux condenser (topped with argon inlet), stopper, and serum cap was charged with 30.4 g (0.24 mol) of ketone 6[16] dissolved in 600 mL of dry benzene at approximately 10 °C. The solution was magnetically stirred and kept under an argon blanket throughout the reaction. A 1 M solution (360 mL) of diisobutylaluminum hydride (DIBAL) in heptane (D. C. R. Inc.) was added to the reaction mixture which, during the course of the addition, gradually turned cloudy. After the addition, which took about 30 min, the solution was stirred at 5–10 °C for another 1 h. Dry methanol (250 mL) was then gradually added, followed by 35 g of a Na_2SO_4/H_2O paste.[25] The solution was stirred again until a white precipitate formed, at which time stirring usually ceased. An additional 500 mL of methanol was added, the precipitate was broken up, and stirring was continued for an additional 30 min. The mixture was vacuum filtered and the salts were washed eight to ten times with boiling methanol. The solvent was removed under reduced pressure and the desired product (27 g, 0.21 mol, 87.8% yield) distilled in the range 92–98 °C (15 mm): NMR ($CDCl_3$) δ 1.73 (m, 4 H), 2.01 (m, 2 H), 3.10 (broad peak, 1 H, hydroxyl), 3.53 (s, 3 H, methoxy), 4.13 (m, 1 H), 4.73 (triplet, 1 H, olefinic); IR (film) 3476 (s), 2956 (s), 1669 (s), 1440 (m), 1400 (m), 1375 (w), 1334 (m), 1305 (m), 1246 (w), 1213 (s), 1190 (s), 1160 (s), 1087 (s), 1066 (s), 1026 (s), 986 (s), 957 (m), 911 (m), 883 (w), 872 (m), 857 (w), 825 (m), 793 cm^{-1} (s); MS (70 eV) *m/e* 128 (M^+).

2-Methoxycyclohexanone (5).[26] A 2-g sample of 2-methoxy-2-cyclohexen-1-one (6) dissolved in 10 mL of dry ether and 0.1 g of 5% palladium on carbon were placed in a Parr hydrogenation apparatus under 50 lb of pressure and shaken for 20 h. Filtration and evaporation of solvent gave 1.95 g of pure 5 as determined by VPC[27] (oven, 200 °C; R_f 4 min): NMR ($CDCl_3$) δ 1.81 (m, 6 H), 2.33 (m, 2 H), 3.38 (s, 3 H), 3.72 (m, 1 H); IR (CCl_4) 2938 (s), 1721 (s), 1442 (m), 1425 (m), 1344 (w), 1322 (w), 1304 (m), 1259 (w), 1224 (w), 1195 (s), 1146 (s), 1113 (s), 1099 (s), 1070 (m), 1034 (w), 1013 (w), 993 (w), 946 (m), 915 (w), 877 (m), 836 cm^{-1} (w); MS (70 eV) *m/e* 128 (M^+).

3-Chloro-2-methoxycyclohexene (2). A three-necked 250-mL round-bottom flask fitted with serum cap, gas inlet tube with stopcock and stopper was charged with 6.4 g (0.05 mol) of 4 and 10.5 mL (8 g, 0.075 mol) of triethylamine dissolved in 175 mL of methylene chloride. The flask was placed under an argon blanket and cooled to −20 °C in a CCl_4/CO_2 slush bath. Then 4.4 mL (6.65 g, 0.055 mol) of mesyl chloride was added over a period of 10 min and the solution was stirred for 30 more min. The reaction flask was placed in a water bath and the methylene chloride and excess triethylamine were distilled (0.1 mm) gradually into a liquid nitrogen trap. Approximately 150 mL of solvent was removed in about 1 h. Then 175 mL of acetone and 21 g (0.05 mol, excess) of lithium chloride were added and the solution was stirred for 4 h at room temperature. Ether (400 mL) was added to precipitate the salts and the solution was vacuum filtered and concentrated down under reduced pressure to a viscous oil. More ether was added and the solution was dried over $MgSO_4$. Filtration, removal of solvent under reduced pressure, and distillation (77–78 °C, 8 mm) gave 5.5 g of product (75% yield): NMR ($CDCl_3$) δ 1.70 (m, 2 H), 2.05 (m, 4 H), 3.55 (s, 3 H, methoxy), 4.43 (t with hyperfine splitting, 1 H), 4.82 (t, 1 H); IR (film) 2959 (s), 2841 (m), 1662 (s), 1455 (m), 1373 (s), 1330 (w), 1296 (w), 1258 (w), 1232 (s), 1214 (s), 1186 (s), 1166 (s), 1087 (m), 1040 (m), 1024 (s), 960 (w), 933 (w), 876 (m), 803 (m), 793 (m), 708 cm^{-1} (s); MS (70 eV) *m/e* 146 (M^+), $M^+ + 2$ is approximately 33% of parent peak.

Preparation of Silver Triflate. A suspension of 12.6 g (0.109 equiv) of Ag_2O[28] in 125 mL of water at 15 °C was stirred vigorously while triflic acid, CF_3SO_3H (3M Corp., Acid FC24),[29] was slowly added. The solution gradually turned from black to a cloudy beige and the addition was stopped when the pH reached approximately 2. The mixture was filtered and the water removed under reduced pressure at 60 °C. The white residue was dissolved in boiling benzene and allowed to boil for a while longer to remove any water. Hexane was then added and the solution placed in the refrigerator. The white needles were placed in a vacuum desiccator and the benzene coordinated during crystallization was removed in vacuo (28 h), yield 23.3 g (83%). Silver triflate should be handled wearing gloves since like silver nitrate it discolors the skin.

General Procedure for the Preparation of Allylic Hydroperoxides. A three-necked 100-mL round-bottom flask fitted with thermometer, dropping funnel, and argon inlet was charged with 50 mL of THF, 6 g (0.04 mol) of silver triflate, and 1.6 g (0.02 mol) of pyridine. The reaction vessel was wrapped in aluminum foil to exclude light.[7] The solution was magnetically stirred and cooled to 6 °C in an ice bath. To the chilled solution 7.5 mL (10.8 g, 0.32 mol) of 98% H_2O_2

was slowly pipetted in. The temperature rose to 10 °C during the 15-min addition and then cooled back down to 6 °C. Then a 0.02-mol sample of the allylic chloride dissolved in 10 mL of THF was added dropwise to the clear solution at a moderate rate from the dropping funnel. A white precipitate (AgCl) formed almost immediately but the reaction was allowed to continue at room temperature in the dark under argon for 24 h. The reaction mixture was gravity filtered into a separatory funnel containing several chips of ice. The THF solution was diluted with ether, extracted several times with iced saturated $NaHCO_3$ solution, and dried over $MgSO_4$. Most of the ether and the THF was removed under reduced pressure and the remaining impurities (THF, pyridine, and starting material) were distilled off under high vacuum at room temperature. The remaining viscous liquid is the desired hydroperoxide.

A. 3-Hydroperoxycyclohexene. This allylic hydroperoxide was prepared in an 83% yield from 3-chlorocyclohexene (Aldrich) as described above in the general procedure. The reaction was followed by VPC[27] (oven, 160 °C), the chloride peak (R_f 2 min) gradually disappearing with the concomitant growth of peaks corresponding to 2-cyclohexen-1-one and -1-ol (R_f ~5.5 min). The hydroperoxide could be distilled under high vacuum (0.1 mm) into a receiver cooled with liquid nitrogen by cautiously warming the distillation flask with a 40 °C water bath [lit. bp 47–48 °C (0.2 mm),[30] 39–40 °C (0.1 mm)[31]]: NMR ($CDCl_3$) δ 1.83 (m, 6 H), 4.5 (m, 1 H), 5.88 (m, 2 H, olefinic), 9.13 (broad s, 1 H, hydroperoxide).

B. 3-Hydroperoxy-2-methoxycyclohexene (1). Enol ether allylic hydroperoxide **1** was obtained in 75% yield from chloride **2** using the above general procedure. It can be stored for long periods of time unchanged at −20 °C under argon: NMR ($CDCl_3$) δ 1.60 and 2.03 (overlapping multiplets, 6 H, probably 4 H and 2 H, respectively), 3.53 (s, 3 H, methoxy), 4.43 (t, 1 H), 4.92 (t, 1 H), 9.17 (broad singlet, variable, 1 H, hydroperoxy); IR (neat) 3400 (m), 2941 (s), 1717 (w), 1660 (s), 1600 (w), 1428 (m), 1370 (m), 1329 (w), 1316 (w), 1292 (w), 1254 (w), 1212 (s), 1189 (s), 1165 (s), 1156 (s), 1087 (m), 1064 (m), 1026 (m), 971 (m), 922 (w), 877 (w), 803 (m), 710 cm^{-1} (w). The absorption at 3400 cm^{-1} is due to the hydroperoxy group, while the 1660 cm^{-1} absorption is attributable to the vinyl ether carbon–carbon double bond.

Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.28; H, 8.25.

C. 2-Methoxy-2-cyclohexen-1-yl Nitrate (3). When a $AgNO_3$/ether/$NaHCO_3$ system replaced the AgO_3SCF_3/THF/pyridine system in the general procedure above, in the case of 3-chlorocyclohexene, the results were essentially unchanged. In the instance of chloride **2**, workup, evaporation of the ether under reduced pressure, and distillation of the residue at 0.005 mm at room temperature into a dry ice cooled receiving flask gave a 50% yield of a compound whose spectral data and combustion analysis were consistent with 2-methoxy-2-cyclohexenyl nitrate. The compound gradually decomposed and turned yellow upon standing in air at room temperature. The compound remaining in the distillation flask proved to be hydroperoxide **1**: NMR ($CDCl_3$) δ 1.90 (m, 6 H), 3.53 (s, 3 H), 5.05 (t, 1 H), 5.45 (m, 1 H); IR (neat) 2968 (m), 1741 (m), 1675 (m), 1634 (s), 1445 (m), 1380 (m), 1334 (w), 1304 (m), 1279 (s), 1217 (s), 1195 (m), 1177 (m), 1164 (m), 1132 (w), 1097 (m), 1056 (m), 1029 (m), 973 (m), 948 (m), 926 (m), 860 (s), 813 (w), 802 (w), 756 (w), 716 (w), 691 cm^{-1} (w). The 1634 and 1279 cm^{-1} absorptions are attributable to the $-ONO_2$ group. MS (70 eV) m/e 173 (M^+), 111 ($M^+ - NO_3$).

Anal. Calcd for $C_7H_{11}NO_4$: C, 48.55; H, 6.40. Found: C, 48.05; H, 6.40.

Registry No.—Silver triflate, 2923-28-6; 3-hydroperoxycyclohexene, 4845-05-0; 3-chlorocyclohexene, 2441-97-6.

References and Notes

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(3) For reviews see (a) O. L. Magelli and C. S. Sheppard in "Organic Peroxides", Vol. I. D. Swern, Ed., Wiley-Interscience, New York, N.Y., 1970, pp 1–19; (b) R. Hiatt, *ibid.*, Vol. II, pp 1–39 and 114–115; (c) A. G. Davies, "Organic Peroxides," Butterworths, London, 1961, pp 1–41; (d) A. V. Tobelsky and R. B. Mesrobian, "Organic Peroxides," Interscience, New York, N.Y., 1954, pp 1–11.
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(6) Silver triflate may also be used (vide infra); when, however, silver acetate was utilized, a 50% yield of 3-acetoxycyclohexene was obtained in addition to the desired allylic hydroperoxide.
(7) These precautions were taken to prevent the reduction of the AgCl salt, which precipitates out as Ag^0. The latter in turn can catalyze the decomposition of the hydrogen peroxide or hydroperoxide. In one run, in which the silver reaction was not run in the dark, the hydroperoxide formed from 3-chlorocyclohexene ignited spontaneously after isolation and concentration.
(8) The reaction proved much more rapid in this case when pyridine was used instead of bicarbonate.
(9) A synthesis, in low yield, of 2-cyclohexen-1-yl nitrate from cyclohexene, ferrous sulfate, and cupric nitrate has been reported.[10] The major product in that preparation was 2-cyclohexen-1-one and the reaction presumably proceeds via a free-radical process.
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(11) The corresponding bromide has been synthesized by Garbisch.[12] Since we were interested in a general synthesis of allylic hydroperoxides, beginning from the corresponding ketone or alcohol, we proceeded as described in the text.
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(17) K. E. Wilson, R. T. Seidner, and S. Masumune, *Chem. Commun.*, 212 (1970). This is the hydride of choice, since others tend to reduce the double bond in 2-en-1-ones as well.
(18) Interestingly enough alcohol **4** boils lower and has a shorter retention time on a Carbowax 20M VPC column than the corresponding ketone **6**, due to intramolecular hydrogen bonding.
(19) R. K. Crossland and K. L. Servis, *J. Org. Chem.*, **35**, 3195 (1970); see also E. W. Collington and A. I. Meyers, *ibid.*, **36**, 3044 (1971).
(20) (a) The ethoxy analogue of **2** has been synthesized[20b] by heating chlorocyclohexanone diethyl acetal with quinoline phosphate at an oil bath temperature of 170–190 °C with a gradually falling pressure of 20–90 mm [bp 92–96 °C (15 mm)]. (b) Winthrop Chemical Co., U.S. Patent 2 119 802 (1934), p 3, lines 19–31.
(21) The NMR spectrum of compound **2** was nearly identical with that of the corresponding bromo analogue, prepared according to the instructions of Garbisch.[12] As would be expected, the only observable difference occurred for the allylic hydrogen α to the halogen (see Table I).
(22) A. D. Walsh, *Trans. Faraday Soc.*, **42**, 99, 269 (1946).
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(25) The aluminum salts tend at times to form a clear, viscous gel and the Na_2SO_4 paste aids in crystalline precipitate formation.
(26) Literature references for alternate methods of preparation: (a) D. D. E. Newman and L. N. Owen, *J. Chem. Soc.*, 4713, 4720 (1952); (b) H. Adkins, R. M. Elofsen, A. G. Rossow, and C. C. Robinson, *J. Am. Chem. Soc.*, **71**, 3622, 3629 (1949); (c) H. W. Durbeck, C. G. B. Frischkorn, and K. Hilpert, *Tetrahedron*, **27**, 2927, 2936 (1971).
(27) 9 ft × 0.25 in. aluminum column packed with 20% Carbowax 20M on Chromosorb W AW DMCS; helium carrier gas flow rate 85 mL/min; injector 200 °C; thermal detector 250 °C.
(28) Silver acetate may also be used.
(29) THe 3M Corp. technical information circular (April 8, 1969) lists the following properties: bp 162 °C (760 mmHg), 84 °C (43 mm), 54 °C (8 mm), density 1.696 (24.5 °C), formula weight 150.02, colorless liquid which fumes in moist air.
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Asymmetric Induction in the Synthesis of Thiophene-Containing Steroidlike Molecules via Olefinic Cyclization. Precoiling as Model Description for the Stereochemical Course of the Reaction

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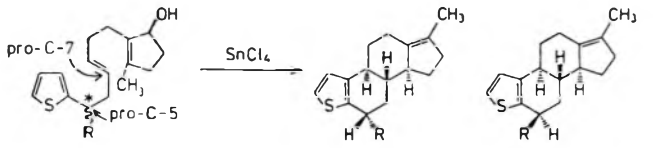
Recently, Corvers et al.[1a] published the preparation of heterocyclic steroids with thiophene as A ring via a cationic

olefinic cyclization. These compounds could be converted into the corresponding "estrogens" with a trans-anti-trans structure.[1b] In order to obtain more insight into the stereochemical pathway of the cyclization process for these compounds and also for similar precursors as were developed by Johnson,[2,3] we introduced a chiral center at position pro-C-5 of compound 1 (R = CH_3, *tert*-butyl; Scheme I). In contrast

Scheme I[a]



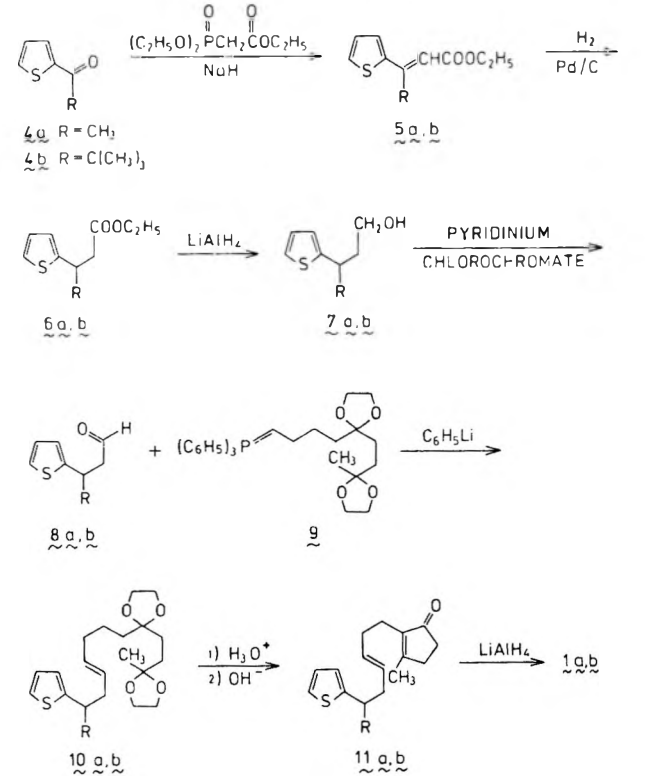
1a R = CH_3 2a R = CH_3 3a R = CH_3
1b R = $C(CH_3)_3$ 2b R = $C(CH_3)_3$ 3b R = $C(CH_3)_3$

[a] The enantiomers are not drawn.

to the work of Johnson, who prepared diastereomeric-free 11α-methylprogesterone via olefinic cyclizations, the asymmetric center in our cases is one C–C distance further from the cyclization initiator, the allylic cation. Johnson ascribed the highly stereochemical outcome of the cyclization reaction in part to the nonbonded interaction in the transition state for the formation of the 11β isomer between the methyl groups attached to pro-C-11, pro-C-10, and possibly pro-C-13. Although in our substrates no alkyl substituent interaction is possible, there is still found *one* enantiomeric pair after cyclization of **1b** and 97% diastereomeric purity after cyclization of **1a.**

The preparation of the latter compounds is outlined in Scheme II. The crucial step in these syntheses was the Wittig

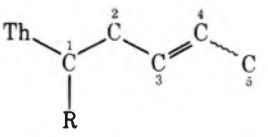
Scheme II



4a R = CH_3
4b R = $C(CH_3)_3$
5a,b
6a,b
7a,b
8a,b
9
10a,b
11a,b
1a,b

condensation of aldehydes **8a** and **8b** with ylide **9**[4] to yield *E* alkenes **10a** and **10b,** respectively. The *E* configuration of the alkenes is a prerequisite, since *Z* isomers fail to give tetracyclic material.[1] The reaction of 8 (R = H) carried out under Schlosser conditions[5] with butyllithium as base afforded *Z*

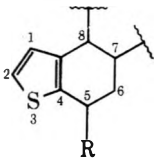
Table I[a,b]



Compd	C_2 (*E*)	C_2 (*Z*)	$\Delta\delta$	C_5 (*E*)	C_5 (*Z*)	$\Delta\delta$
10, R = H[c]	35.71	30.54	5.17	33.80	28.50	5.30
10a	43.41			33.75		
10b	34.85	30.88	3.97	33.61	28.54	5.07
11, R = H[c]	35.55			32.15		
11a	43.38			32.15		
11b	35.25	30.64	4.61	32.09	26.94	5.15

[a] Values given in parts per million downfield from Me_4Si. [b] Th = 2-substituted thiophene. [c] The values for these compounds are obtained from ref 1.

Table II[a]



Compd	C-5	C-6	C-7	C-8
2, R = H[b]	26.29	29.29	42.48	49.76
2a	33.22	39.22	42.70	50.33
2b	48.72	33.45	42.35	50.05

[a] Values in parts per million downfield from Me_4Si. [b] The values of this compound are obtained from ref 1.

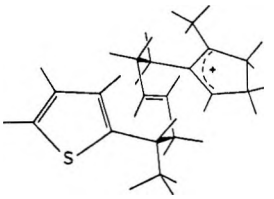
alkenes predominantly, whereas the use of phenyllithium resulted in the formation of *E* alkenes quantitatively.[6] Aldehydes **8a** and **8b** yielded *E* alkenes only if the reactions were carried out at temperatures between −30 and −50 °C. The configuration of the alkenes could be confirmed unequivocally with ^{13}C NMR spectroscopy.[7] The differences in chemical shift ($\Delta\delta$) between the allylic carbon atoms are characteristic for *E* and *Z* isomers. In Table I the data are given for the compounds under discussion.

Cyclization of alkenes **1a** and **1b** with 1.2 equiv of $SnCl_4$ afforded tetracyclic material in 50% yield, which is in good agreement with the experiments performed on the unsubstituted alkenes 1 (R = H).[1] This correspondence in yields is important, otherwise other factors than asymmetric induction might play a role. Variation of the $SnCl_4$ equivalency lowered the yield of tetracyclic product. The by-products consisted of polymers[8] (caused by the action of the Lewis acid on thiophene) and Diels–Alder products, generated from the unstable cyclopentenole ring. Upon cyclization of racemic **1a** and **1b, 2a** and **2b** were formed, respectively. The corresponding diastereomer **3b** could not be detected. *Thus this cyclization occurred with complete asymmetric induction.* If this experiment was carried out with material in a pure enantiomeric form, the tetracyclic product would also be enantiomerically pure.[2] Upon cyclization of **1a,** 97% of the tetracyclic products consisted of **2a,** as shown by HPLC. Presumably, the remaining 3% is diastereomer **3a** (M^+ *m/e* 258; see Experimental Section). No further experiments have yet been carried out to increase the amount of **3a** for further ^{13}C NMR structure identification. Based on the ^{13}C NMR data (Table II) the configuration of the products **2a** and **2b** could be determined. If substituent R occupies the β position, a γ-gauche interaction would cause an upfield shift of C-7 in the order of 1–3 ppm as compared with 1 (R = H). A similar effect amounts to 6.3 ppm in methyl-substituted cyclohexanes, where the axial position of a methyl substituent has been firmly established.[9,14] This

effect is not observed. Therefore, we concluded that compounds were formed with R in the α position. The small downfield shift of C-8 is also in accordance with the α position of R.

The fact that the *tert*-butyl group renders a total asymmetric induction is not very surprising because of its bulkiness. However, such a high specificity induced by a relatively small methyl substituent at a large distance from the cyclization initiator is quite unexpected. This implies that we are dealing with a concerted cyclization[10] starting from the allylic cation via a distinct productlike transition state in which the nonbonded interaction between the alkyl group at pro-C-5 and the hydrogen atoms at pro-C-7 and at pro-C-9 is in favor of the α isomer. Apparently (at low temperatures) the initially formed ion pair of the allylic cation, resulting from heterolysis of the allylic–O bond, manifests itself via a conformational equilibrium in which the precoiled conformer given in Chart I (illustrated for methyl at pro-C-5 in α position) is the most

Chart I



favorable one. This conformer leads to the thermodynamically most stable tetracyclic product. Molecular orbital calculations are in progress to support this model description.

Experimental Section

The ^{1}H NMR data were obtained on a Varian EM-360A spectrometer using Me_4Si as internal standard (δ 0.00). The ^{13}C NMR data were recorded on a Varian HA-100 equipped with a Digilab FTS-NMR-3. Microanalyses were carried out in our laboratories by Messrs. P. van den Bosch and H. Eding. HPLC analyses were carried out by Mr. G. J. Bezemer. 2-Acetylthiophene (**4a**)[11] and pivaloylthiophene (**4b**)[12] were prepared according to the literature.

3-(2-Thienyl)but-2-enoic Acid Ethyl Ester (5a). To a suspension of 0.2 mol (6 g) of sodium hydride (80% in paraffin) in 100 mL of dimethoxyethane (under a nitrogen atmosphere) was added 0.2 mol (42.4 g) of triethyl phosphonoacetate at a temperature below 20 °C. After the solution was stirred for 1 h 0.2 mol (25.2 g) of acetylthiophene was added and refluxed for 16 h. The mixture was poured into water and the product extracted into ether. After the combined ether layers were dried with $MgSO_4$, the solvent was stripped off. Distillation gave 24 g of **5a** (61%), bp 147–154 °C (14 mm). This product was obtained as a mixture of *Z* and *E* isomers (*Z*/*E* ~3/10): NMR (CCl_4) δ 1.06–1.50 (2 t, 3, CH_2CH_3), 2.25–2.54 (m, 1, C=CCH_3), 3.84–4.39 (2 q, 2, CH_2CH_3), 5.73, 6.12 (m, 1, C=CH), 6.76–7.66 (m, 3, ThH).

3-(2-Thienyl)-4,4-dimethylpent-2-enoic acid ethyl ester (5b) was prepared as for **5a**. Only the *E* isomer was obtained: bp 99–103 °C (0.25 mm); yield 60%; NMR (CCl_4) δ 0.99 (t, 3, CH_2CH_3), 1.12 [s, 9, $C(CH_3)_3$], 3.86 (q, 2, CH_2CH_3), 5.99 (s, 1, C=CH), 6.54–7.20 (m, 3, ThH).

3-(2-Thienyl)butanoic Acid Ethyl Ester (6a). A mixture of 0.12 mol (23.8 g) of **5a** was hydrogenated in 150 mL of ethanol with 3 g of Pd on carbon (10%) as catalyst. After 20 h the mixture was filtered to yield after distillation 21.4 g (89%) of **6a:** bp 123 °C (12 mm); NMR (CCl_4) δ 1.13 (t, 3, CH_2CH_3), 1.31 (d, 2, CH_3), 2.15–2.85 (AA'B, 2, CH_2CHCH_3), 3.15–3.70 (m, 1, CH), 3.96 (q, 2, CH_2CH_3), 6.55–7.05 (m, 3, ThH).

3-(2-Thienyl)-4,4-dimethylpentanoic acid ethyl ester (6b) was prepared analogous to **6a:** yield 75%; bp 79–80 °C (0.25 mm); NMR (CCl_4) δ 1.00 (t, 3, CH_2CH_3), 0.95 [s, 9, $C(CH_3)_3$], 2.48–2.65 (AA'B, 2, CH_2CO_2), 3.12–3.38 (m, 1, $CHCH_2$), 3.88 (q, 2, CH_2CH_3), 6.63–7.04 (m, 3, ThH).

3-(2-Thienyl)butanol (7a). A solution of 0.02 mol (3.96 g) of **6a** in 10 mL of ether was added dropwise to a suspension of 0.02 mol (0.76 g) of $LiAlH_4$ in 30 mL of ether at 0 °C. After 1 h of stirring at room temperature and 1 h of refluxing, 1 N sodium hydroxide was added. Filtering, drying, and distillation yielded 2.81 g (90%) of **7a:** bp 121 °C (12 mm); NMR (CCl_4) δ 1.23 (d, 3, $CHCH_3$), 1.72 (m, 2, CH_2CH_2OH), 2.80–3.50 (m, 1, $CHCH_3$), 3.43 (t, 3, CH_2OH), 3.96 (s, 1, OH), 6.70–7.10 (m, 3, ThH).

3-(2-Thienyl)-4,4-dimethylpentanol (7b) was prepared as for **7a:** yield 99%; bp 82–85 °C (0.01 mm); NMR (CCl_4) δ 0.88 [s, 9, $C(CH_3)_3$], 1.50–2.08 (m, 2, CH_2CH_2OH), 2.61–2.87 (m, 1, CH), 3.28 (s, 1, OH), 3.18–3.42 (m, 2, CH_2OH), 6.60–7.03 (m, 3, ThH).

3-(2-Thienyl)butanal (8a). A solution of 6.4 mmol (1 g) of **7a** in 6 mL of dichloromethane was rapidly added to a suspension of 9.6 mmol (2.1 g) of pyridinium chlorochromate[13] in 12 mL of dichloromethane at room temperature. After 3 h of stirring no alcohol could be monitored. A fivefold excess of ether was added and the solution filtered over Florisil. Distillation afforded 0.9 g of aldehyde **8a** (91%): bp 104 °C (13 mm); NMR (CCl_4) δ 1.33 (d, 3, $CHCH_3$), 2.20–3.05 (m, 2, CH_2CHO), 3.20–3.87 (m, 1, $CHCH_3$), 6.43–7.06 (m, 3, ThH), 9.49 (t, 1, CHO).

3-(2-Thienyl)-4,4-dimethylpentanal (8b). This compound was prepared analogous to **8a:** yield 67%; bp 84 °C (0.03 mm); NMR (CCl_4) δ 0.88 [s, 9, $C(CH_3)_3$], 2.58–2.70 (m, 2, CH_2CHO), 3.17–3.40 (m, 1, $CHCH_2CHO$), 6.69–7.05 (m, 3, ThH), 9.39 (t, 1, CHO).

2,5-Bis(ethylenedioxy)-12-(2-thienyl)-(*E*)-tridec-9-ene (10a). Phenyllithium (16 mL, 2 N solution) was added to 0.032 mol (20.23 g) of phosphonium salt **9** in 75 mL of tetrahydrofuran (THF) at 0 °C under a nitrogen atmosphere. At −70 °C 0.032 mol of **8a** in 5 mL of THF was added, followed by a second equivalent of C_6H_5Li. The mixture was maintained between −30 and −50 °C during 1 h, after which 7 mL of ethanol was added. The mixture was poured into water from which the product was extracted with petroleum ether. Chromatography yielded 6.0 g (50%) of **10a:** NMR (CCl_4) δ 1.23 (s, 3, diox CH_3), 1.27 (d, 3, $CHCH_3$), 1.62 (s, 4, $O_2CCH_2CH_2CO_2$), 2.67–3.27 (m, 1, $CHCH_3$), 3.88 (s, 8, 4 $-OCH_2$), 5.10–5.47 (m, 2, CH=CH), 6.54–7.45 (m, 3, ThH).

2,5-Bis(ethylenedioxy)-13,13-dimethyl-12-(2-thienyl)-(*E*)-tetradec-9-ene (10b) was prepared as for **10a:** yield 41%; NMR (CCl_4) δ 0.92 [s, 9, $C(CH_3)_3$], 1.23 (s, 3, diox CH_3), 1.61 (s, 4, $O_2CCH_2CH_2CO_2$), 1.61–2.75 (m, 9, aliphatic H), 3.79 (s, 8, 4 OCH_2), 5.00–5.37 (m, 2, CH=CH), 6.60–7.18 (m, 3, ThH).

2-[6-(2-Thienyl)-(*E*)-hept-3-enyl]-3-methylcyclopent-2-enone (11a). A mixture of 6.8 mmol (2.6 g) of diketal **10a**, 30 mL of 0.5 N HCl, and 60 mL of ethanol was refluxed under a nitrogen atmosphere during 1.5 h, whereupon the solution was rendered alkaline with 1 g of sodium hydroxide and refluxed for another 1.5 h. After evaporation of the ethanol and extraction with pentane, chromatography yielded 1.6 g (86%) of pure product **11a;** bp 142–143 °C (0.01 mm).

Anal. Calcd for $C_{17}H_{22}OS$: C, 74.40; H, 8.09. Found: C, 74.51; H, 8.15.

NMR (CCl_4) δ 1.25 (d, 3, $CHCH_3$), 1.50–2.57 (m, 13, aliphatic H), 2.57–3.26 (m, 1, $CHCH_3$), 4.97–5.40 (m, 2, CH=CH), 6.45–7.20 (m, 3, ThH).

2-[7,7-Dimethyl-6-(2-thienyl)-(*E*)-oct-3-enyl]-3-methylcyclopent-2-enone (11b) was prepared as for **11a:** yield 70%; bp 156–157 °C (0.01 mm).

Anal. Calcd for $C_{20}H_{28}OS$: C, 75.90; H, 8.92. Found: C. 75.70; H, 8.75.

NMR (CCl_4) δ 0.90 [s, 9, $C(CH_3)_3$], 1.89 (s, 3, cyclopent-CH_3), 1.98–2.67 (m, 11, aliphatic H), 5.00–5.11 (m, 2, CH=CH), 6.58–7.05 (m, 3, ThH).

2-[6-(2-Thienyl)-(*E*)-hept-3-enyl]-3-methylcyclopent-2-enol (1a). 2-[7,7-Dimethyl-6-(2-thienyl)-(*E*)-oct-3-enyl]-3-methylcyclopent-2-enol (1b). At −30 °C 1.8 mmol (78 mg) of $LiAlH_4$ was added in small portions to a solution of 1.8 mmol of ketone **1a** or **1b**. After 0.5 h 1 N sodium hydroxide was added. The mixture was filtered, dried, and concentrated at low temperature. Due to their susceptibility to dehydration, the cyclopentenols were used immediately for cyclization experiments. The products obtained from the cyclization experiments were first purified by column chromatography. On TLC pure tetracyclic material HPLC (Lichrosorb RP 18) was carried out to determine the diastereomeric ratio.

5,11α-Dimethyl-12,13[*b*]-thienotricyclo[7.4.0.0^{4,8}]tridec-4-ene (2a). To a solution of 500 mg of unsaturated alcohol **1a** in 10 mL of dichloromethane at −95 °C, 1.2 equiv of $SnCl_4$ was added dropwise. After 1 h the solution was poured into saturated ammonium chloride and the product extracted with dichloromethane. Chromatography yielded 250 mg of product (50%). HPLC analysis revealed that the product consisted of 97% **2a** and 3% **3a** (M^+ *m/e* 258).

Anal. Calcd for $C_{17}H_{22}S$: C, 79.01; H, 8.48. Found: C, 78.86; H, 8.48.

NMR (CCl_4) δ 1.27 (d, 3, $CHCH_3$), 1.60 (s, 3, C=CCH_3), 1.00–3.30 (m, 14, aliphatic H), 6.66–6.95 (AB, 2, ThH).

5-Methyl-11α-*tert*-butyl-12,13[*b*]-thienotricyclo[7.4.0.0^{4,8}]-

tridec-4-ene (2b) was prepared as for **2a**, yield 50%.

Anal. Calcd for $C_{20}H_{28}S$: C, 79.94; H, 9.39. Found: C, 80.07; H, 9.60. This product turned out to be diastereomeric free.

NMR (CCl_4) δ 1.00 [s, 9, $C(CH_3)_3$], 1.58 (s, 3, $C{=}CCH_3$), 1.80–2.90 (m, 14, aliphatic H), 6.70–6.95 (AB, 2, ThH).

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Registry No.—**1a**, 62815-66-1; **1b**, 62815-67-2; **2a**, 62815-68-3; **2b**, 62815-69-4; **3a**, 62928-71-6; (*E*)-**5a**, 62815-70-7; (*Z*)-**5a**, 62815-71-8; **5b**, 62815-72-9; **6a**, 62815-73-0; **6b**, 62815-74-1; **7a**, 62815-75-2; **7b**, 62815-76-3; **8a**, 62815-77-4; **8b**, 62815-78-5; **9**, 62815-79-6; **10a**, 62815-80-9; **10b**, 62815-81-0; **11a**, 62815-82-1; **11b**, 62815-83-2; triethyl phosphonoacetate, 867-13-0; 2-acetylthiophene, 88-15-3; 2-pivaloylthiophene, 20409-48-7.

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An Unusual Side Reaction of 1-Succinimidyl Esters during Peptide Synthesis

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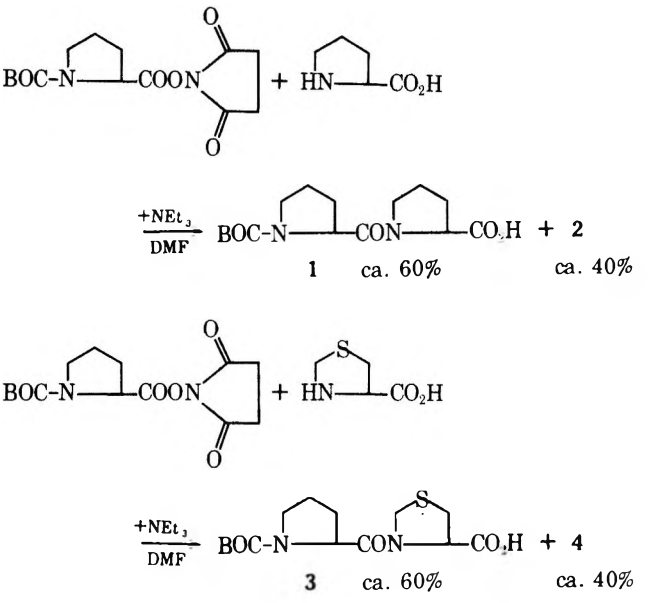
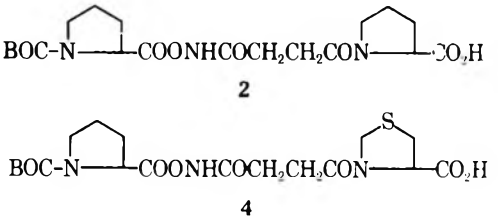
Peptide bond formation mediated through 1-succinimidyl ester couplings in aqueous or nonaqueous solvents is a standard procedure of peptide synthesis.[2] In the present communication we wish to report the observation of a new side reaction of 1-succinimidyl esters.

Coupling of a N-protected amino acid 1-succinimidyl ester with a free amino acid in anhydrous dimethylformamide in the presence of triethylamine results usually in high yields of the dipeptide derivative, as loss through hydrolysis of the activated ester is minimized. As an example, the preparation of *N*-benzyloxycarbonylglycyl-L-proline, containing an 85% ^{13}C-enriched proline residue,[3] is described in the Experimental Section. However, when *N*-tert-butyloxycarbonyl-L-proline 1-succinimidyl ester was coupled under identical conditions with free proline or 4-thiazolidinecarboxylic acid, the expected N-protected dipeptides **1** and **3** were accompanied by secondary products formed in nearly the same amount



(BOC = *tert*-butyloxycarbonyl)

(contaminants **2** and **4**). Coupling of the activated ester with the sodium salt of proline in an ethanol–water mixture resulted in an important hydrolysis of the ester. The by-products **2** and **4**, which were not chromatographically identical, could not be obtained pure enough for elemental analysis. However, they were obtained free from the corresponding N-protected dipeptides and accompanied only by a trace amount of proline or 4-thiazolidinecarboxylic acid through repeated precipitations. Infrared and NMR spectroscopy as well as mass spectrometry have shown the contaminants to have structures **2** and **4**.

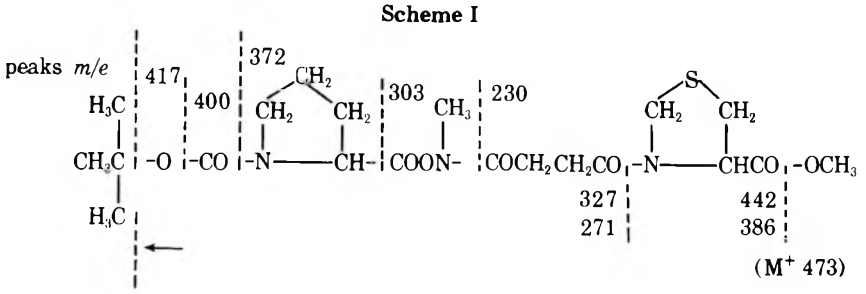


In the infrared region the carbonyl stretching vibrations of the two N-protected dipeptides **1** and **3** appeared as three bands of approximately the same intensity located at 1605, 1682, and 1755 cm^{-1}, while compounds **2** and **4** showed two strong absorptions centered at 1605 and 1685 cm^{-1} and a band of medium intensity at 1790 cm^{-1}. The appearance of an absorption at higher frequency (1790 cm^{-1}) is consistent with the presence of a carbonyl group implicated in a *O*-acylhydroxylamine linkage.[4]

The general aspect of the proton NMR spectra of contaminants **2** and **4**, in chloroform solution, was essentially the same as that of the corresponding dipeptides[5] **1** and **3**. In particular, the observation of two singlets at δ 1.40 (smaller) and 1.47 ppm (larger) for compound **2** and at δ 1.43 (smaller) and 1.49 ppm (larger) for compound **4** confirmed the presence of the *tert*-butyloxycarbonyl group. On the other hand, contaminants **2** and **4** presented an additional unresolved peak centered at δ 2.75 ppm, corresponding to four protons, which was absent from the spectrum of **1** and **3**, and which is assigned to the methylene protons of the succinic acid group.

Mass spectra of the methylated (diazomethane) contaminants **2** and **4** confirmed the proposed structure and showed that methylation occurred on the carboxylic acid function and on the nitrogen proton of the *O*-acylhydroxylamine derivatives **2** and **4**. The observed fragmentation of the methylated

Scheme I



contaminant 4 is presented in Scheme I. From the peak at *m/e* 417, corresponding to the thermal decomposition of the *tert*-butyloxycarbonyl group with departure of isobutylene, a normal fragmentation is again observed with peaks at *m/e* 386 and 271. A parallel fragmentation pattern was observed for methylated **4**, which gave a molecular peak at M^+ 455.

O-Acylated hydroxamic acid derivatives have been found to be "activated esters" and have proved useful in peptide synthesis.[6,7] It is therefore surprising that when *N-tert*-butyloxycarbonylproline 1-succinimidyl ester was allowed to react with a twofold excess of proline or 4-thiazolidinecarboxylic acid, contaminants **2** and **4**, which are "activated esters" of hydroxamic acid as shown by the high infrared frequency carbonyl absorption (1790 cm^{-1}), were still formed in the same proportion and did not react further to give the corresponding N-protected dipeptide. It is reassuring to find that, among the activated esters of pivalohydroxamic acid and *N*-benzyloxycarbonyl amino acids,[7] the ester of *N*-benzyloxycarbonylproline is the only one which does not react with amines of amino acids to form a peptide bond. This observation might explain in part why we were able to isolate in both experiments the side products **2** and **4**.

The formation of an intermediate of the type of compounds **2** and **4** was also observed during the coupling of *N-tert*-butyloxycarbonylproline 1-succinimidyl ester with sarcosine. Thin-layer chromatography of the reaction mixture revealed, besides the expected dipeptide and starting materials, a compound developing a characteristic blue color with ninhydrin as do **2** and **4** and giving a positive hydroxamic acid test when sprayed with ferric chloride solution. In no other 1-succinimidyl ester coupling we tried were we able to demonstrate the presence of intermediates of the type of compounds **2** and **4**. Thus, thin-layer chromatography of couplings of sterically hindered amino acid residues, such as the coupling of *N-tert*-butyloxycarbonylproline 1-succinimidyl ester with valine or leucine, or of *N-tert*-butyloxycarbonyl-β-benzylaspartic acid 1-succinimidyl ester with proline, showed the presence of only the starting materials and the corresponding dipeptides. Infrared spectra of the partially purified products, free from interfering 1-succinimidyl ester and hydroxysuccinimide, did not present a carbonyl band at an unusually high frequency.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 337 infrared spectrometer in Nujol using sodium chloride plates; ^1H NMR spectra were obtained on a Perkin-Elmer R32 (90 MHz) spectrometer. We are indebted to Dr. B. C. Das who recorded and interpreted mass spectra of methylated compounds **2** and **4**, taken at 200 °C with an AEI mass spectrometer, Model MS9, at the Institut de Chimie des Substances Naturelles in Gif-sur-Yvette. Chromatograms on silica gel plates (Merck) were run in 1-butanol–acetic acid–water, 3:1:1, mixtures.

***N*-Benzyloxycarbonylglycyl-L-proline[8] with ^{13}C-Enriched Proline.**[3] ^{13}C-enriched L-proline (85%, 240 mg, 2 mmol) was suspended in dry dimethylformamide (3 mL), triethylamine (0.28 mL, 2 mmol) was added followed by *N*-benzyloxycarbonylglycine 1-succinimidyl ester (612 mg, 2 mmol), and the reaction mixture was left to stir overnight at room temperature. After dilution with water and acidification to pH 2 with 6 N hydrochloric acid, the product was extracted with ethyl acetate. The organic solution was washed with water, the product extracted with saturated sodium bicarbonate, and the alkaline solution was acidified with hydrochloric acid to pH 5 and evaporated to a small volume. On acidification to pH 2 with 6 N hydrochloric acid the product crystallized out (566 mg, 91%): mp 156–158 °C, lit.[8] mp 158–159 °C. This product was identical to an authentic sample of *N*-benzyloxycarbonylglycyl-L-proline.[8]

***N-tert*-Butyloxycarbonyl-L-prolyl-L-proline[5] (1) and Contaminant 2.** The *N-tert*-butyloxycarbonyl-L-proline 1-succinimidyl ester was coupled with proline and the reaction mixture worked up as described for the preparation of *N*-benzyloxycarbonylglycyl-L-proline, except that the product was precipitated from ethyl acetate by addition of *n*-hexane. From a concentrated ethyl acetate solution of this product, chromatographically pure *N-tert*-butyloxycarbonyl-L-prolyl-L-proline crystallized out (48%). After recrystallization from ethyl acetate, the protected dipeptide (37%) had mp 187–188 °C, lit.[5] mp 186–187 °C; R_f 0.70 on silica gel plates (ninhydrin negative when spotted on cellulose). This product was identical with an authentic sample of *N-tert*-butyloxycarbonyl-L-prolyl-L-proline.[5]

The combined ethyl acetate recrystallization filtrates were highly enriched in contaminant **2** but still contained some protected dipeptide. After evaporation and drying, the oil represented a 40% yield. Repeated trituration in ether, which was accompanied with great losses of material, gave **2** (R_f 0.63) as a solid free from the dipeptide **1** and contaminated by only a trace amount of a slow-moving, ninhydrin-positive material (R_f 0.17). Contaminant **2** gave a positive blue ninhydrin reaction on silica gel and cellulose plates. It gave a positive hydroxamic acid test in the presence of ferric chloride.

Attempts at further purification of compound **2** for analytical purposes or attempts to obtain **2** in larger quantities through column chromatography (Kieselgel 60, Merck; ethyl acetate–methanol, 2:1, or chloroform–methanol, 2:1) resulted in extensive degradation of this compound.

***N-tert*-Butyloxycarbonyl-L-prolyl-L-4-thiazolidinecarboxylic Acid (3) and Contaminant 4.** The protected dipeptide and contaminant **4** were prepared in the same manner as described for the preparation of dipeptide **1**.

The N-protected dipeptide **3** was obtained analytically pure in 32% yield: mp 154–156 °C; $[\alpha]^{22}_D$ −129° (c 1.0, $CHCl_3$), R_f 0.72. Anal. Calcd for $C_{14}H_{22}N_2O_5S$: C, 50.9; H, 6.7; N, 8.5; S, 9.7. Found: C, 50.9; H, 6.8; N, 8.4; S, 9.9.

Contaminant **4** had R_f 0.66, ninhydrin positive on silica gel and cellulose plates. It gave a positive hydroxamic acid test in the presence of ferric chloride.

Registry No.—**1**, 15401-08-8; **2**, 62726-56-1; **3**, 62726-57-2; **4**, 62726-58-3; *N-tert*-butyloxycarbonyl-L-proline 1-succinimidyl ester, 3392-10-7; proline, 147-85-3; 4-L-thiazolidinecarboxylic acid, 34592-47-7.

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(1) This work was carried out at the Institut de Biochimie, Université Paris-Sud, Equipe de recherche sur les Peptides No. 15, CNRS, 91405 Orsay, France, and was supported by a grant from the Action Spécifique AAPIS, CNRS.
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Synthesis of 11-Deoxy-8-azaprostaglandin E_1

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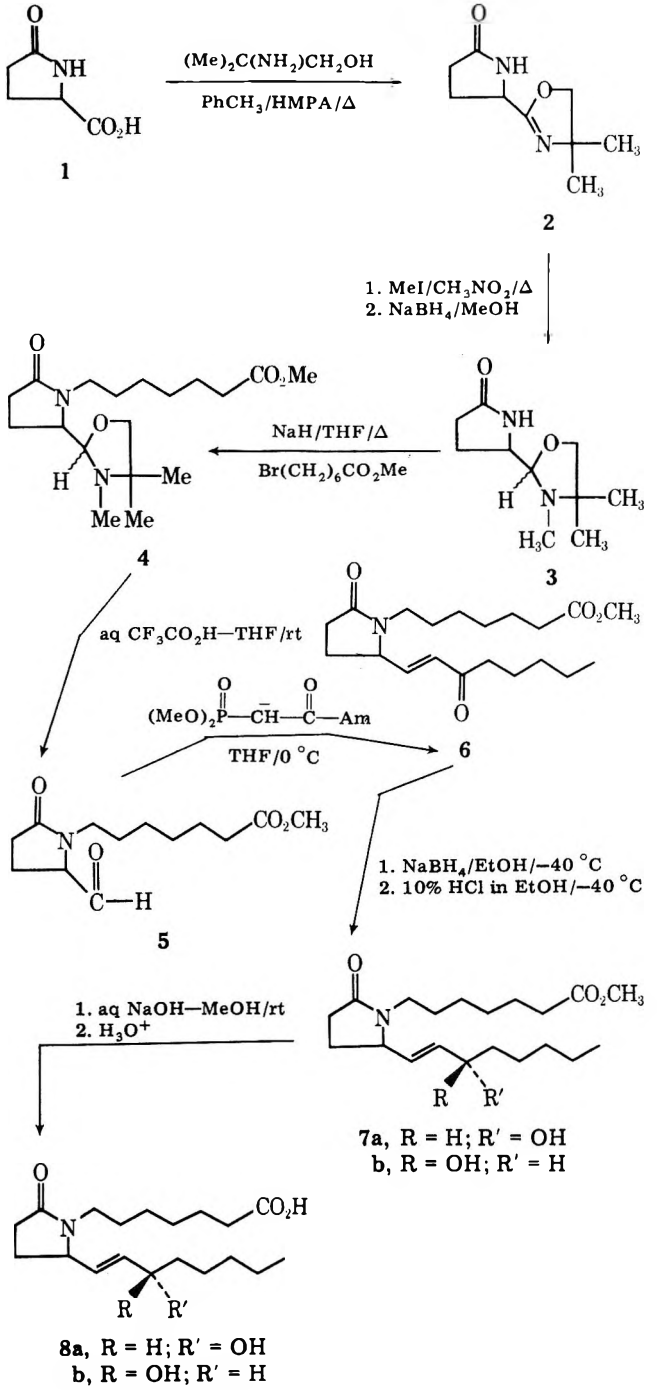
In two recent communications, Bolliger and Muchowski[2] and DeKoning and co-workers[3] reported the synthesis of 11-deoxy-8-aza-PGE_1. A similar route to that of Bollinger and Muchowski has also been reported in a patent by Himizu and co-workers.[4] We would like to report herein an alternative synthetic sequence to 8-aza-PGE_1 (**8a**) and 8-aza-15-*epi*-PGE_1 (**8b**) as outlined in Scheme I.

Reaction of pyroglutamic acid (1) with 2-amino-2-methyl-1-propanol in refluxing $PhCH_3$ containing HMPA afforded the oxazoline **2**[5] (64%; mp 92–95 °C). Methylation of **2** with methyl iodide in refluxing nitromethane and subsequent reduction of the resulting oxazolinium iodide with sodium borohydride[6] in methanol yielded the oxazolidines **3** (54%; mp 93–96 °C).

Scheme I



7a, R = H; R′ = OH
b, R = OH; R′ = H

8a, R = H; R′ = OH
b, R = OH; R′ = H

Alkylation of the sodium salt of the oxazolidines **3** with methyl 7-bromoheptanoate in refluxing THF and subsequent chromatography on silica gel G and elution with ether–hexane solutions afforded the esters **4** (49%). Hydrolysis of **4** with an aqueous trifluoroacetic acid–THF solution at room temperature for 3.5 h yielded the aldehyde **5** (77%). The aldehyde proved to be relatively stable, if chromatographed immediately on silica gel G with ether–hexane solutions and stored at −5 °C.

Reaction of the aldehyde **5** with the lithium salt of dimethyl (2-oxo-heptyl)phosphonate in THF at 0 °C and subsequent chromatography on silica gel G with ether–hexane solutions afforded the enone **6** (76%). The enone **6** was allowed to react with an ethanolic sodium borohydride solution at −40 °C for a 2.5-h period. The excess $NaBH_4$ was destroyed with a 10% ethanolic hydrochloric acid solution at −40 °C and the crude reaction product was passed through a short column of silica gel G to afford a 1:1 mixture of the ester alcohols **7a** and **7b** (82%). A more extensive column chromatography of the epimeric C-15 alcohols **7a** and **7b** on silica gel G and elution with ether–hexane solutions yielded a faster moving (less polar) diastereoisomer and a diastereoisomeric mixture of **7a** and **7b** enriched in **7a** as determined by TLC analysis. The less polar compound was tentatively assigned to the 15β-epimer **7b**, in analogy with the characteristic TLC behavior of methyl 11-deoxy-15-*epi*-PGE_1 and methyl 11-deoxy-PGE_1.

Reaction of the ester alcohol **7b** with an aqueous methanolic sodium hydroxide solution at room temperature and subsequent acidification afforded 8-aza-11-deoxy-15-*epi*-PGE_1 (**8b**) (mp 89–90 °C).

Hydrolysis of the diastereoisomeric mixture of **7a** and **7b** (enriched in **7a** via column chromatography) with an aqueous methanolic sodium hydroxide solution at room temperature and subsequent acidification yielded a C-15 epimeric mixture of acids. Trituration of these acids with a hot ether–hexane solution afforded the higher melting diastereoisomer, 8-aza-11-deoxy-PGE_1 (**8a**) (mp 108.5–110 °C).

Saponification of the 1:1 mixture of the ester alcohols **7a** and **7b** with an aqueous methanolic sodium hydroxide solution at room temperature followed by acidification yielded a C-15 epimeric mixture of acids **8a** and **8b** [72%; mp 82.5–85 °C].

The acid alcohols were found[7] to be active in inhibiting gastric acid secretion.

Experimental Section

2-(5-Oxo-2-pyrrolidinyl)-4,4-dimethyl-2-oxazoline (2). *dl*-Pyroglutamic acid (1) (25.0 g, 0.194 mol) was dissolved in 70 mL of hexamethylphosphoramide (HMPA). 2-Amino-2-methylpropanol (17.3 g, 0.194 mol) and 250 mL of toluene were added and the resulting mixture was heated to reflux for 72 h utilizing a Dean–Stark trap. After cooling, toluene was removed with a rotary evaporator and the remaining toluene and unreacted amino alcohol were removed by distillation at 12 mm, and the HMPA at 0.15 mm. Distillation of the resulting residue afforded 22.9 g (64%) of the oxazoline **2**: bp 140–147 °C (0.15 mm); mp 92–95 °C (washed with hexanes); NMR ($CDCl_3$) δ 7.0 (s, 1 H), 4.10–4.33 (m, 1 H), 3.95 (s, 2 H), 2.15–2.52 (m, 4 H), 1.30 (s, 6 H); IR (CCl_4) 1670 and 1711 cm^{-1}.

Anal. Calcd for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.74; N, 15.37. Found: C, 59.06; H, 7.75; N, 15.34.

2-(5-Oxo-2-pyrrolidinyl)-3,4,4-trimethyloxazolidines (3). The oxazoline **2** (53.0 g, 0.29 mol) was dissolved in 175 mL of dry CH_3NO_2. Methyl iodide (82.7 g, 0.58 mol) was added to the above solution and the resulting mixture was heated at 70 °C for 2 days with stirring. Additional methyl iodide was added to maintain a decent CH_3I reflux rate over a 2-day period. Excess methyl iodide and nitromethane were removed by distillation at 12 mm, thus affording 89 g (94%) of the oxazolinium iodide, a viscous brown syrup which turned to a glassy solid on standing at room temperature: NMR [CH_3NO_2 (δ 4.33) and

CH_3I (δ 2.15), standards] δ 7.25 (s, br, 1 H), 4.95–5.25 (m, 1 H), 4.85 (s, 2 H), 3.39 (s, 3 H), 2.20–2.60 (m, 4 H), 1.58 (s) and 1.62 (s) (6 H).

Since the oxazolinium iodide is very hygroscopic, the salt was reduced directly to the oxazolidines **3**.

A solution of $NaBH_4$ (6.5 g, 0.17 mol) dissolved in 250 mL of absolute MeOH was cooled at 0 °C. A solution of the oxazolinium iodide (20 g, 0.062 mol) dissolved in 82 mL of MeOH was added dropwise over a 30-min period with stirring. The reaction was stirred at 0 °C for 45 min and then between 0 and 20 °C for an additional 45 min. The reaction was concentrated on a rotary evaporator, poured into 150 mL of H_2O, and extracted with three 250-mL portions of $CHCl_3$. The chloroform extracts were washed with NaCl solution, dried ($MgSO_4$), and filtered, and concentration of the chloroform solution with a rotary evaporator yielded an oil which solidified on standing in a freezer. The crude solid was chromatographed with silica gel G and elution with ether afforded 6.6 g (54%) of the pure oxazolidines **3**: NMR (CCl_4) δ 7.35 (s, br, 1 H), 3.90–3.95 (truncated peak, 1 H), 3.52 (s) and 3.30–3.70 (m) (3 H), 2.22 (s) and 1.80–2.30 (m) (7H), 1.13 (s, 3 H), and 0.97 (s, 3 H): IR (CCl_4) 3455, 3215, 3100, and 1710 cm^{-1}; mp 93–96 °C.

Anal. Calcd for $C_{10}H_{18}N_2O_2$: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.68; H, 9.17; N, 13.96.

2-[5-Oxo-1-(6-carbomethoxyhexyl)-2-pyrrolidinyl)]-3,4,4-trimethyloxazolidines (4). The oxazolidine **3** (7.94 g, 0.04 mol) was dissolved in 100 mL of dry THF. A 50% suspension of sodium hydride in mineral oil (1.92 g, 0.04 mol) was added and the resulting mixture was stirred for 1.4 h at room temperature under N_2. Methyl 7-bromoheptanoate (8.92 g. 0.04 mol) dissolved in 20 mL of dry THF was added dropwise over a 5-min period, and the addition funnel was rinsed with an additional 10 mL of THF. The resulting reaction mixture was refluxed for 91 h and then allowed to cool. The solvent was removed and the resulting oil was poured into 150 mL of H_2O and extracted with three 200-mL portions of CH_2Cl_2. The dried methylene chloride extracts were concentrated to give 14.1 g of crude **4**. The crude oil was chromatographed with silica gel G, and elution with ether–hexane solutions yielded 6.7 (49%) of the ester oxazolidines **4**: NMR (CCl_4) δ 4.17 (d, 1 H, methine of oxazolidine), 3.61 (s, $-CO_2CH_3$), 3.54 (s, $-OCH_2-$), 3.0–3.75 (m, methine of pyrrolidinone) (6 H), 2.19 and 2.22 (singlets, two *N*-methyls of oxazolidine), 2.50–1.80 (multiplets, buried, $-CH_2C(O)N$, $-CH_2N$, $-CH_2CO_2Me$. $-CH_2CHN$), 1.80–1.20 (m, $-(CH_2)_4$ of side chain), 0.99 and 1.10, and 1.03 and 1.14 (singlets, *gem*-dimethyls) (25 H); IR (neat) 1741 and 1684 cm^{-1}.

Anal. Calcd for $C_{18}H_{32}O_4N_2$: C, 63.50; H, 9.47; N, 8.23. Found: C, 63.64; H, 9.45; N, 8.14.

Methyl 7-(2-Formyl-5-oxo-1-pyrrolidinyl)heptanoate (5). The ester oxazolidine (500 mg, 0.001 47 mol) was dissolved in an aqueous THF–CF_3CO_2H solution [0.5 mL of THF, 0.5 mL of H_2O and trifluoroacetic acid (0.24 g, 0.0021 mol)] and stirred for 3.5 h at room temperature. The reaction was poured into 20 mL of H_2O and extracted with three 50-mL portions of CH_2Cl_2. The methylene chloride extracts were combined, washed with 40 mL of a 5% $NaHCO_3$ solution, and dried. Concentration of the CH_2Cl_2 solution with a rotary evaporator and pumping the resulting oil at 0.1 mm with heat afforded 0.29 g (77%) of the aldehyde **5**: NMR (CCl_4) δ 9.54 (d, 1 H, J = 3 Hz), 3.75–4.15 (m), 3.60 (s), and 2.55 and 3.50 (m) (6 H), 1.90–2.50 (br, m) and 1.0–2.80 (br, m) (8 H); IR (neat) 2860, 2715, 1740 and 1730 (saw tooth) and 1670 cm^{-1}. The aldehyde proved to be stable, if chromatographed immediately and stored in a freezer at −5 °C. TLC analysis showed **5** as one spot; however, after Kugelrohr distillation [200 °C (0.08 mm)] TLC analysis indicated a less polar top spot (~20%) present in distilled **5**. The aldehyde **5** was therefore committed directly, after column chromatography, to the Wadsworth–Emmons reaction.

Methyl 8-Aza-9,15-dioxo-13,14-dehydroprostanoate (6). A three-neck flask fitted with a condenser, nitrogen inlet tube, magnetic stirring bar, and serum cap was flamed and deaerated with nitrogen. Dimethyl (2-oxoheptyl)phosphonate (627 mg, 0.0028 mol) dissolved in 25 mL of THF was placed in the reaction vessel under N_2 and cooled to 0 °C. A hexane solution of 2.5 M BuLi (1.12 mL, 0.0028 mol) was added with a syringe and the reaction was allowed to stir at 0 °C for 20 min. The ester aldehyde **5** (800 mg, 0.003 14 mol) dissolved in 25 mL of dry THF was added to the reaction all at once at 0 °C and the resulting reaction mixture was allowed to stir at 0 °C for 2.5 h. The milky white reaction was poured into an ice–water mixture and extracted with CH_2Cl_2. The dried extracts were concentrated to give 1.25 g of an oil. The oil (1.25 g) was chromatographed immediately using silica gel G and elution with ether–hexane solutions yielded 750 mg (76%) of pure enone **6**: NMR (CCl_4) δ 6.60 (q, J_{12-13} = 8, J_{13-14} = 16 Hz) and 6.11 (d, J_{13-14} = 16 Hz) (2 H), 4.85–4.30 (m), 3.60 (s), and 3.55–2.63 (m) (6 H), 2.00–2.55 (m), 1.08–1.92 (br peak), and 0.95 (t, distorted) (25 H); IR (neat) 1735, 1690, and 1680 (shoulder) cm^{-1}; mass spectrum *m/e* 351 (M), 320 (M − OCH_3), 252 (M − COC_5H_{11}), 222 [M − $(CH_2)_5CO_2CH_3$].

Anal. Calcd for $C_{20}H_{33}NO_4$: C, 68.34; H, 9.46; N, 3.99. Found: C, 68.39; H, 9.55; N, 3.83.

Methyl 15α- and 15-*epi*-11-Deoxy-8-aza-PGE$_1$ (7a and 7b). A three-neck flask fitted with two addition funnels, a magnetic stirring bar, and a nitrogen inlet tube was flamed and deaerated with nitrogen. $NaBH_4$ (180 mg, 0.0048 mol) was placed in the reaction vessel and the vessel was cooled to −40 °C. Dry ethanol was added to obtain a clear ethanolic $NaBH_4$ solution at −40 °C. The enone **6** (820 mg, 0.0023 mol) dissolved in 30 mL of absolute ethanol was added all at once and the reaction mixture was allowed to stir for 2.5 h at −40 °C. Excess $NaBH_4$ was killed with a 10% ethanolic HCl solution at −40 °C and the reaction mixture was concentrated with a rotary evaporator. The resulting residue was poured into 50 mL of H_2O and extracted with three 150-mL portions of CH_2Cl_2. The dried methylene chloride extracts were concentrated; chromatography with a short silica gel column and elution with ether–hexane solutions yielded 800 mg of a 1:1 epimeric mixture of the ester alcohols **7a** and **7b**: NMR (CCl_4) δ 5.15–5.80 (m, 2 H), 3.75–4.15 (m), 3.60 (s), and 2.55–3.45 (m) (8 H), 1.90–2.50 (br peak), 1.15–1.85 (br peak), and 0.90 (t, distorted) (25 H); IR (CCl_4) 1745 and 1680 cm^{-1}; mass spectrum *m/e* 353 (m), 336 (M − OH), 335 (M − H_2O), 322 (M − OCH_3), 278 [M − OH and $(CH_2)_3CH_3$], 252 (M − $C_5H_{11}CHOH$), 226 (M − CH=$CHCHOHC_5H_{11}$), 224 [M − $(CH_2)_5CO_2Me$], 194 (M − CH=$CHCHOHC_5H_{11}$ and CH_3OH or M − CH_2=$CH(CH_2)_4CO_2CH_3$ and OH), 178 (M − $C_5H_{11}CHOH$ and $CH_3CO_2CH_3$).

Anal. Calcd for $C_{20}H_{35}NO_4$: C, 67.95; H, 9.98; N, 3.96. Found: C, 67.77; H, 10.03; N, 3.79.

Chromatography of the 1:1 epimeric mixture of ester alcohols **7a** and **7b** on silica gel G and elution with ether–hexane solutions afforded 200 mg of a faster moving (less polar) diastereoisomer and 510 mg of a diastereoisomeric mixture of **7a** and **7b** which was enriched in **7a** as determined by TLC analysis. The less polar compound was tentatively assigned to the 15β epimer **7b** in analogy with the characteristic TLC behavior of methyl 11-deoxy-15-*epi*-PGE$_1$ and methyl 11-deoxy-PGE$_1$. The less polar diastereoisomer **7b** was not characterized further, but was subjected directly to basic hydrolysis.

15-*epi*-11-Deoxy-8-aza-PGE$_1$ (8b). Methyl 15-*epi*-11-deoxy-8-aza-PGE$_1$ (**7b**) (0.20 g, 0.000 567 mol) was dissolved in 2.6 mL of methanol. An aqueous sodium hydroxide solution [NaOH (0.026 g, 0.000 65 mol) and 1.04 mL of H_2O] was added to the above solution and the resulting mixture was stirred at room temperature for 20 h.

The reaction mixture was poured into 10 mL of H_2O and extracted with ether. The aqueous layer was acidified with concentrated HCl and extracted with methylene chloride. The dried extracts were concentrated to give approximately 200 mg of the acid (**8b**).

An ether–hexane solution was added to the acid (**8b**) and the resulting solid was filtered with suction and triturated with hot Et_2O to afford 80 mg (42%) of pure 15-*epi*-11-deoxy-8-aza-PGE$_1$ (**8b**): mp 89–90 °C (Et_2O); IR (KBr) 3550–3150 (br), 1735 and 1665 cm^{-1}; mass spectrum *m/e* 339 (M), 322 (M − OH), 321 (M − H_2O), 268 (M − C_5H_{11}), 264 [M − H_2O and $(CH_2)_3CH_3$], 250 (M − C_5H_{11} and H_2O), 238 (M − $C_5H_{11}CHOH$), 225 [M − CH_2=$CH(CH_2)_4CO_2H$], 224 [M − $(CH_2)_5CO_2H$], 212 (M − CH=$CHCHOHC_5H_{11}$), 210 [M − $(CH_2)_6CO_2H$].

Anal. Calcd for $C_{19}H_{33}NO_4$: C, 67.22; H, 9.80; N, 4.13. Found: C, 67.09; H, 9.78; N, 4.04.

11-Deoxy-8-aza-PGE$_1$ (8a). The diastereoisomeric mixture **7a** and **7b**, enriched in **7a** (400 mg, 0.001 13 mol), was dissolved in 6 mL of methanol. An aqueous sodium hydroxide solution [NaOH (0.052 g, 0.00130 mol) and 2.5 mL of H_2O] was added to the above solution and the resulting mixture was stirred at room temperature for 23 h.

The reaction mixture was poured into 15 mL of H_2O and extracted with two 25-mL portions of Et_2O. The aqueous layer was acidified with concentrated HCl and extracted with three 60-mL portions of CH_2Cl_2; 390 mg of the acids **8a** and **8b** was obtained.

Addition of an ether–hexane solution to the epimeric acids **8a** and **8b** afforded a solid. Repeated trituration of the solid with a hot ether–hexane solution afforded the higher melting diastereoisomer, 11-deoxy-8-aza-PGE$_1$ **8a**: mp 108.5–110 °C; IR (KBr) 3500–3100 (br), 1735 and 1665 cm^{-1}; mass spectrum *m/e* 339 (M), 322 (M − OH), 321 (M − H_2O), 268 (M − C_5H_{11}), 264 [M − H_2O and $(CH_2)_3CH_3$], 250 (M − C_5H_{11} and H_2O), 238 (M − $C_5H_{11}CHOH$), 225 [M − CH_2=$CH(CH_2)_4CO_2H$], 224 [M − $(CH_2)_5CO_2H$], 212 (M − CH=$CHCHOHC_5H_{11}$), 210 [M − $(CH_2)_6CO_2H$].

Anal. Calcd for $C_{19}H_{33}NO_4$: C, 67.22; H, 9.80; N, 4.13. Found: C, 67.56; H, 9.64; N, 4.03.

A 1:1 Epimeric Mixture of 15α- and 15-*epi*-11-Deoxy-8-aza-

PGE_1 (8a and 8b). The 1:1 mixture of epimeric ester alcohols **7a** and **7b** (1.15 g, 0.003 26 mol) was dissolved in 15 mL of methanol. An aqueous sodium hydroxide solution [NaOH (150 mg, 0.00375 mol) and 6 mL of H_2O] was added to the above solution and the resulting mixture was stirred at room temperature for 20 h.

The reaction mixture was poured into 50 mL of H_2O and extracted with two 50-mL portions of ether. The aqueous layer was acidified with concentrated HCl at 0 °C and extracted with three 200-mL portions to CH_2Cl_2. The dried methylene chloride extracts were concentrated to give 1.0 g (90%) of an oil, crude **8**, which solidified on standing at −5 °C. The solid was chromatographed using silica gel G and elution with hexane–ether and ether–CH_2Cl_2 solutions yielded 800 mg (72%) of a pure 1:1 epimeric mixture of 15α- and 15-*epi*-11-deoxy-8-aza PGE_1: mp 82.5–85 °C; NMR ($CDCl_3$) δ 0.87 (t, distorted, 3 H), 1.10–1.90 (br hump), 2.0–2.60 (m) and 2.8–3.70 (m) (24H), 4.28–3.86 (m, 1 H), 5.48–5.75 (m, 2 H) and 6.37 (s, 2 H). After addition of D_2O the resonance peak at δ 6.37 disappeared: IR (KBr) 3400 (shoulder), 3200, 2910, 2600 (shoulder), 1715 and 1650 cm^{-1}; mass spectrum *m/e* 339 (M), 322 (M − OH), 321 (M − H_2O), 268 (M − C_5H_{11}), 264 [M − H_2O and $(CH_2)_3CH_3$], 250 (M − C_5H_{11} and H_2O), 238 (M − $C_5H_{11}CHOH$), 225 [M − $CH_2{=}CH(CH_2)_4CO_2H$], 224 [M − $(CH_2)_5CO_2H$], 212 (M − $CH{=}CHCHOHC_5H_{11}$), 210 [M − $(CH_2)_6CO_2H$)].

Anal. Calcd for $C_{19}H_{33}NO_4$: C, 67.22; H, 9.80; N, 4.13. Found: C, 67.08; H, 9.91; N, 4.08.

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Registry No.—**1**, 149-87-1; **2**, 62842-02-8; **2** methiodide, 62861-45-4; **3** isomer 1, 62861-46-5; **3** isomer 2, 62842-03-9; **4** isomer 1, 62861-47-6; **4** isomer 2, 62861-48-7; **5**, 57740-57-5; **6**, 57740-58-6; **7a**, 57740-59-7; **7b**, 57740-60-0; **8a**, 57740-61-1; **8b**, 57740-62-2; 2-amino-2-methylpropanol, 124-68-5; methyl 7-bromoheptanoate, 54049-24-0; dimethyl (2-oxoheptyl)phosphonate, 36969-89-8.

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Use of Insoluble Polymer Supports in Organic Synthesis. 9. Synthesis of Unsymmetrical Carotenoids on Solid Phases[1]

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Carotenoids have been synthesized by many routes.[2] One of the most attractive routes to *symmetrical* carotenoids, such as β-carotene, is the $C_{15} + C_{10} + C_{15}$ approach,[3] whereby 2 mol of a suitable C_{15} Wittig reagent reacts with the *symmetrical* C_{10} dialdehyde, 2,7-dimethyl-2,4,6-octatrien-1,8-dial (**1**).[4] This approach has also been used in the synthesis of *unsymmetrical* carotenoids such as γ-carotene, whereby the symmetrical dialdehyde **1** first reacts with one C_{15} Wittig reagent to yield the product from reaction at just one end of the aldehyde, namely an apocarotenal.[3,5,6] All these cases give apocarotenals or their analogues <60% yield and in some cases under 5% yield.[6] Subsequent reaction of the apocarotenal with a second C_{15} Wittig reagent yields the unsymmetrical carotenoid. Alternatively, the symmetrical dialdehyde **1** can react with a 1:1 mixture of two different C_{15} Wittig reagents to give unsymmetrical carotenoids contaminated with large quantities of symmetrical carotenoids.[6] The unsymmetrical carotenoids are formed in moderate to poor yields by solution methods due to the formation of substantial amounts of symmetrical products and recovery of unreacted reagents. The pure products are then obtained only after careful chromatography.

Table I. Yields of Apocarotenals and Analogues Prepared on Solid Phases

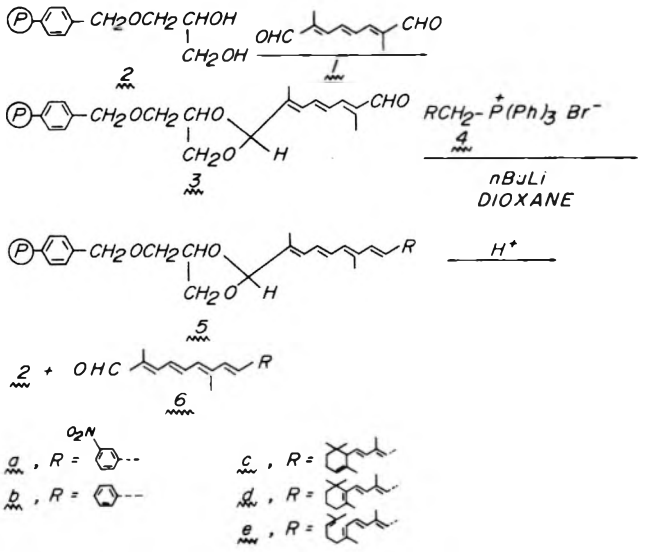
Apocarotenal or analogue	Registry no.	Quantity of 1 bound to 3, mmol/g	Quantity of apocarotenal or analogue, mmol/g	Yield, %
6a	62930-48-7	0.26	0.182	70
6b	62930-49-8	0.26	0.22	86
6c	62948-59-8	0.195	0.195	100[a]
6d	1638-05-7	0.195	0.056	29
6e	1071-52-9	0.195	0.140	72[a]

[a] The literature yields[3] by solution methods were 45 and 52% for **6c** and **6e**, respectively.

In our laboratory, we have shown that insoluble polymer supports[7] can be used as monoblocking groups for symmetrical diols and have applied this advantage to the synthesis of insect sex attractants.[8] Similarly, polymer-bound 1,2- and 1,3-diols have been used as monoblocking agents of symmetrical aromatic dialdehydes,[9,10] although attempted monoprotection of symmetrical aliphatic dialdehydes failed.[10] In any event, the completely conjugated symmetrical dialdehyde **1** reacted with the previously prepared 2% cross-linked divinylbenzene–styrene copolymer **2**,[9] containing vicinal diol groups, in anhydrous dioxane containing *m*-benzenedisulfonic acid as catalyst. This product gave the monoblocked polymer-bound aldehyde **3**, which exhibited an absorption in its IR spectrum at 1680 cm^{-1}. Cleavage of the aldehyde from the polymer in 0.5 N HCl in wet tetrahydrofuran (THF) led to recovered **1** and **2**, the latter exhibiting no absorption in the carbonyl region of its IR spectrum. Based on recovered **1**, the capacity of **3** was 0.2–0.3 mmol of **1**/g. Condensation of **3** with the Wittig reagent prepared from *m*-nitrobenzyltriphenylphosphonium bromide (**4a**) and base[11] yielded the polymer-bound Wittig product **5a**, exhibiting IR absorption bands at 1530 and 1350 cm^{-1} typical of the nitro group. Indeed, as IR spectroscopy remains one of the few tools by which reactions can be followed on polymer supports, the nitro-Wittig reagent was carefully selected in the first instance in order to follow the progress of this synthetic route. Thus, in this reaction a polymer-bound product **5a** containing a diagnostic IR absorption band was obtained. Acid hydrolysis of **5a** gave the mono Wittig adduct, 2,7-dimethyl-9-(*m*-nitrophenyl)-2,4,6,8-nonatetraen-1-al (**6a**) in good yield (Table I). Similarly, the Wittig reagent, prepared from benzyltriphenylphosphonium bromide (**4b**)[11] gave the polymer-bound product **5b**, which on acid cleavage yielded 2,7-dimethyl-9-phenyl-2,4,6,8-nonatetraen-1-al (**6b**) in high yield (Table I).

The Wittig reagents, prepared from α[3], β[12], and ψ-ionylideneethyltriphenylphosphonium bromides[3] and *n*-butyllithium, respectively, reacted with polymer-bound aldehyde **3** in anhydrous dioxane to give the polymer-bound apocarotenals **5c**, **5d**, and **5e**, respectively. Cleavage of **5c–e** under acidic conditions led to α-apo-12′-carotenal (**6c**),[3] β-apo-12′-carotenal (**6d**),[13] and apo-12′-lycopenal (**6e**)[3] in good yields (Table I). The formation of **6d** was accompanied by the recovery of 64% of unreacted dialdehyde **1**, but no dialdehyde

Scheme I



1 was recovered in the synthesis of **6a, 6b, 6c,** and **6e.** As apocarotenals have been previously converted to unsymmetrical carotenoids,[3] the above procedure represents an improved procedure for the total synthesis of unsymmetrical carotenoids. The almost quantitative formation of the Wittig product in one instance, the generally high yields of the Wittig products (except for **6d**), and the general lack of recovery of starting dialdehyde 1 upon isolation of the Wittig products precludes the possibility that symmetrical dialdehyde 1 was initially bound to the polymer at both ends; thus, we feel that 1 was almost exclusively monoblocked by polymer **2.**

In conclusion, the synthesis of apocarotenoids can be readily achieved from the symmetrical dialdehyde 1 in high yield by using insoluble polymer supports without concomitant formation of symmetrical by-products and the recovery of starting material. This procedure represents a useful addition to the repertoire of synthetic procedures for the preparation of unsymmetrical carotenoids.

Experimental Section

All melting points were determined on a Kofler hot stage and are uncorrected. Infrared spectra were recorded on a Unicam SP1000 IR spectrophotometer using KBr disks unless otherwise stated. Ultraviolet spectra were measured using a Unicam SP800A UV spectrometer. The NMR spectra were measured on a Varian A60 spectrometer using tetramethylsilane as an internal standard (δ 0) and deuteriochloroform as solvent. Mass spectra were recorded on a Hitachi-Perkin-Elmer RMU-6 mass spectrometer. The number in brackets after the indicated ion shows the percent of the base peak represented by that ion. Silica gel was used for thin- and thick-layer chromatography. Microanalyses were performed by G. Gygli of Toronto. Filtering procedures were done under vacuum using a sinterglass funnel. All the stirring described below was performed using a Fisher magnetic stirrer.

Preparation of Polymer-Bound Aldehyde 3. Excess symmetrical dialdehyde 1 (4.0 g, 0.024 mol) and polymer **2** (8.5 g) in 120 mL of dioxane, containing anhydrous sodium sulfate (2.0 g) and *m*-benzenedisulfonic acid (0.5 g), were stirred under argon for 48 h in a 250-mL round-bottom flask fitted with a septum cap. The light yellow product **3** was isolated by a procedure previously described.[9] The infrared spectrum of **3** exhibited an absorption at 1680 cm^{-1} (m) typical of a conjugated aldehyde.

Determination of the Quantity of Dialdehyde 1 Bound to Polymer Aldehyde 3. Polymer-bound aldehyde **3** (0.5 g) was suspended in a solution of 0.5 N anhydrous HCl and wet THF and stirred for 48 h under argon. The polymer was filtered and washed six times with 10-mL portions of water, six times with acetone (10 mL), three times with ethanol (10 mL), and three times with ether (10 mL). The filtrate was extracted with ether–tetrahydrofuran, washed with water, dried ($MgSO_4$), and evaporated to give crude 1. This product on preparative TLC (ether–benzene 3:7) yielded pure recovered dialdehyde 1 (21 mg, 0.13 mmol), which represents a loading capacity of 0.26 mmol of 1/g of polymer **3.** Recovered polymer **2** did not exhibit a residual absorption at 1680 cm^{-1}, indicative of uncleaved polymer-bound aldehyde **3.**

General Procedure for the Preparation of Apocarotenoids from Polymer-Bound Aldehyde 3. In a typical procedure, an excess of the Wittig precursor α-ionylideneethyltriphenylphosphonium bromide (**4c**) (1.75 g, 3.2 mmol) was added to 20 mL of anhydrous dioxane in a 50-mL round-bottom flask, fitted with a Claisen adapter. Polymer-bound aldehyde **3** (2.0 g, containing 0.39 mmol of 1) was added to the side arm of the adapter. The flask was tilted so that the polymer did not fall into the flask. The two outlets of the Claisen adapter were fitted with septum caps. The stirred solution was purged with argon and 2 mL of 1.6 M *n*-butyllithium in hexane was added dropwise through the septum with a syringe. The solution was stirred for an additional 5 min, polymer **3** was washed into the reaction flask with 20 mL of anhydrous dioxane, and the suspension stirred under argon for 24 h. The polymer was filtered and washed three times with 20-mL portions each of dioxane–water (1:1), water, methanol, and ether. The orange-brown polymer-bound Wittig product (**5c**) did not exhibit an absorption band at 1680 cm^{-1} in its IR spectrum, indicative of unreacted **3.** In the preparation of **5e,** however, some residual absorption at 1680 cm^{-1}, due to unreacted **3,** was observed.

Isolation of the apocarotenals was achieved by acid cleavage of the polymer-bound Wittig products as described for the determination of 1 in **3.** Purification of the filtrate by preparative TLC (ether–benzene 1:7) gave the known apocarotenals **6c–e** in yields outlined in Table I.

2,7-Dimethyl-9-(*m*-nitrophenyl)-2,4,6,8-nonatetraen-1-al (6a) and 2,7-Dimethyl-9-phenyl-2,4,6,8-nonatetraen-1-al (6b). Polymer **3** (2.0 g), containing 0.52 mmol of 1, was treated with **4a** (4.8 g, 10 mmol) in a Wittig reaction as described above. The polymer-bound Wittig product **5a** was cleaved under acidic conditions similar to that for the cleavage of **3.** Purification by preparative TLC (ether–benzene 1:10) gave 103 mg (yield, Table I) of pure **6a** as deep red crystals: mp 60–63 °C; UV (THF) λ_{max} 378 and 398 nm (ϵ 24 650 and 21 750); IR 1657 (aldehyde, C=O) 1530 (NO_2), 1350 (NO_2), and 961 (trans CH=CH) cm^{-1}; NMR δ 9.50 (s, 1, aldehyde proton), 8.35–7.2 (m, 4, aromatic protons), 7.1–6.1 (m, 6, olefinic protons), 2.05 (s, 3, 2-methyl protons), and 1.88 (s, 3, 7-methyl protons); mass spectrum *m/e* 283 (100) (M^+), 254 (15), 145 (33).

Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.88; H, 6.31; N, 4.78.

Similarly, treatment of **3** (1.0 g, containing 0.26 mmol of 1) with **4b** (2.2 g, 5 mmol) yielded **5b,** which on acid cleavage and purification yielded 53 mg (yield, Table I) of pure **6b** as orange crystals: mp 62–64 °C; UV (cyclohexane) λ_{max} 364, 383, and 402 nm (ϵ 14 360, 19 880, and 16 500); IR 1668 (aldehyde, C=O) and 960 (trans CH=CH) cm^{-1}; NMR δ 9.45 (s, 1, aldehyde proton), 7.4–7.3 (m, 5, aromatic protons), 7.1–6.1 (m, 6, olefinic protons), 2.05 (s, 3, 2-methyl protons), and 1.88 (s, 3, 7-methyl protons); mass spectrum *m/e* 238 (100) (M^+), 209 (15), 147 (27).

Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.23; H, 7.96.

Acknowledgment. The authors wish to thank the National Research Council of Canada for a grant in aid of this research.

Registry No.—**1,** 5056-17-7; **4a,** 1530-41-2; **4b,** 1449-46-3; **4c,** 62930-50-1; **4d,** 62285-98-7; **4e,** 59060-56-9.

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Analysis of the Stereochemical Integrity at C_α in Sequences Employing Ketone Tosylhydrazones

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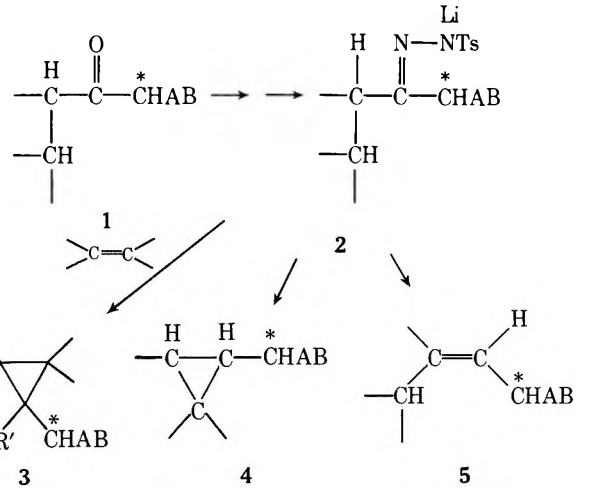
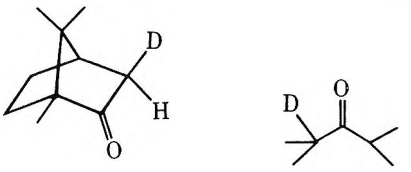
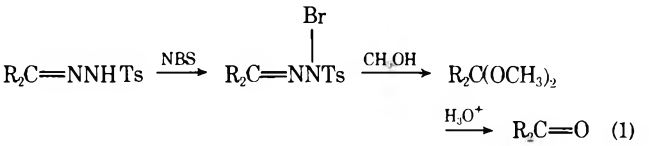
The tosylhydrazones of ketones and their alkali metal salts are most useful synthetic intermediates. Ketones generally may be readily converted in high yields to alkali metal salts of tosylhydrazones (**2**). Pyrolysis or photolysis may be used to create either an alkene (**5**) or cyclopropane (**4**) species in an intramolecular process or a cyclopropane adduct (**3**) as a consequence of an intermolecular reaction with an olefin.[1] In mechanistic studies of carbene intermediates ketone tosylhydrazones and their alkali metal salts usually represent the most readily available precursors for the generation of dialkyl carbenes. In either a synthetic or mechanistic application the preservation of stereochemical integrity at the α position may be of paramount importance. Conversion of a ketone to tosylhydrazone (H_2NNHTs, H^+) and then to lithium salt (CH_3Li) might very well alter the stereochemical environment at C_α through enolization. One convenient method to check on this might involve the reconversion of ketone tosylhydrazone salt **2** to ketone **1**, using a procedure which is mild enough not to cause additional enolization.



We chose to consider *exo*-3-deuteriocamphor[2] (**6**) and 4-deuterio-2,4-dimethyl-3-pentanone (**7**) as representative ketone substrates and cleavage using pyruvic acid catalysis[3] or the method of Rosini (*N*-bromosuccinimide)[4] (eq 1). Since





the *exo*-3-deuterium should be lost in preference to *endo*-3-hydrogen in the case of *exo*-3-deuteriocamphor,[2,5] deuterium loss from either **6** or **7** should be a sensitive measure of enolate formation.

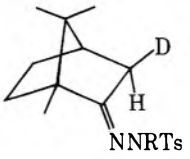
The deuterium content of ketones **6** and **7** was determined and both were converted to tosylhydrazone (**8a** and **9**). Analysis of cleavage back to ketone from tosylhydrazone (**8a**, **9**) or lithium salt of tosylhydrazone (**8b**) (Table I) clearly demonstrates that the *N*-bromosuccinimide method is an eminently suitable method to check the stereochemical integrity at C_α in tosylhydrazone intermediates.

Experimental Section

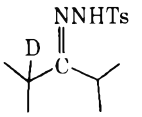
Melting points were obtained using either a Buchi melting point apparatus or a Mel-Temp device and are uncorrected. NMR spectra were recorded at 100 MHz with a Varian HA-100 or at 60 MHz with a Varian Anaspect EM-360. Infrared spectra were obtained with either a Beckman IR-8 or a Perkin-Elmer Model 621. Vapor-phase chromatographic analyses were carried out using a Varian Aerograph A-90-P, an 18 ft × 1/4 in. 5% OV-17 on 60/80 chromosorb G column; yields were determined using *p*-cymene as an internal standard.

Deuterium analyses were accomplished by a low-voltage, mass-spectral technique using a Varium MAT CH-7 spectrometer, inter-

Table I. Reconversion of Ketone Tosylhydrazones to Parent Ketone



8a, R = H
b, R = Li



9

Cleavage method		Pyruvic acid	NBS	NBS
% yield		75	70	93
D content of initial ketone	D_0	7.0 ± 0.4[a]	7.0 ± 0.4	27.4 ± 0.6
	D_1	79.3 ± 0.4	79.3 ± 0.4	49.1 ± 0.6
	D_2	13.7 ± 0.3	13.7 ± 0.3	23.5 ± 0.5
D content of final ketone from reconversion of 8a or 9	D_0	63.1 ± 1.0	7.1 ± 0.4	27.7 ± 1.1
	D_1	32.8 ± 1.0	79.2 ± 0.4	49.8 ± 1.1
	D_2	4.1 ± 0.5	13.7 ± 0.2	22.5 ± 0.9
D content of ketone from reconversion of 8b	D_0		7.4 ± 0.4	
	D_1		78.8 ± 0.6	
	D_2		13.8 ± 0.8	

[a] Standard deviation.

faced with a pdp-8/m computer. Before analyzing a deuterated sample, the nondeuterated sample was run to determine the exact intensities of P, P + 1, and P + 2 at a voltage which eliminated the P − 1 peak (usually 18–20 eV). The molecular ion region was scanned 10–20 times; the mean and standard deviation are reported.

Spectral grade $CDCl_3$ was supplied by Merck, Sharp, and Dohme, CCl_4 by Mallinckrodt, D_2O by Stohler Isotope Chemicals. Pyruvic acid was purified by distillation in vacuo using a Kugelrohr distillation apparatus.

4-Deuterio-2,4-dimethyl-3-pentanone. CH_3OD was prepared by the general method of Streitwieser.[6] Using carefully dried apparatus, a solution prepared from 15 mL of CH_3OD, 3.0 g (0.026 mol) of ketone, and 0.08 g of Na was stirred for 9 h at room temperature. The solution was then quenched with D_2O, extracted with ether, washed with H_2O, and dried over $MgSO_4$; NMR (CCl_4) δ 2.7 (heptet, 0.9 H, J = 7 Hz), 1.06 (m, 12 H); mass spectrum % D_0 = 27.4 ± 0.6, % D_1 = 49.1 ± 0.6, % D_2 23.5 ± 0.5.

4-Deuterio-2,4-dimethyl-3-pentanone Tosylhydrazone. Ketone (2.2 g, 0.019 mol), tosylhydrazine (3.59 g, 0.019 mol), 40 mL of ethanol (95%), and 1 drop of concentrated HCl were combined and the resulting solution placed on a steam bath for 4 h. The solvent was largely removed by evaporation. Refrigeration produced 3.5 g (65%) of a white crystalline solid which was used without further purification, mp 95–99 °C. An analytical sample of undeuteriated tosylhydrazone had mp 106.9–108.7 °C.

Anal. Calcd for $C_{14}H_{22}N_2O_2S$: C, 59.54; H, 7.85. Found: C, 59.66; H, 7.87.

3-Deuteriocamphor. An adaptation of the procedure of Tidwell[5d] was used. In a dry 250-mL round-bottom flask, 60 mL of reagent grade dioxane and 30 mL of D_2O were combined. The flask was cooled to 0 °C, and 0.08 g of Na was added in three portions. The ice bath was removed and the solution was allowed to come to room temperature. Camphor (2.0 g.) was dissolved in 5 mL of dioxane and then added to the above solution. After 30 h of stirring, the solution was extracted with ether, washed with H_2O, and dried over $MgSO_4$; mass spectrum % D_0 = 7.0 ± 0.4, % D_1 = 79.3 ± 0.4, % D_2 = 13.7 ± 0.3.

The Tosylhydrazone (8a) and the Lithium Salt of the Tosylhydrazone (8b) of *exo*-3-Deuteriocamphor. Tosylhydrazone **8a** was prepared as described above for 2,4-dimethyl-3-pentanone, giving a 75% yield, mp 157–159 °C.[7] The lithium salt of tosylhydrazone **8a** (**8b**) was prepared by treating **8a** (0.2916 g, 0.908 mmol) in 10 mL of THF with 1 equiv of methyllithium (2 M solution in THF). The lithium salt **8b** was then reconverted to tosylhydrazone by neutralization with 0.1 N acetic acid. This mixture was extracted with ether, washed with water, and dried ($MgSO_4$); evaporation of solvent gave an 80% recovery of **8a**.

The Tosylhydrazone to Ketone Conversion Using *N*-Bromosuccinimide. This procedure is an adaptation of the method of Rosini.[4] Tosylhydrazone (10^{-4} mol) and internal standards, if desired, were dissolved in a mixture of 14 mL of acetone and 4 mL of water. When dissolution was complete, the mixture was cooled to 0 °C using an ice/water bath. *N*-Bromosuccinimide (4×10^{-4} mol) was then added. Stirring, using a magnetic stirring bar, was continued for 2 min. (Evolution of N_2 was apparent after 10–15 s, and the resulting solution was yellow.) The reaction was quenched with 1–2 mL of saturated sodium bisulfite. The ice bath was removed and the stirring continued while adding ca. 10 mL of water. The ketone was extracted with ether and the combined organic extracts were washed with water, 10% Na_2CO_3, water, and then dried over $MgSO_4$.

The Tosylhydrazone to Ketone Conversion Using Pyruvic Acid. Tosylhydrazone (10^{-4} mol) was combined with 10^{-4} mol of *p*-cymene (internal standard), 4 mL of glacial acetic acid, 1 mL of water, and 0.5 g of purified pyruvic acid. The solution was heated at reflux for 2 h. After cooling, it was extracted with ether, washed with water, 10% Na_2CO_3, water, and finally dried over $MgSO_4$. Yields were typically ca. 75%.

Registry No.—**6**, 27808-88-4; **7**, 60877-43-2; **8a**, 62930-36-3; **8b**, 62930-37-4; **9**, 62930-38-5; CH_3OD, 1455-13-6; 2,4-dimethyl-3-pentanone, 565-80-0; tosylhydrazine, 1576-35-8; camphor, 76-22-2.

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Gas Chromatographic Analysis of Ortho Esters as a Convenient New General Method for Determining the Enantiomeric Purities of Chiral δ-Lactones

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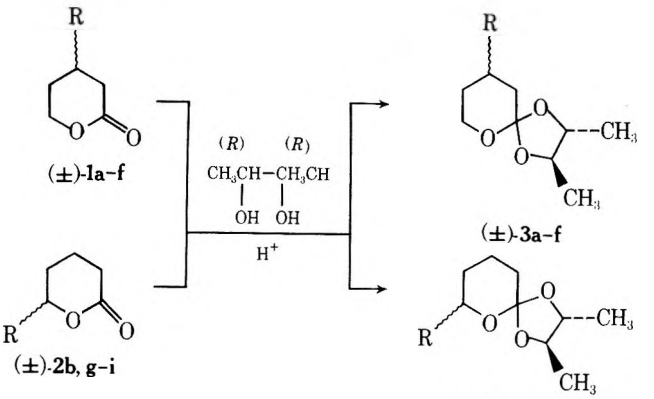
The rapid developments being made in the area of asymmetric synthesis have increased the demand for methods of measuring enantiomeric purities. The traditional dependence on optical rotation comparisons for this purpose is well recognized to be unreliable at times and techniques permitting enantiomeric excesses to be measured directly are much to be preferred. Determination of optical purities by NMR analysis, either of appropriate diastereomeric derivatives[1] or in the presence of chiral shift reagents,[2] has proven to be the most powerful of the generally applicable approaches to the problem. However, at the present time there are many compounds whose enantiomeric purities cannot be readily evaluated by the NMR techniques because the preferred structural features or functionalities are absent. Lactones of the type **1a,d,e**,[4a]

Scheme I



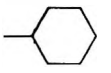
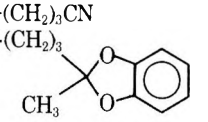
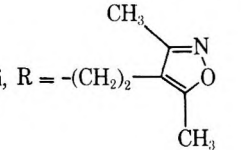
a, R = Me
b, R = Et
c, R = *n*-Pr
d, R = *i*-Pr
e, R = C_6H_5
f, R = 
g, R = $-(CH_2)_3CN$
h, R = $-(CH_2)_3$ 
i, R = $-(CH_2)_2$ 

Table I. Diastereomeric Ortho Ester Mixtures

Compd[a]	Method[b]	Yield, %[c]	Formula[d]	GC retention times, min[e]		Column temp, °C
3a	A	52	$C_{10}H_{18}O_3$	6.30	6.89	100
3b	A	73	$C_{11}H_{20}O_3$	8.90	9.55	110
3c	A	57	$C_{12}H_{22}O_3$	9.91	10.69	120
3d	A	50	$C_{12}H_{22}O_3$	8.97	9.82	125
3e	A	54	$C_{15}H_{20}O_3$	17.20	18.50	165
3f	A	43	$C_{15}H_{26}O_3$	16.20	17.30	155
4b	A	60[h]	$C_{11}H_{20}O_3$	2.18[i]	2.47[i]	220
4g	B	62	$C_{13}H_{21}NO_3$	5.25	5.76	220
4h	A	60[h]	$C_{20}H_{28}O_5$	13.08	14.24	220
4i	A	53[h]	$C_{16}H_{25}NO_4$	13.25	14.51	220
4i	B	86[f,h]		84.60[g]	85.60[g]	

[a] All ortho ester mixtures prepared from racemic lactone. [b] See Experimental Section. [c] Data refer to ortho ester mixtures purified by column chromatography. [d] Microanalyses within ±0.3% of theory (C, H) (also N in the case of **4g** and **4i**) were obtained for these compounds. [e] The observed ratios of diastereomers were within 3% of the expected 50:50 relative proportions. [f] Reaction mixture heated for a total of 19 h. [g] Analysis performed on a 3 m, 10% OV-101 column packed on GCQ 100/120 mesh with a temperature program of 2 °C/min over 80–260 °C; N_2 carrier gas flow rate 30 mL/min. [h] Purified by chromatography on alumina (method B) rather than silica gel. [i] Retention times of 37 and 40 min, respectively, observed when analysis was carried out using a 3 m × 0.4 mm (i.d.) column of 10% OV-17, at 130 °C, N_2 carrier gas flow rate of 30 mL/min; these conditions were employed for analyzing the sample derived from (−)-(*S*)-**2b**.

1b,c,f,[4b] **2b,**[3a] **2g,**[3b] **2h,**[3c] and **2i**[3d] are in this category and our interest in developing chemical[3] and enzymic[4] methods for preparing such compounds in optically active form prompted us to seek alternative methods of establishing their enantiomeric purities. In this paper we describe a convenient GC analytical technique which permits enantiomeric excesses of variously substituted chiral δ-lactones to be accurately measured.[5]

The method involves conversion of the lactones to their ortho esters with (−)-(2*R*,3*R*)-2,3-butanediol as shown in Scheme I, followed by GC analysis of each mixture of diastereomers.[6] Of the methods available for effecting this type of condensation,[9-13] *p*-toluenesulfonic acid catalyzed dehydration in refluxing benzene was used first (method B). Subsequently, it was found that the reaction could also be carried out under milder conditions, viz. with sulfuric acid catalysis in tetrahydrofuran at room temperature in the presence of triethyl orthoformate (method A).

Good (~40–85%) yields[14] of the ortho esters were obtained from each of the Scheme I lactones and each pair of diastereomers were easily and quantitatively resolvable by GC. The results are summarized in Table I. From the peak area ratios observed, the accuracy of this method of enantiomeric purity determination is generally ≤±3%. Furthermore, the approach lends itself to preparative scale applications. This was demonstrated by the isolation of both diastereomers of **4g** by preparative GC.

One example of an enantiomerically enriched δ-lactone was examined. Thus, (−)-(*S*)-**2b** of estimated 85% optical purity,[3a] upon reaction with (−)-(2*R*,3*R*)-2,3-butanediol (method A), furnished ortho ester **4b**, whose GC analysis revealed a diastereomer ratio of 94.5:5.5 corresponding to an optical purity of 89% for the starting lactone. The observed peaks were identical with those derived from (±)-**4b** by coinjection, the major diastereomer (*R,R,S*) exhibiting the greater retention time. In order to provide assurance that racemization of the 5-substituted δ-lactones does not occur under the conditions of ortho ester formation, this highly enriched ortho ester sample was hydrolyzed to lactone (dilute H_2SO_4, acetone, room temperature), which was then reconverted to **4b** under vigorous conditions (method B). GC analysis of the ortho ester so obtained revealed a composition virtually identical with that of the initial **4b**, specifically 94.2% (*R,R,S*) and 5.8% (*R,R,R*), indicating that alteration of the initial δ-lactone composition is not observed under the acidic conditions employed for derivatization.

The above method of enantiomeric purity determination is clearly applicable to a broad structural range of chiral δ-lactones[15] and is now in routine use for this purpose in our laboratories.

Experimental Section

D-(−)-(2*R*,3*R*)-2,3-Butanediol was prepared by the method of Watson et al.[17] It is also available from Aldrich. NMR analyses were performed in $CHCl_3$ on Varian A-60, T-60, or HA-100 spectrometers with Me_4Si as internal standard. GC analyses were carried out using an F&M 400 chromatograph equipped with a 4 mm × 1 m glass column of 3% QF-1 on Chromosorb G, 80–100 mesh (for **3a–f**), and a Hewlett-Packard 402 instrument using a 6 mm × 1 m glass column of 10% XE-60 on Chromosorb W, 80–100 mesh (for **4b,g–i**). All GC analytical results are recorded in Table I.

Representative Experimental Procedures. (A) Trimethyl Orthoformate Method. Preparation of (2*R*,3*R*,9(*R,S*))-2,3,9-Trimethyl-1,4,6-trioxaspiro[4.5]decane ((±)-3a). To 3-methylvalerolactone[4] [(±)-**1a**, 228 mg, 2 mmol] in dried (with $LiAlH_4$)tetrahydrofuran (5 mL) was added, under nitrogen, D-(−)-2,3-butanediol [$[\alpha]_D$ −12.95° (neat), 270 mg, 3 mmol], trimethyl orthoformate (318 mg, 3 mmol), and 3 drops of concentrated sulfuric acid. The mixture was stirred at room temperature (21 °C) for 24 h and then treated with triethylamine (0.5 mL) and poured into saturated aqueous sodium bicarbonate. (Alternatively, solid sodium bicarbonate may be used.) The mixture was then extracted three times with benzene and the benzene extracts washed first with aqueous sodium bicarbonate, then with brine, and finally dried over anhydrous $MgSO_4$ or Na_2SO_4. Rotary evaporation of the solvent afforded a yellow oil (341 mg) suitable for direct GC analysis. It was purified by passing through silica gel (50 g, 60–200 mesh); elution with hexane–acetone (9:1) followed by evaporative distillation (0.1–0.2 Torr) yielded (±)-**3a** (192 mg, 52%): NMR δ 0.99 (d, 3 H, *J* = 6.0 Hz), 1.10–2.05 (m, 5 H), 1.30 (d, 6 H, *J* = 6.0 Hz), and 3.53–4.25 (m, 4 H).

(B) With *p*-Toluenesulfonic Acid. Preparation of [2*R*,3*R*,7(*R,S*)]-7-(3′-Cyanopropyl)-1,4,6-trioxaspiro[4.5]decane ((±)-4g). To a stirring solution of the lactone (±)-**2g**[3b] (3.3 g, 20 mmol) in benzene (85 mL) were added, under nitrogen, D-(−)-2,3-butanediol (2.14 g, 24 mmol) and *p*-toluenesulfonic acid (0.1 g, 0.5 mmol). The mixture was refluxed using a Dean–Stark trap. More *p*-toluenesulfonic acid (0.1 g) and D-(−)-2,3-butanediol (1.05 g, 12 mmol) were added after 1.5 and 2.4 h, respectively. After heating under reflux for a further 2 h the mixture was cooled and neutralized with triethylamine (1 mL) and powdered sodium bicarbonate (0.5 g). It was then poured into saturated aqueous sodium bicarbonate and was extracted three times with benzene. The combined extracts were washed (aqueous sodium bicarbonate followed by brine), dried (Na_2SO_4), and concentrated to give 4.2 g of a light yellow oil. The crude product was purified by passing through a column of alumina (grade III, 125 g). Fractions eluted with 4:1 hexane–ether yielded 2.93 g (62%) of (±)-**4g**, which was evaporatively distilled (0.05–0.2 Torr):

NMR δ 1.26, 1.31 (2d, 6 H, J = 6.0 and 5.5 Hz), 1.41–1.89 (m, 10 H), 2.35 (br t, 2 H), 3.54–4.16 (m, 3 H).

Isolation of the two diastereoisomers was achieved using a Varian Autoprep 705 gas chromatograph with a 9 mm × 2 m aluminum column of KOH-modified 20% polyethylene glycol 20M on Chromosorb W (60–80 mesh). The column temperature was held at 230 °C for 75 min and then was increased to 240 °C. A nitrogen flow rate of 150 mL/min was maintained throughout. The two samples obtained were chromatographed separately on alumina (grade III). Fractions eluted with 2:1 hexane–ether contained the pure products: NMR (diastereomer I) δ 1.28 (2d, 6 H, J = 5.5 Hz), 1.41–1.96 (m, 10 H), 2.33 (br t, 2 H), and 3.55–3.91 (m, 3 H); NMR (diastereomer II) δ 1.26 (d, 6 H, J = 6.0 Hz), 1.42–1.96 (m, 10 H), 2.32 (br t, 2 H), and 3.56–4.21 (m, 3 H).

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Registry No.—(±)-**1a**, 62989-38-2; (±)-**1b**, 62989-39-3; (±)-**1c**, 62948-63-4; (±)-**1d**, 21754-22-3; (±)-**1e**, 61949-75-5; (±)-**1f**, 62948-64-5; (±)-**2b**, 35221-77-3; (±)-**2g**, 35337-27-0; (±)-**2h**, 30665-84-6; (±)-**2i**, 28458-39-1; **3a** isomer 1, 62948-65-6; **3a** isomer 2, 62989-40-6; **3b** isomer 1, 62948-66-7; **3b** isomer 2, 62989-41-7; **3c** isomer 1, 62948-67-8; **3c** isomer 2, 62989-42-8; **3d** isomer 1, 62948-68-9; **3d** isomer 2, 62989-43-9; **3e** isomer 1, 62948-69-0; **3e** isomer 2, 62989-44-0; **3f** isomer 1, 62948-70-3; **3f** isomer 2, 62989-45-1; **4b** isomer 1, 62948-71-4; **4b** isomer 2, 62989-46-2; **4g** isomer 1, 62948-72-5; **4g** isomer 2, 63038-29-9; **4h** isomer 1, 62948-73-6; **4h** isomer 2, 62989-47-3; **4i** isomer 1, 62948-74-7; **4i** isomer 2, 62989-48-4; (−)-(2R,3R)-2,3-butanediol, 24347-58-8.

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(14) When the yield of any such reaction is less than quantitative, the possibility always exists that rate differences in the reaction of the individual enantiomers may result in the formation of unequal amounts of the diastereomeric products. That this reservation does not apply here is indicated by the fact that the proportions of each diastereomeric pair of ortho esters was within 3% of the 1:1 ratio expected from using racemic lactone precursors. The last entry demonstrates that, if desired, yields very close to quantitative can be attained using method B.
(15) Attempts to extend the analysis to chiral γ-lactones using a variety of ortho ester synthetic methods[9–13] have not been successful.[16] Recently, an NMR method for determination of enantiomeric composition of γ-lactones was published: W. H. Pirkle, D. L. Sikkenga, and M. S. Pavlin, *J. Org. Chem.*, **42**, 384 (1977); W. H. Pirkle and D. L. Sikkenga, *ibid.*, **42**, 1370 (1977).
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The Pomeranz–Fritsch Reaction, Isoquinoline vs. Oxazoles

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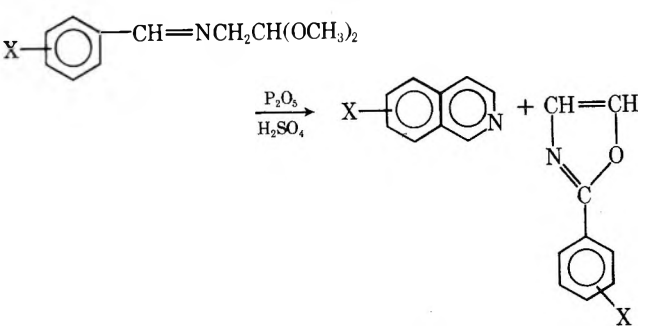
The Pomeranz–Fritsch reaction has been used for the preparation of a number of isoquinolines with varying yields.[1] As ordinarily carried out it involves the condensation of benzal aminoacetal to the isoquinoline. The yield varies from quite good with certain methoxy substituents to zero with nitro groups; in the latter case, the products are oxazoles.[2,3]



In this work we report the percent of oxazole formed with methyl, chloro, and nitro groups present in the original benzaldehyde. The Pomeranz–Fritsch reaction has been run with both o- and p-tolualdehyde. The yield of 8-methylisoquinoline in the first case is 18% and of 6-methylisoquinoline in the second case is 21%. We have also run the reaction with m-tolualdehyde and have obtained a yield of crude mixed 5- and 7-methylisoquinolines of 22%. A very careful search for 2-(tolyl)oxazole by chromatography and mass spectra analysis has shown yields of 3, 1, and 6%, in the cases of o-, m-, and p-tolaldehydes in the crude isolated products.

When acetals of the three chlorobenzaldehydes were subjected to conditions of the Pomeranz–Fritsch reaction, the oxazole production became appreciable. In the case of ortho it was 36% of the crude product isolated, in meta 23%, and in para 61%. The acetals of o-, m-, and p-nitrobenzaldehyde were cyclized and the yields were 54, 50, and 40%, respectively, of oxazole with no evidence for any isoquinoline. The three 2-nitrophenyloxazoles were then reduced and the amino compounds subjected to Sandmeyer[4] reactions to give the corresponding chloro compounds. These were then compared to the chlorophenyloxazoles formed by direct Pomeranz–Fritsch reaction (Table I).

Experimental Section

Separations were carried out on a Hewlett-Packard 5750 chromatograph with a 20 ft × ¼ in. column filled with Carbowax M on Anakrom 50/60 AB.

2-(x-Nitrophenyl)oxazoles. 2-(p-Nitrophenyl)oxazole (mp 163–164 °C) and 2-(o-nitrophenyl)oxazole (mp 43–46 °C) were prepared by the method of Cass and co-workers.[2,3] Heating 100 g (0.67 mol) of m-nitrobenzaldehyde and 70 g (0.67 mol) of dimethyl aminoacetal to 100 °C for 2 h and cooling gave a crude m-nitrobenzal aminoacetal. Twenty grams of this was dissolved in 100 mL of concentrated H_2SO_4, and poured into 40 g of P_2O_5 and 10 mL of H_2SO_4 at 180 °C and heated for 20 min. The solution was cooled and neutralized with NH_4OH to give 9 g (56%) of crude oxazole, mp 96–98 °C. Recrystallization from ethanol gave material with mp 97–98 °C, m/e (M^+) 190. Anal. Calcd for $C_9H_6N_2O_3$: C, 56.84; H, 3.15. Found: C, 56.88; H, 3.20.

2-(x-Aminophenyl)oxazoles. All three of the nitrophenyloxazoles above were hydrogenated in methanol with 10% Pd–C. 2-(o-Aminophenyl)oxazole[2] (mp 32–33 °C), 2-(p-aminophenyl)oxazole[3] (mp 121–123 °C), and the new 2-(m-aminophenyl)oxazole (mp 69–70 °C) were obtained.

Table I

Starting benzaldehyde	Registry no.	Isoquinoline	Registry no.	Pomeranz–Fritsch vs. oxazole: Total mixed, %	Pomeranz–Fritsch vs. oxazole: Oxazole/ isoquinoline	Registry no. of oxazole
o-Methyl	529-20-4	8-Methyl[5]	62882-00-2	18	3/97	62882-03-5
p-Methyl	104-87-0	6-Methyl[5]	42398-73-2	21	6/94	62882-04-6
m-Methyl	620-23-5	5- + 7-Methyl	62882-01-3 (5) 54004-38-5 (7)	22	6/94	62882-05-7
o-Chloro	89-98-5	8-Chloro[6]	34784-07-1	9	36/64	62881-98-5
p-Chloro	104-88-1	6-Chloro	62882-02-4	25–50	61/39	46047-24-9
m-Chloro	587-04-2	5- + 7-Chloro[7]	5430-45-5 (5) 34784-06-0 (7)	14	23/77	62882-06-8
o-Nitro	552-89-6			All oxazole[2]		62882-07-9
m-Nitro	99-61-6			All oxazole		35582-07-1
p-Nitro	555-16-8			All oxazole[6]		62882-08-0

Anal. Calcd for $C_9H_8N_2O$: C, 67.50; H, 5.00. Found: C, 67.49; H, 5.10.

2-(x-Chlorophenyl)oxazoles. The three aminophenyloxazoles (3-g samples) were subjected to Sandmeyer reactions.[4] 2-(*m*-Chlorophenyl)oxazole (mp 34–35 °C) was obtained after recrystallization from methylcyclohexane. The yield of crude compound before recrystallization was 3 g (90% of the theoretical).

Anal. Calcd for C_9H_6NOCl: C, 60.17; H, 3.34. Found: C, 60.05; H, 3.25.

2-(*p*-Chlorophenyl)oxazole, mp 80–81 °C after recrystallization. The crude product weighed 3.2 g (93% of the theoretical).

Anal. Calcd for C_9H_6NOCl: C, 60.17; H, 3.34. Found: C, 60.25; H, 3.30.

2-(*o*-Chlorophenyl)oxazole was a liquid, bp 130 °C (7.5 mm), picrate mp 114–115 °C. There was obtained 3 g (90% of the theoretical). The chlorophenyloxazoles were compared with those prepared by the Pomeranz–Fritsch reactions.

Anal. Calcd for C_9H_6NOCl: C, 60.17; H, 3.34. Found: C, 60.30; H, 3.10.

Pomeranz–Fritsch Reactions with Chloro Substituents. Pomeranz–Fritsch reactions were run on benzal aminoacetals from *o*-,[5,6] *p*-,[5] and *m*-chlorobenzaldehydes.[7]

The yields of chloroisoquinolines obtained were as indicated in the literature. However, the crude products in each case were separated on a Hewlett-Packard 5750 research chromatograph. The temperature was maintained at 240 °C with 30 psi He pressure. An 20-ft column containing 20% Carbowax 20M on Anakrom 50/60 AB was used and peaks were separated in collection tubes and submitted to mass spectrometry. Peaks for the respective aldehyde, its corresponding acid, the oxazole, and chloroisoquinoline were noted but only the oxazole and chloroisoquinoline were compared quantitatively. The yield of oxazole as compared to isoquinoline for *o*-chlorobenzal aminoacetal was 36% oxazole to 64% 8-chloroisoquinoline, for the meta 23% oxazole to 77% 5- and 7-chloroisoquinoline mixture, and for para 61% oxazole to 39% 6-chloroisoquinoline.

A crude dimethyl *p*-chlorobenzalaminoacetal (40 g, from equivalent weights of aldehyde and aminoacetal heated to 120 °C to remove water) was dissolved in 200 mL of concentrated H_2SO_4 at 5 °C, added to 80 g of P_2O_5 and 20 mL of H_2SO_4, and heated to 160 °C for an additional 20 min. The mixture was cooled, neutralized, and steam-distilled. An ether extract of the steam distillate was evaporated to dryness to give 10 g of crude material. This was first extracted with 13% aqueous HCl to remove 6-chloroisoquinoline, then with 38% HCl to remove the oxazole, leaving *p*-chlorobenzaldehyde.

2-(*p*-Chlorophenyl)oxazole. Analysis, see above; mixture melting point was correct.

6-Chloroisoquinoline. Anal. Calcd for C_9H_6NCl: C, 66.06; H, 3.67. Found: C, 66.10; H, 3.70.

Methylisoquinolines by the Pomeranz–Fritsch Reaction. *o*-Methylbenzalaminoacetal and *p*-methylbenzalaminoacetal have been cyclized by Pomeranz[5] to 8-methylisoquinoline and 6-methylisoquinoline, respectively. We have cyclized the *m*-methylbenzalaminoacetal to a mixture of 5- and 7-methylquinolines. *m*-Tolualdehyde and aminoacetaldehyde dimethyl acetal were heated in equivalent amounts to 120 °C until the water was removed. This crude product (50 g) was then dissolved in 250 mL of H_2SO_4 at 5 °C and this mixture added to a mixture of 75 g of P_2O_5 and heated at 160 °C for 25 min.

The reaction product was cooled, neutralized, and steam-distilled. The crude distillate was ether extracted and subjected to gas chromatography. The 5- and 7-methylisoquinoline mixture was extracted with dilute acid and recovered. It was possible to crystallize 6 g of 7-methylisoquinoline, melting at 66 °C from the 10 g of crude product. The yield of 2-(*m*-methylphenyl)oxazole was only 1% in this case.

Registry No.—Dimethyl aminoacetal, 22483-09-6; *m*-nitrobenzal aminoacetal, 62882-09-1; 2-(*o*-aminophenyl)oxazole, 62882-10-4; 2-(*p*-aminophenyl)oxazole, 62882-11-5; 2-(*m*-aminophenyl)oxazole, 35582-08-2; 2-(*o*-chlorophenyl)oxazole picrate, 62881-99-6; dimethyl *o*-chlorobenzalaminoacetal, 62882-12-6; dimethyl *m*-chlorobenzalaminoacetal, 62882-13-7; dimethyl *p*-chlorobenzalaminoacetal, 54879-73-1; dimethyl *o*-methylbenzalaminoacetal, 54879-71-9; dimethyl *p*-methylbenzalaminoacetal, 54879-70-8; dimethyl *m*-methylbenzalaminoacetal, 62882-14-8.

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Conjugate Addition of Grignard Reagents to Ethyl Acrylate

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The homologation of alkyl and aryl halides with a three-carbon chain terminating in a carboxyl or ester function is of some importance in synthesis,[1,2] and a variety of methods can be utilized to accomplish the transformation. Among these methods is the reaction of aryl and heterocyclic iodo compounds with the copper(I) salt of ethyl propiolate,[3] palladium-catalyzed vinylic hydrogen substitution reaction of methyl acrylate with aryl, benzyl, and styryl halides,[4] ethylenation of secondary and tertiary alkyllithiums, followed by carbonation,[5] alkylation of metalated α,β-ynamines with allyl and *n*-alkyl halides, followed by hydrolysis,[6] and conjugate addition of methyl propiolate with organocopper reagents[7] or mixed cuprate reagents.[8] These methods suffer, however, the following disadvantages. Firstly, although some of them give satisfactory yields, none of them has wide applicability, and furthermore, certain reagents, such as 1-propynyl-2,2,6,6-tetramethylpiperidine,[6] are not readily accessible. Secondly, when the product is an unsaturated ester, e.g., $CH_2{=}CHCH_2CH{=}CHCOOCH_3$,[7] subsequent hydrogenation

Table I. Reaction of Grignard Reagents with Ethyl Acrylate

$$(RX + Mg \rightarrow RMgX)$$

$$RMgX + CH_2{=}CHCOOEt \rightarrow RCH_2CH_2COOEt$$

RX	Registry no.	Temp, °C	RCH_2CH_2COOEt[a]	Registry no.	Bp, °C (mm)	Yield, %[b]
Bromobenzene	108-86-1	−20[c]	$PhCH_2CH_2COOEt$	2021-28-5	85 (2)[d]	54
1-Bromopentane	110-53-2	−40	$CH_3(CH_2)_6COOEt$	106-32-1	99 (40)[e]	80
Vinyl bromide	593-60-2	−35 ~ −40[f]	$CH_2{=}CHCH_2CH_2COOEt$	1968-40-7	55 (40)[g]	41
6-Bromo-1-hexene	2695-47-8	−45 ~ −50	$CH_2{=}CH(CH_2)_6COOEt$	35194-39-9	72 (2)[h]	73
Benzyl chloride	100-44-7	−25[c]	$PhCH_2CH_2CH_2COOEt$	10031-93-3	112 (3.5)[i]	69
Cyclohexyl bromide	108-85-0	−45 ~ −50	Ethyl 3-cyclohexylpropanoate	10094-36-7	72 (2)[j]	68

[a] All products gave satisfactory spectroscopic data. [b] Yields given represent distilled product. [c] Cooling below this temperature will cause the Grignard reagent to solidify. [d] Lit.[15] 123 °C (16 mm). [e] Lit.[16] 104 °C (80 mm). [f] −25 °C at onset of the reaction. [g] Lit.[17] 144–146 °C. [h] Lit.[18] 114–116 °C (15 mm). [i] Lit.[19] 130–131 °C (10 mm). [j] Lit.[20] 105–113 °C (17 mm).

is clearly incompatible with the presence of other unsaturation in the molecule. There has been one report of conjugate addition of lithium di-*sec*-butylcuprate to ethyl acrylate giving ethyl 4-methylhexanoate.[2]

In spite of these methods for the extension of a three-carbon chain, the most obvious approach would be the conjugate addition of Grignard reagents with acrylate esters. However, although the 1,4 additions of Grignard reagents to substituted acrylates, such as crotonate, tiglate, and cinnamate, in the presence of copper catalyst under well-defined reaction conditions generally give good to fair yields,[9,10] *sec*-butyl acrylate itself was reported to give only polymerization material.[11]

We reasoned that the key to effecting 1,4 addition to acrylate lay simply in conducting the reaction at low temperature, thus reducing the extent of polymerization. We therefore examined the reactions of ethyl acrylate with Grignard reagents generated from primary, secondary, aryl, benzylic, and vinyl halides and found that it was indeed the case. For example, when ethyl acrylate in ether was added very slowly to a solution of a threefold excess of pentylmagnesium bromide in ether at −40 °C and a catalytic amount of cuprous chloride[12] was added in 13 portions during the course of the reaction, ethyl octanoate could be isolated in 80% yield.[13] Some of our results are given in Table I.

In summary, we feel that the three-carbon homologation is easy to operate and gives good to fair yields with a variety of halides, and we expect that it will find use in synthesis.

Experimental Section

General Reaction Procedure. Ethyl Octanoate. The solution of pentylmagnesium bromide was prepared from 6 g (0.25 g-atom) of magnesium turnings and 37.75 g (0.25 mol) of 1-bromopentane in 400 mL of ether[14] under a nitrogen atmosphere. The solution was cooled to −40 °C and kept at that temperature throughout the reaction. Cuprous chloride[12] (50 mg) was added and then 8.3 g (0.083 mol) of ethyl acrylate in 250 mL of ether was added dropwise over a 3-h period with vigorous stirring. After each 15-min interval during the addition another 50 mg of cuprous chloride was added. After each addition, the system was evacuated and then filled with nitrogen. The last portion was added just after completion of the addition of ethyl acrylate. A total of 650 mg (2.6 mol % with respect to the Grignard reagent) of cuprous chloride was used. The cooling bath was then removed and the reaction mixture was stirred at ambient temperature for 30 min and at room temperature for 20 min. The dark solution was poured rapidly into a mixture of crushed ice and concentrated hydrochloric acid with vigorous stirring. The aqueous solution was separated and extracted with ether. The combined ether extracts were washed with saturated sodium bicarbonate, water, and with saturated brine, then dried ($MgSO_4$), filtered, and concentrated. The residue was distilled to yield 11.4 g (80%) of pure ethyl octanoate, bp 99 °C (40 mm) [lit.[16] 104 °C (80 mm)]. The product was identified by comparison of its infrared and NMR spectra and its VPC behavior with those of an authentic sample.

Acknowledgment is made to the Stanford Research Institute for financial support of this work.

Registry No.—$CH_2{=}CHCOOEt$, 140-88-5.

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Chromium(VI) Oxidations of Secondary Alcohols in the Presence of Amino Groups, or How to Solubilize Chromium(III) in Base

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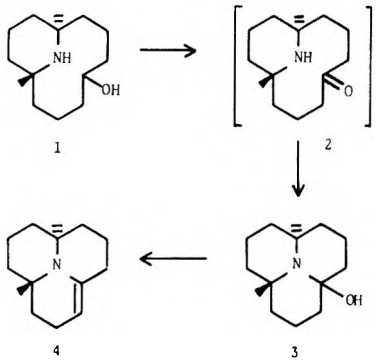
We wish to report a method for the facile solubilization of Cr(III) in basic water; this method conveniently overcomes serious product isolation difficulties in the oxidation of alcohols containing amino groups.

In connection with another problem, we recently desired to effect transformation of the amino alcohol 1 to the amino ketone 2 (actually expected to exist as the carbinolamine 3 or the enamine 4).[1] We wished to perform this oxidation under acidic conditions for several reasons: to protect the amino



group from oxidation and to prevent conversion of the product to the enamine **4** (expected to be very sensitive to oxidation) in the presence of the oxidizing agent. Only after oxidation of the alcohol was complete and after excess oxidant was destroyed would the amino ketone **2** be liberated by base and allowed to condense to **4**. Our first choice method for this conversion was oxidation with the Jones reagent;[2] Cr(VI) oxidations generally give high yields, are usually fast and complete, and are experimentally simple and inexpensive.[3] In practice, oxidation of **1** by Jones reagent in acidic aqueous acetone appeared to work well, but the isolation of the product was exceptionally tedious. Addition of base to the reaction mixture after destruction of excess oxidant resulted in formation of Cr(III) hydroxide, a thick, gelatinous precipitate, difficult if not impossible to filter; attempted extraction of this suspension with ether resulted in a stable emulsion. Also, some of the product was undoubtedly adsorbed and/or entrapped by the precipitate. All in all, a single experience with this almost intractable workup method was sufficient to prompt a search for an alternative workup procedure.

We reasoned that if the Cr(III) could be complexed by an appropriate ligand (e.g., trisodium citrate), the Cr(III) would be solubilized in the basic medium and thus not interfere with the isolation of the product. However, addition of trisodium citrate to the reaction mixture followed by addition of NaOH after 1 h resulted in the same thick precipitate of Cr(III) hydroxide. The lack of complexation is due to the well-known (at least among inorganic chemists) reluctance of Cr(III) to exchange ligands at a reasonable rate.[4] On the other hand, Cr(II) exchanges ligands quickly[4] and, in fact, can catalyze the exchange of ligands by Cr(III).[5] Thus, trisodium citrate *and* a small piece of amalgamated mossy Zn were added to the reaction mixture after oxidation was complete and excess oxidant was consumed; after 10 min at 25 °C under N_2, addition of excess NaOH resulted in a clear, dark solution from which the product was extracted without difficulty. With this workup procedure, the enamine **4** can be obtained in 80% isolated yield by oxidation of the amino alcohol **1**.

The presumed mechanism for the Cr(II)-catalyzed Cr(III) ligand exchange process is shown below.

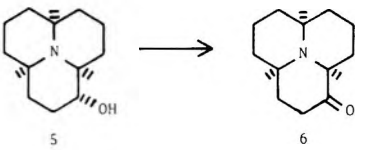
$$Zn(Hg) + 2Cr(III) \rightarrow Zn(II) + 2Cr(II) \quad (1)$$

$$Cr(II) + nL \rightarrow Cr(II)L_n \quad (2)$$

$$Cr(II)L_n + Cr(III) \rightarrow Cr(III)L_n + Cr(II) \quad (3)$$

The amalgamated zinc serves to generate a small amount of Cr(II) (step 1), which then exchanges ligands quickly (step 2). Electron transfer then occurs rapidly (step 3) to generate a complexed Cr(III) and a fresh Cr(II), ready to reenter the cycle at step 2. Eventually all the Cr(III) is complexed in a base-soluble form under mild conditions. An important feature is that only a catalytic amount of Cr(II) suffices to complete the exchange within a short time.

We have also oxidized amino alcohol **5** to the amino ketone **6**. Oxidation of **5** under conditions described for **1** was slow and



incomplete. A procedure using Jones reagent in glacial acetic acid resulted in faster reaction.

Na_2EDTA may be used in place of the trisodium citrate with equal efficacy; we prefer the citrate as it is less expensive and more easily handled.

This workup procedure should also be applicable to other reactions in which Cr(III) is generated and a basic workup is desired.

Experimental Section

Infrared spectra were obtained of liquid films between KCl plates with a Perkin-Elmer 727 spectrophotometer. ^1H NMR spectra were obtained of $CDCl_3$ solutions with a Perkin-Elmer R32 spectrometer; chemical shifts are reported in parts per million downfield from internal tetramethylsilane. The sweep width was calibrated with internal $CHCl_3$ taken as δ 7.24. Combustion analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Vapor-phase chromatography was performed with a Perkin-Elmer 880 flame ionization or a Varian 1400 thermal conductivity instrument. Columns used were 5% OV-1 and 1.5% OV-101 on Chromosorb G and 3% OV-225 on Gas-Chrom Q.

Oxidation of 13-Azabicyclo[7.3.1]tridecan-5-ol (1) to *trans*-1,2,3,3a,4,5,6,6a,7,8-decahydropyrido[2.1.6-*de*]quinolizine (4). **1**[1] (2.65 g, 13.5 mmol) was dissolved in 15 mL of acetone in a 250-mL round-bottom flask. The flask was placed in an ice/water bath and 6 mL (18 mmol) of 3 M H_2SO_4 was added over 3 min with magnetic stirring. Then 4 mL of Jones reagent [10.7 mmol Cr(VI), 20% excess] was added over 3 min. After 15 min, the initial red-orange solution had become a yellow-green suspension; the ice/water bath was removed and the mixture was stirred another 15 min. Excess oxidant was destroyed by addition of 2 mL of *i*-PrOH to give a blue-green suspension within 5 min. Water (50 mL) was added along with 15 g (51 mmol) of trisodium citrate. The flask was flushed with Ar and a small piece of amalgamated mossy Zn (140 mg) was added. After 10 min, 50 mL of Et_2O was added and the reaction mixture was made strongly basic with 20% aqueous NaOH solution (about 15 mL). The very dark but clear water layer was separated and extracted with three 50-mL portions of Et_2O. The combined organic layer was washed with 5 mL of saturated aqueous Na_2SO_4 solution and dried over solid Na_2SO_4. The solvent was removed in vacuo to afford a light yellow solid, presumably the carbinolamine **3**. Dehydration was effected by refluxing 15 min in hexane under a Dean–Stark trap. The hexane was removed in vacuo and the resulting yellow oil was bulb-to-bulb distilled [80 °C (0.2 mm)] to afford 1.91 g (80% yield) of the enamine **4** as a clear, colorless liquid, identical with material prepared by another route.[6] TLC (silica gel, 10 mL of THF + 2 drops of concentrated NH_4OH) showed the absence of starting alcohol; TLC and VPC (OV-1, -101, -225) indicated a purity of 99%. The enamine discolors in air; it is best stored sealed in glass or as a salt: IR (film) 3050, 2935, 2865, 2800, 1655 cm^{-1}; NMR δ 4.70 (1 H, br s), 3.05 (1 H, dd, J = 6, 12 Hz), 2.40 (1 H, mult). Anal. Calcd for $C_{12}H_{19}N$: C, 81.30; H, 10.80; N, 7.90. Found: C, 81.24; H, 10.80; N, 7.88.

Oxidation of (1β,3aα,6aα,9aα)-Dodecahydropyrido[2.1.6-*de*]quinolizin-1-ol (5) to (3aα,6aα,9aα)-Decahydropyrido-[2.1.6-*de*]quinolizin-1(2*H*)-one (6). Amino alcohol **5**[7] (565 mg, 2.9 mmol) was dissolved in 5.8 mL of HOAc in a 100-mL round-bottom flask equipped with a magnetic stirring bar. Concentrated H_2SO_4 (0.16 mL, 2.9 mmol) was added all at once followed by 1.1 mL of Jones reagent [2.9 mmol Cr(VI), 50% excess] over 5 min. After 30 min, 1 mL of *i*-PrOH was added to consume the excess oxidant. After dilution of the mixture with 17 mL of water, 2.52 g (8.6 mmol) of trisodium citrate was added along with a small piece of amalgamated mossy Zn. The flask was flushed with N_2. After 10 min, the mixture was made strongly basic with aqueous NaOH and then extracted with five 20-mL portions of Et_2O. The combined extract was diluted with hexane, washed with saturated aqueous NaCl solution, and dried over Na_2SO_4. After removal of the solvent in vacuo, the pale yellow oil obtained was bulb-to-bulb distilled [ca. 85 °C (0.2 mm)] to give 495 mg (85% yield) of the amino ketone **6** as a clear oil. VPC (OV-101) and TLC (silica gel, 4:1 cyclohexane/EtOAc and 99:1 Et_2O/NH_4OH) indicated a trace (~1%) of remaining alcohol with no other detectable impurities: IR 2959, 2865, 2790, 2730, 1725 cm^{-1}; NMR, no peaks

below δ 2.65 ppm. The analytical sample was obtained by silica gel chromatography (cyclohexane/EtOAc) followed by bulb-to-bulb distillation. Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; H, 7.25. Found: C, 74.53; H, 9.92; N, 7.22.

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Registry No.—**1**, 61714-12-3; **3**, 62930-44-3; **4**, 57147-61-2; **5**, 62930-45-4; **6**, 62930-46-5; Cr, 7440-47-3.

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Generation and Alkylation of the Dianion (Homoenolate) of a 1-Indanone

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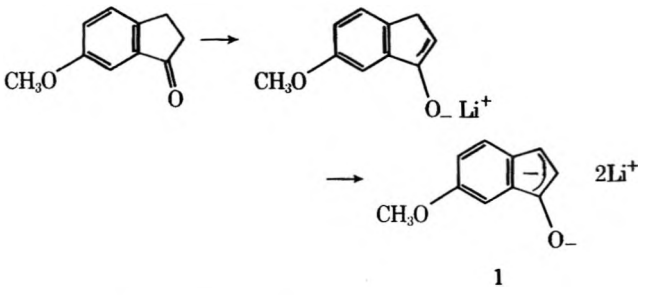
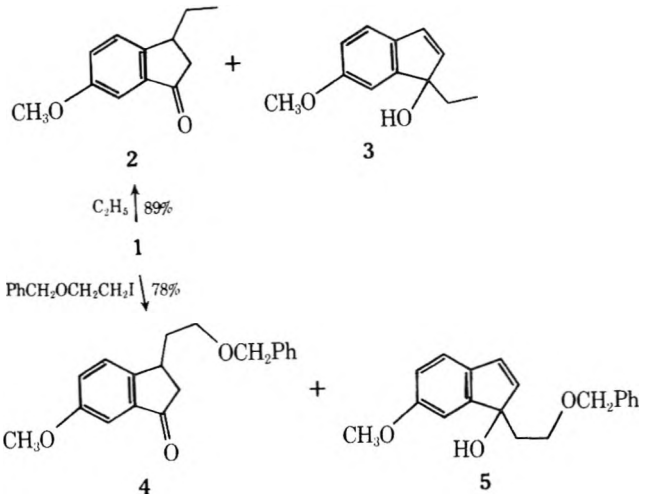
The generation of dianions from monofunctional compounds has been seldom observed and utilized.[1] In conjunction with the chemistry of gibberillins, we required a facile route to 3-substituted 1-indanones. Metalation of the enamines of 1-indanones followed by alkylation does provide access to such compounds.[2] However, a more direct method was envisioned based upon the fact that the enolate of indanone is an oxyindene which should still be reasonably acidic as a result of the generation of the aromatic indenyl anion. We wish to report the facile direct generation of the homoenolate of 1-indanone and its utility in forming both 3-monosubstituted and 2,3-disubstituted 1-indanones.

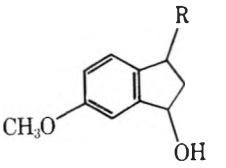


1

Treatment of 6-methoxy-1-indanone[3] with 2 equiv of lithium diisopropylamide at −78 °C in THF produced a white suspension in a yellow solution, which turned deep red upon warming to 0 °C for 4 h. Addition of 1 equiv of ethyl iodide followed by aqueous workup gave a 89% yield of 3-ethyl-1-indanone (**2**) and <3% of 3-ethyl-3-hydroxy-1-indene (**3**).



Similar results were obtained upon alkylation with 2-benzyloxyethyl iodide. The assignment of the 3-substitution for **2** and **4** follows from NMR spectra of the compounds and that of their corresponding alcohols **6** and **7**, respectively.



6, R = C_2H_5
7, R = $PhCH_2OCH_2CH_2$

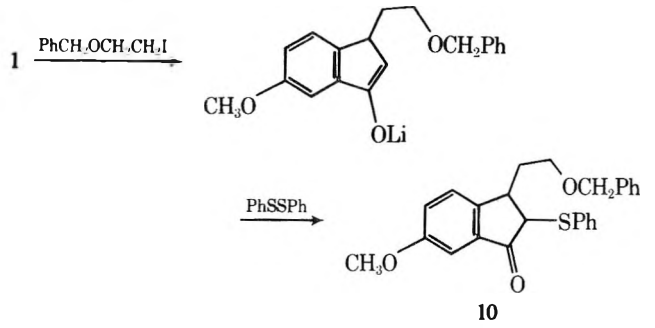
In the starting indanone, the protons at C(2) and C(3) appear at δ 2.66 and 3.05, respectively. In **2** and **4** the absorptions for the benzylic protons appear as a multiplet at δ 3.20 and 3.44, respectively, for one proton each and the methylene groups α to the carbonyl groups appear as a clean doublet of doublets [**2**, δ 2.23 (J = 19, 4 Hz) and 2.74 (J = 19, 7 Hz); **4**, δ 2.32 (J = 19, 3 Hz) and 2.76 (J = 19, 7 Hz)]. In **7** the proton α to the hydroxyl group appears as a doublet of doublets (J = 8, 5 Hz) at δ 5.1 in the presence of D_2O which demands a methylene group at C(2). Further transformations of these compounds reaffirm these conclusions.[4]

While full characterization of the trace by-products was not obtained, spectral data clearly suggest the assigned structures, **3** and **5**. The infrared spectra show the presence of an alcohol group, but the absence of any carbonyl group. The NMR spectra are essentially first order. For example, **5** shows a clean AB pattern for the vinyl protons (δ 6.44 and 6.19, J = 6 Hz) and a single high-field methylene group comprised of diastereotopic protons coupled only to an adjacent methylene group—each proton is a doublet (J = 15 Hz) of triplets (J = 7 Hz) at δ 2.20 and 1.89. Reaction at C(1) of **1** points out the analogy to **8**[5] and **9**,[1h,i] in which the problem of α vs. γ attack

8 **9**

is well recognized. In contrast to **8**, X = alkyl or silyl, **1** should and does show almost exclusive γ attack due to the electronic repulsion of the charged oxygen, which will be reinforced by the preference to maintain maximum charge stabilization by delocalization in the initial product.

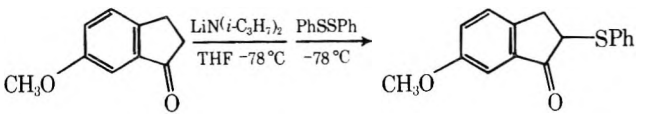
Since the initial product is an enolate, further substitution is quite feasible. Indeed, after alkylation of **1** with benzyloxyethyl iodide, addition of diphenyl disulfide[6] led to the 2,3-disubstituted product **10**. Based upon the fact that the base is the limiting reagent under these conditions, **10** was obtained in 84% yield. The substitution of the phenylthio group at C(2)



10

was confirmed by the NMR spectrum **10** and its corresponding alcohol. No absorptions appeared between δ 2.2 and 3.1 for the methylene group α to the carbonyl group in **10**. The corresponding alcohol showed the methine proton at C(1) as a doublet (J = 6 Hz) at δ 4.9, indicating the presence of a methine group at C(2).

Dianion formation requires warming to 0 °C. Quenching the initial product mixture at −78 °C with diphenyl disulfide led only to 2-phenylthio-1-indanone rather than the 3-substituted isomer. The utility of this method is clearly indicated by its directness and ease of scale-up. The great difference in reactivity between the dianions and monoanion allows facile and flexible substitution at the 3 or 2,3 positions in one step. Further, the direct generation of homoenolates in special cases is clearly feasible and suggests that further exploration in this area would be quite exciting.



Experimental Section

Preparation of 3-Substituted 1-Indanones: 3-(2′-Benzyloxyethyl)-6-methoxyindan-1-one. To a −78 °C solution of 57 g (80 mL, 0.57 mol, 2.37 equiv) of diisopropylamine in 0.4 L of dry THF was added 370 mL (concentrated to 50 mL under vacuum) (0.52 M, 2.18 equiv) of 1.4 N n-butyllithium in hexane. After 1 h, 38.5 g (0.238 M) of 6-methoxyindan-1-one in 500 mL of THF was added dropwise over a 20-min period by cannula. After stirring for 1 h at −78 °C, the yellow slurry was allowed to warm to room temperature for 4 h, during which time the solution became deep wine red. This solution was cooled to approximately −20 °C and a solution of 75 g (0.28 mol, 1.2 equiv) of 2-benzyloxyethyl iodide[4] in 100 mL of THF was added rapidly with vigorous stirring. The red color dissipated almost instantly with substantial evolution of heat and lightening of color to orange red. After 15–30 min the reaction mixture was further quenched by addition of 1 L each of 3 N aqueous hydrochloric acid solution and saturated aqueous sodium chloride solution. Extraction with three 500-mL portions of ether, washing the combined organic layers with water, saturated aqueous sodium bicarbonate solution, saturated aqueous sodium thiosulfate, solution, and brine, followed by drying over magnesium sulfate and concentration in vacuo, yielded 80 g of crude product. This crude product showed only alkyl iodide and desired product spots upon TLC, although multiple elutions showed trace amounts of the 1-alkyl inden-1-ol. Purification by HPLC[7] with ether–hexane (1:3) yielded 54.5 g (0.183 mol, 78%) of alkylated material shown by NMR integration to be >95% of the 3-alkyl indanone. Due to the difficulty of separating the minor component and the ease of removal after subsequent reduction of the indanone, this material was used without further purification. A small sample of the crude mixture, 100 mg, was purified by PLC[8] (two elutions with 3:1 hexane–ether) to yield 67 mg of 3-alkyl indanone (R_f 0.7, 1:1 ether–hexane, two elutions) and 2 mg of the 1-alkyl inden-1-ol (R_f 0.65). Slightly larger amounts of the indenol were seen when the alkylation was performed at room temperature.

3-(2′-Benzyloxyethyl)-6-methoxyindan-1-one: NMR (CCl_4) δ 1.5–1.9 (1 H, m), 2.0–2.3 (1 H, m), 2.33 (1 H, dd, J = 8, 2 Hz), 2.74 (1 H, dd, J = 18, 8 Hz), 3.30–3.65 (3 H, m with td superimposed), 3.80 (3 H, s), 4.48 (2 H, m), 7.05–7.20 (2 H, m), 7.3 (6 H, br s); IR (CCl_4) 3600–3400 (w), 3090, 3060, 3030, 2960, 2940, 2880, 1710, 1610, 1495, 1435, 1320, 1285, 1250, 1115, 1055, 1045, 705 cm^{-1}; MS m/e 296 (5), 206 (11), 205 (100), 194 (25), 188 (24), 187 (10), 175 (40), 165 (10), 162 (5), 161 (30), 147 (15), 92 (6), 91 (65). Anal. Calcd for $C_{19}H_{20}O_3$: 296.141 24. Found: 296.140 97.

1-(2′-Benzyloxyethyl)-6-methoxyinden-1-ol: NMR (CCl_4) δ 1.98 (1 H, dt, J = 18, 7 Hz), 2.20 (1 H, dt, J = 18, 7 Hz), 2.49 (1 H, br s, exchangeable), 3.56 (2 H, t, J = 7 Hz), 3.70 (3 H, s), 4.40 (2 H, s), 6.15 (1 H, d, J = 5.5 Hz), 6.40 (1 H, d, J = 5.5 Hz), 6.60 (1 H, dd, J = 2.5, 8.5 Hz,), 6.83 (1 H, d, J = 2.5 Hz), 6.93 (1 H, d, J = 8.5 Hz), 7.22 (5 H, s); IR ($CHCl_3$) 3580, 3450, 3000, 2920, 2870, 1600, 1450, 1280, 1090, 1020 cm^{-1}.

Preparation of 2,3-Disubstituted 1-Indanones: 2-Phenylthio-3-(2′-benzyloxyethyl)-6-methoxyindan-1-one. To a −78 °C solution of 0.40 mL (2.28 mmol, 2.88 equiv) of diisopropylamine in 2.0 mL of THF was added 1.5 mL (2.1 mmol, 2.1 equiv) of 1.4 N n-butyllithium. After 30 min, 165 mg (1.0 mmol) of 6-methoxyindan-1-one in 1.0 mL of THF was added dropwise over 5 min. After 1 h the solution had developed a white precipitate. The bath was removed and the solution allowed to slowly come to room temperature over 4 h, during which time the precipitate dissolved to yield a yellow solution which turned reddish-orange upon further warming. The solution was then cooled to approximately −10 °C and 300 mg (1.15 mmol, 1.15 equiv) of 2-benzyloxyethyl iodide in 0.5 mL of THF was added rapidly by syringe. After 10 min this solution was added to a room temperature solution of 300 mg (1.61 mmol, 1.61 equiv) of diphenyl disulfide in 2 mL of THF and 0.5 mL of HMPA. After 30 min the mixture was diluted with ether and washed twice with aqueous 3 N hydrochloric acid and water, and dried over sodium sulfate and magnesium sulfate. Concentration in vacuo yielded 0.4 g of crude material which was purified by PLC[8] to yield 170 mg (42% or 84% based upon a maximum of 50% conversion) of desired material as a yellow oil, R_f 0.4 in 1:1 ether–hexane: NMR (CCl_4) δ 1.6–2.3 (2 H, m), 3.2–3.5 (1 H, m), 3.50 (2 H, t, J = 7 Hz), 3.64 (1 H, d, J = 3 Hz), 3.78 (3 H, s), 4.38 (2 H, s), 6.95–7.6 (13 H, m with a singlet at 7.20); IR (CCl_4) 3400 (w), 3010, 2940, 1720, 1615, 1490, 1280, 1215, 1100, 1030, 690, 660 cm^{-1}; MS 405 (2), 404 (6), 296 (2), 295 (4), 205 (3), 204 (2), 203 (10), 189 (3), 188 (13), 163 (7), 162 (26), 161 (90), 160 (100), 145 (14), 135 (9), 134 (13), 133 (25), 110 (70), 109 (37), 91 (58), 77 (52). Anal Calcd for $C_{25}H_{24}O_3S$: 404.144 61. Found: 404.145 66.

Preparation of 3-(2′-Benzyloxyethyl)-6-methoxyindan-1-ol. To a 0 °C slurry of 13.6 g (0.36 mol, 2.0 equiv) of lithium aluminum hydride in 300 mL of THF was added dropwise a solution of 54.5 g (0.184 mol) of 3-(2′-benzyloxyethyl)-6-methoxyindan-1-one in 200 mL of THF. The reaction mixture was maintained at 0 °C for 4 h and then quenched by successive addition (carefully) of 13.6 mL of water, 13.6 mL of 15% (w/v) aqueous sodium hydroxide solution, and 40 mL of water. After 5 min of continued vigorous stirring, the off-white to grey precipitate was filtered and the filtrate concentrated under reduced pressure to yield a semisolid mass from which 38.6 g of crystalline alcohol was obtained (mp 64–66 °C dichloromethane–hexane), apparently as one diastereomer. The mother liquor was concentrated and purified by HPLC (1:1 ether–hexane) to yield 5.3 g of crystals from tubes 41–76. The total yield of 43.9 g (0.147 mol) is 80% from the 3-alkyl indanone or 61.7% from 6-methoxyindan-1-one: NMR (CCl_4) (100 MHz) δ 1.5–2.0 (2 H, m), 2.0–2.9 (3 H, m with a br s at 2.4), 2.95–3.2 (1 H, m), 3.5–3.9 (5 H, m with sharp singlet at 3.80), 4.50 (2 H, s), 5.0–5.3 (1 H, m), 6.83 (1 H, dd, J = 8, 2 Hz), 6.95 (1 H, d, J = 2 Hz), 7.10 (1 H, d, J = 8 Hz), 7.38 (5 H, s); IR (CCl_4) 3600, 3450, 3060, 3020, 3000, 2930, 2850, 1610, 1485, 1260, 1090, 1040, 910, 695 cm^{-1}; MS 299 (4), 298 (15), 297 (2), 296 (4), 282 (5), 281 (18), 280 (83), 205 (15), 191 (8), 190 (34), 189 (44), 176 (5), 175 (21), 174 (50), 173 (10), 172 (25), 171 (5), 165 (8), 164 (15), 163 (12), 162 (5), 161 (20), 160 (18), 159 (100), 158 (10), 157 (9), 149 (8), 148 (7), 146 (25), 145 (23), 144 (16), 143 (5), 141 (6), 133 (13), 131 (13), 130 (9), 129 (22), 128 (20), 127 (14), 115 (22), 91 (60). Anal. Calcd for $C_{19}h_{22}O_3$: 298.156 89. Found: 298.157 60. Calcd: C, 76.51; H, 7.38. Found:[9] C, 76.41; H, 7.36.

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Registry No.—2, 30211-64-4; **3,** 62841-73-0; **4,** 62841-74-1; **5,** 62841-75-2; **7,** 62841-76-3; **10,** 62841-77-4; **10** alcohol, 62841-78-5; 6-methoxyindan-1-one, 13623-25-1; 2-benzyloxyethyl iodide, 54555-84-9.

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(7) A medium-pressure preparative liquid chromatography unit fitted with a 2.5 × 100 cm column packed with 32–63 μm Woelm silica gel. The system utilized a single-stage constant flow pump with a flow of approximately 22 mL/min. The eluent was directed to a Gilson fraction collector.
(8) Plates (10 × 20 or 20 × 40 cm) of Merck (Darmstadt) silica gel PF 254 of 1.5–2.0-mm thickness were employed.
(9) Analysis performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Communications

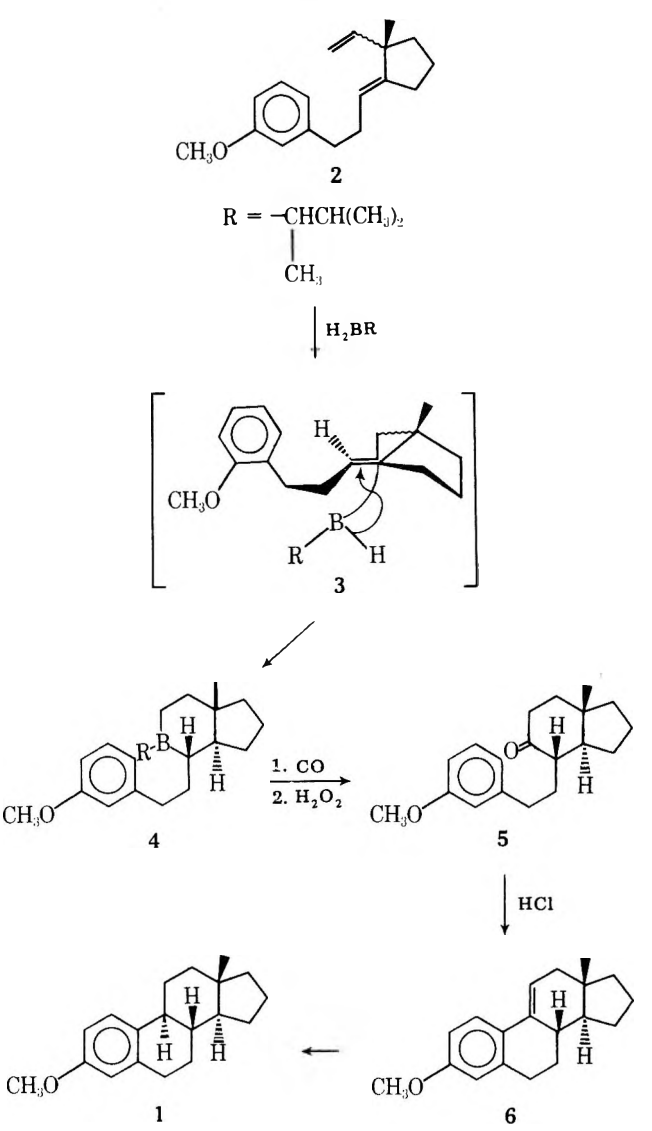
Synthesis of (±)-3-Methoxyestra-1,3,5(10)-triene: Stitching and Riveting as a Tool for Steroid Synthesis

Summary: (±)-3-Methoxyestra-1,3,5(10)-triene has been prepared from 1-chloromethylcyclopentene and 2-(*N*,*N*-dimethylamino)-4-(*m*-methoxyphenyl)butyronitrile.

Sir: We have been exploring the synthetic strategy of stitching and riveting,[1] hydroboration–carbonylation, as a means of preparing steroids and other stereochemically demanding natural products. Described herein are some of the initial results from our investigations directed toward the synthesis of 3-methoxyestra-1,3,5(10)-triene (**1**). This well-characterized steroid[2] was chosen as our first synthetic objective due to the presence of the natural configuration of the ring junctures along with its lack of complicating functional groups, and we envisioned it as evolving from diene **2** through the hydroboration–carbonylation procedures of Brown (Scheme I).[3] The well-documented theory of selectivity in the addition of alkylboranes to olefins led us to the proposition that thexylborane[4] would regioselectively add to the monosubstituted double bond in **2**, boron becoming bonded to the least-substituted end of that double bond, generating carborane **3**. This compound (**3**) would then be predisposed to deliver boron and hydrogen (cis addition) to the trisubstituted olefin (*E* geometry) of compound **3** in an intramolecular process that is stereochemically guided by attachment of these groups to the steroidal "*D* ring" as illustrated in Scheme I. Realization of this stitching process would force formation of all trans tricyclic carborane **4**. Carbonylation and oxidation of **4** would then form hydrindanone **5**, a structure analogous to compounds previously converted to estrone derivatives by Cohen and Smith.[5]

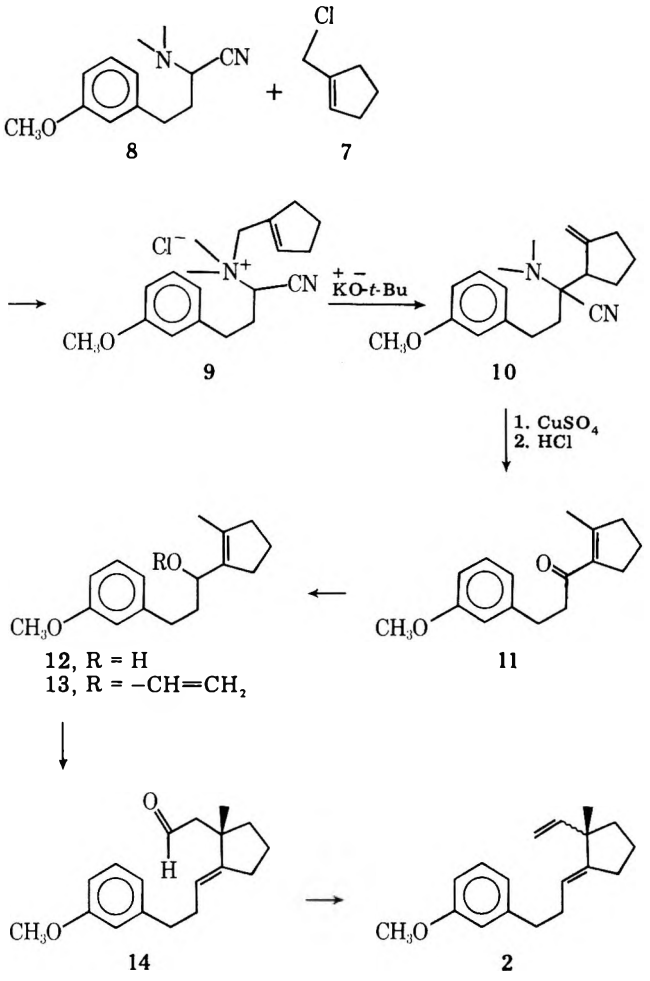
Pursuing these considerations, compound **2** was prepared and added to a solution of thexylborane (BH_3 was generated in situ, $LiAlH_4/BF_3OEt_2$, −78 °C; then 2,3-dimethyl-2-butene was added at 0 °C) forming crude carborane **4** (vinyl proton resonances of **2** absent in ^1H NMR of **4**). This material was immediately treated with carbon monoxide (1200 psi, 50 °C, 5 h) and then oxidized (NaOAc, H_2O_2, aqueous THF) affording **5** (53% from **2**). Studies on **5** have been strongly suggestive of the all trans structure shown in Scheme I.[6,7] Acid-catalyzed cyclization of **5** (10 N HCl/methanol)[5] gave 3-methoxyestra-1,3,5(10),9(11)-tetraene (**6**, mp 82–85 °C),[8] which forms the desired 3-methoxyestra-1,3,5(10)-triene (**1**) via reduction (1 atm H_2, Pd/C; mp 78 °C from methanol).[2] Chromatographic and spectroscopic comparison of this (±)-steroid with optically active 3-methoxyestra-1,3,5(10)-triene (**1**) prepared from natural 3-methoxyestra-1,3,5(10)-trien-17-one via deoxygenation (tosylhydrazone, NaH_3BCN)[9] confirmed the structural identity of these two substances.

Scheme I



Bicyclic diene **2** is accessible (Scheme II) through two sigmatropic rearrangements starting with 1-chloromethylcyclopentene (**7**)[10] and the *N*,*N*-dimethylaminonitrile **8**,[11] the latter of which is derived from *m*-methoxyhydrocinnamaldehyde. These two reagents (**7** and **8**) react to form amorphous salt **9**,[12] which was rearranged to amino nitrile **10** by the action of base (potassium *tert*-butoxide, Me_2SO/THF, −30 °C).[13] Copper sulfate (pentahydrate) assisted hydrolysis[13] (refluxing EtOH, 10 min) and acid-catalyzed bond migration (HCl

Scheme II



aqueous in THF, 8 h) forms enone **11** [46% from **8**: IR 1680, 1650 cm^{-1}; ^1H NMR δ 2.05 (allylic CH_3)]. Reduction (**11** to **12**, $LiAlH_4$, ether, 15 min), vinyl ether exchange [**12** to **13**, ethyl vinyl ether, $Hg(OAc)_2$], and Claisen rearrangement affords aldehyde **14** [55% from **11**; IR 2740, 1725 cm^{-1}; ^1H NMR δ 9.51, 5.12 (aldehyde and vinyl H's)] with the transoid geometry of the trisubstituted olefin in **14** (Scheme II) resulting from this rearrangement. Diene **2** was cleanly formed by reduction ($LiAlH_4$, THF) and dehydration using the multiple step procedure of Sharpless (MsCl, o-$NO_2C_6H_4SeNa$, H_2O_2, Δ).[14]

The ease with which we have been able to prepare steroid **1** with the all trans natural configuration starting from simple starting materials via stitching and riveting has encouraged us to pursue more complex natural products, the report of which will be forthcoming.

Acknowledgment. We gratefully acknowledge the National Institutes of Health (HEW) for support of this work (Grant AM-18802).

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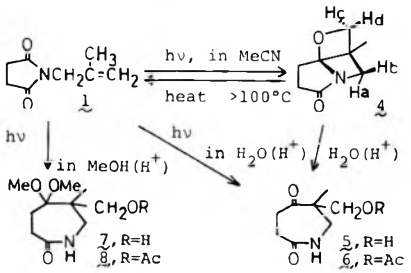
Formation of Intramolecular Oxetanes in the Photolysis of *N*-2-Alkenyl Alicyclic Imides

Summary: On irradiation in acetonitrile, *N*-(2-methylallyl)-succinimide (**1**) underwent intramolecular ring closure to give oxetane **4**. On the other hand, in weakly acidified methanol (or water) **1** gave the corresponding ring-enlarged compound **7** (or **5**) via oxetane **4**.

Sir: We wish to report on the first example of intramolecular oxetane formation in the photolysis of imides.[1,2] *N*-(2-Methylallyl)succinimide (**1**), *N*-allylsuccinimide (**2**), and *N*-allylglutarimide (**3**) were examined in this work.

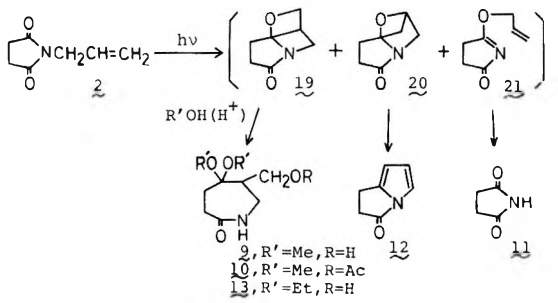
Irradiation of **1** (0.05 M) in acetonitrile with a 120-W low-pressure Hg-arc lamp for about 120 h gave, after evaporation of the solvent, an oily product **4** almost quantitatively. After a prolonged heating at about 100 °C, **4** decomposed into the starting material **1**. The structure of **4** (oxetane) is assigned on the basis of its ^{13}C and ^1H NMR spectra.[3] The ^{13}C NMR spectrum of **4** revealed the presence of eight different carbon atoms: δ ($CDCl_3$) 14, 15, 27, 30, 50 (NCC), 59 (OCC), 79 (NCO), 181 (NC=O). In the ^1H NMR spectrum the observed long-range coupling between H_a and H_c, which is confirmed by the spin decoupling, clearly demonstrates the fixed W configuration (H_aCCCH_c) for **4**: δ ($CDCl_3$) 1.32 (s, 3 H, CH_3), 1.9–2.9 (m, 4 H, $-CH_2CH_2-$), 3.68 (dd, J = 2, 9 Hz, 1 H, H_a), 4.10 (d, J = 9 Hz, 1 H, H_b), 4.36 (dd, J = 2, 6 Hz, 1 H, H_c), 4.69 (d, J = 6 Hz, 1 H, H_d). By treatment with aqueous acid, **4** was converted to **5** (oil), then to acetate **6**: mp 111.0–112.5 °C; ^1H NMR ($CDCl_3$) δ 1.02 (s, 3 H, CH_3), 2.04 (s, 3 H, OAc), 2.4–3.0 (m, 4 H), 3.24 (dd, J = 6, 16 Hz, 1 H), 3.44 (dd, J = 6, 16 Hz, 1 H), 4.20 (br s, 2 H, CH_2OAc), 7.20 (br t, 1 H, NH); IR (KBr) 3320, 3090 (NH), 1737 (ester), 1706 (keto), 1663 (amide) cm^{-1}. Irradiation of **1** in water acidified with a trace of hydrochloric acid also gave **5** in a good yield. On the other hand, irradiation of **1** (0.05 M) in acidic methanol acidified with a trace of hydrochloric acid for about 20 h afforded a ketal **7** (88%): mp 160.0–161.0 °C; ^1H NMR ($CDCl_3$) δ 0.98 (s. 3 H, CH_3), 1.8–2.6 (m, 4 H, $-CH_2CH_2-$), 3.34 (s, 3 H, OCH_3), 3.39 (s, 3 H, OCH_3), 2.8–4.0 (m, 5 H), 6.80 (br t, 1 H, NH); IR (KBr) 3400 (OH), 3240, 3070 (NH), 1655 (amide) cm^{-1}. Acetate of **7** (**8**): mp 124.0–126.0 °C; ^1H NMR ($CDCl_3$) δ 1.02 (s, 3 H, CH_3), 2.06 (s, 3 H, OAc), 1.8–2.6 (m, 4 H, $-CH_2CH_2-$), 3.28 (s, 3 H, OCH_3), 3.34 (s, 3 H, OCH_3), 2.8–3.5 (m, 2 H), 4.02 (d, J = 12 Hz, 1 H), 4.23 (d, J = 12 Hz, 1 H), 6.36 (br t, 1 H, NH); IR (KBr) 3200, 3080 (NH), 1735 (ester), 1670 (amide) cm^{-1} (Scheme I).

Scheme I



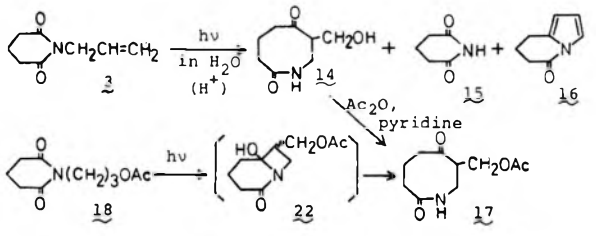
In acetonitrile, photolysis of **2** gave no detectable products even after irradiation for 160 h. However, irradiation of **2** (0.05 M) in acidified methanol for 50 h gave, after chromatography (SiO_2), a crystalline compound **9** (70%), mp 123.5–124.5 °C, as the major product. Acetate of **9** (**10**): mp 153.0–154.0 °C. The minor products were succinimide **11** (~5%) and 1,2-dihydro-3*H*-pyrrolizin-3-one **12** (~5%). **12:** mp 72.5–74.0 °C (lit. 71 °C);[4] ^1H NMR ($CDCl_3$) δ 3.02 (s, 4 H), 6.02 (d, 1 H), 6.50 (t, 1 H), 7.10 (d, 1 H); IR (KBr) 1730 (C=O), 1565 (C=C), 1280 cm^{-1}. Similarly, irradiation of **2** in ethanol gave **13** (70%), mp 132.0–133.5 °C, together with **11** (~10%) and **12** (~10%) (Scheme II).

Scheme II



Again, irradiation of **3** in acetonitrile gave no products, but photolysis of it (0.05 M) in acidified water for about 50 h gave **14** (~65%), glutarimide **15** (~2%), and an oily product **16** (~15%) after chromatography (SiO_2). **14:** mp 110.0–113.0 °C. Acetate of **14** (**17**); mp 145.0–147.0 °C. We obtained the same compound, **17**, by another route: photolysis of *N*-(3-acetoxypropyl)glutarimide (**18**) in acetonitrile in a yield of 30%[2a,b] (Scheme III).

Scheme III



These results unambigously disclose the formation of intramolecular oxetanes in the photolysis of *N*-2-alkenyl alicyclic imides. Oxetane **4** obtained in the photolysis of **1** is the initial photoproduct without doubt. By treating in methanol or water it converts to **7** or **5**. Similarly, in the photolysis of **2** or **3**, we can safely conclude that oxetanes could be possible intermediates. For example, in the photolysis of **2** in acidified methanol oxetane **19** converts to the final product **9**, and the formation of **12** may be explainable in terms of the decomposition of oxetane **20**. To support our conclusion, it was reported that 5-oxa-1-methylbicyclo[2.1.1]hexane, which is one of the oxetanes obtained from the photolysis of 5-hexen-2-one, easily decomposed to a mixture of methylcyclopentadienes even under mild conditions.[1c] In the photolysis of **2** in methanol, **11** was also obtained. The formation of **11** we may reasonably explain taking into account that the nucleophilic attack of solvent to **21** resulted from the "photo-Cope reaction".[1e,5]

So far as our researches are concerned the oxetane formation reaction should be regarded as one of the most typical photochemical reactions of imides. The detailed mechanism of this reaction is under investigation.

References and Notes

(1) It is well known that a wide variety of carbonyl compounds undergo photocycloaddition with olefins to form oxetane.[1a] Especially, photochemical reaction of γ,δ-unsaturated carbonyl compounds often results in formation of intramolecular oxetanes.[1b-e] In addition, oxetane formation of some types of esters has been recently reported, and its mechanisms have been investigated in detail.[1f-l] (a) N. J. Turro, "Molecular Photochemistry", W. A. Benjamin, New York, N.Y., 1966, Chapter 6; (b) R. Srinivasan, *J. Am. Chem. Soc.*, **82**, 775 (1960); (c) N. C. Yang, M. Nussim, and D. R. Coulson, *Tetrahedron Lett.*, 1525 (1965); (d) S. R. Kurowsky and H. Morrison, *J. Am. Chem. Soc.*, **94**, 507 (1972); (e) J. D. Dalton and S. J. Tremont, *ibid.*, **97**, 6916 (1975), and papers cited therein; (f) Y. Odaira, T. Shimadaira, and S. Tsutsumi, *Chem. Commun.*, 757 (1967); (g) T. Tominaga, Y. Odaira, and S. Tsutsumi, *Bull. Chem. Soc. Jpn.*, **40**, 2451 (1967); (h) Y. Shigemitsu, H. Nakai, and Y. Odaira, *Tetrahedron*, **25**, 3039 (1969); (i) Y. Shigemitsu and Y. Odaira, *Tetrahedron Lett.*, 2887 (1971); (j) Y. Katsuhara, Y. Shigemitsu, and Y. Odaira, *Bull. Chem. Soc. Jpn.*, **44**, 1169 (1971); (k) R. A. Neunteufel and D. R. Arnold, *J. Am. Chem. Soc.*, **95**, 4080 (1973); (l) T. S. Cantrell, *J. Chem. Soc., Chem. Commun.*, 468 (1973).

(2) In the photochemical reactions of alicyclic imides, the "hydrogen abstraction reaction"[2a,b] and "α-cleavage reaction"[2c,d] have been known. (a) Y. Kanaoka, *Yuki Gosei Kagaku Kyokai Shi*, **33**, 949 (1975), and papers cited therein; (b) Y. Hatanaka and Y. Kanaoka, *J. Org. Chem.*, **41**, 400 (1976); (c) G. Scharf and B. Fuchs, *J. Chem. Soc., Chem. Commun.*, 244 (1975); (d) J. A. Schutyser and F. C. De Schryver, *Tetrahedron*, **32**, 251 (1976).

(3) All new compound described in this paper showed reasonable spectral properties (^1H NMR, IR, UV, and mass spectra) and all crystalline compounds showed satisfactory analytical results.

(4) W. Flitsch and U. Neumann, *Chem. Ber.*, **104**, 2170 (1971).

(5) Similarly, on the photolysis in methanol, *N*-(2-phenylallyl)phthalimide gave phthalimide (~55%) together with methyl 2-phenylallyl ether (~45%).

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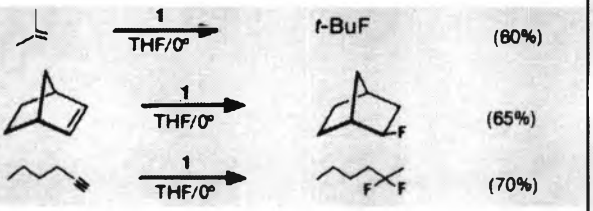
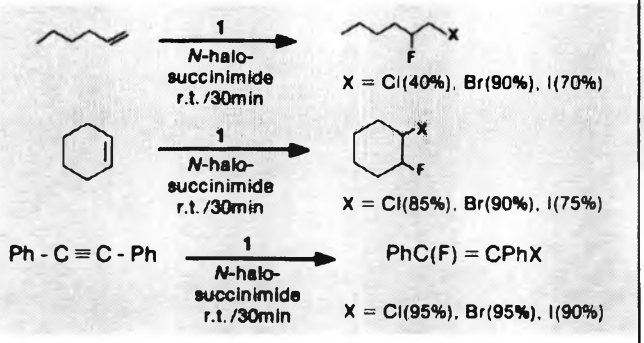
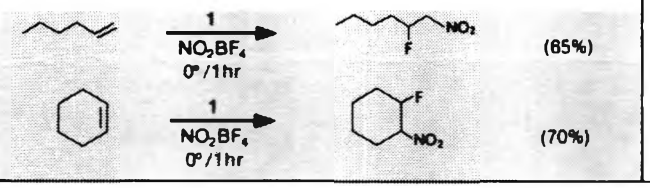
Hydrogen Fluoride-Pyridine Reagent

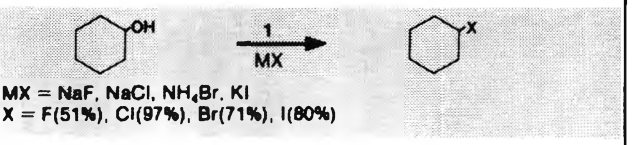
Professor George Olah has pioneered the development of the **hydrogen fluoride-pyridine** reagent (**1**) as a convenient form of anhydrous HF.[1-6] This remarkable reagent consists of pyridinium polyhydrogen fluoride in equilibrium with a small amount of free HF. It is a relatively stable liquid which suffers no appreciable loss of volatile hydrogen fluoride at temperatures up to 50°C.

Below are some of the synthetic transformations that have been achieved by the use of the **hydrogen fluoride-pyridine** reagent.

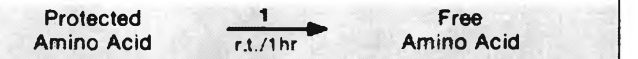








R = Et, *c*-Hex, Ph, EtO
R'X = *N*-halosuccinimide or alkali halide
X = H, Cl, Br, I



Substrate	Yield (%)
Box-Glu(OBzl)-OH	100
Boc-Ser(Bzl)-OH	93
Boc-Thr(Bzl)-OH	95
Boc-His(Tos)-OH	95
Boc-Met-OH	92
H-Phe-OBzl	94
H-Lys(Boc)-O-*t*-Bu	97
Boc-Leu-resin	96
Boc-Pro-resin	92

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1) G.A. Olah, M. Nojima, and I. Kerekes, *Synthesis*, 779 (1973).
2) G.A. Olah, M. Nojima, and I. Kerekes, *ibid.*, 780 (1973).
3) G.A. Olah and M. Nojima, *ibid.*, 785 (1973).
4) G.A. Olah and J. Welch, *ibid.*, 653 (1974).
5) G.A. Olah and J. Welch, *ibid.*, 652 (1974).
6) G.A. Olah and J. Welch, *ibid.*, 896 (1974).
7) S. Matsuura, C.-H. Niu, and J.S. Cohen, *Chem. Commun.*, 451 (1976).