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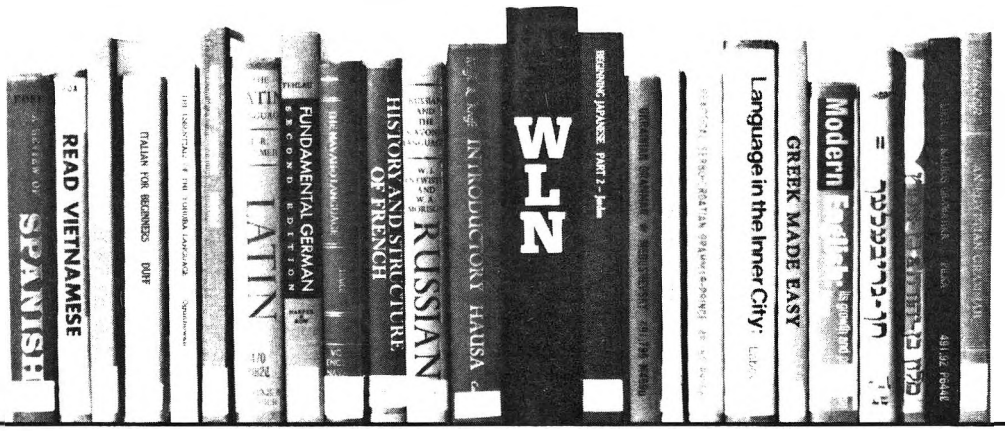

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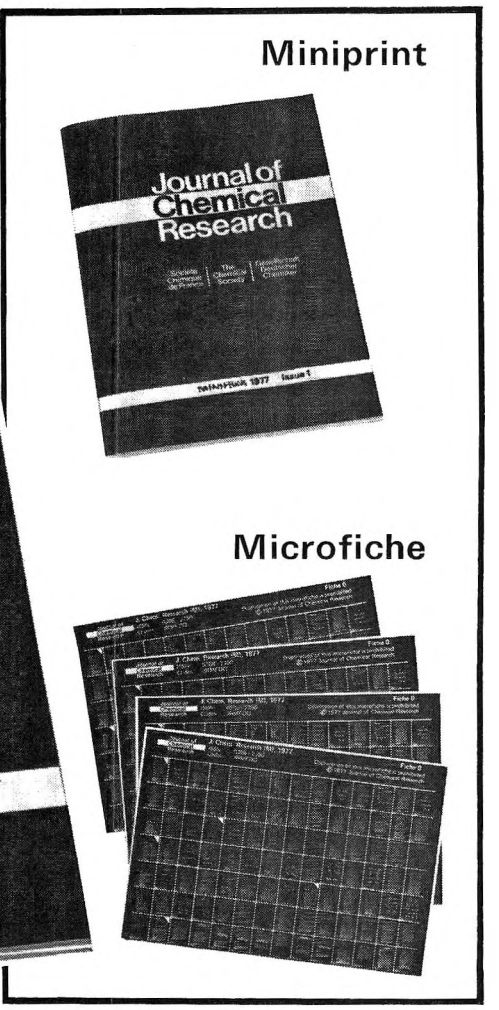

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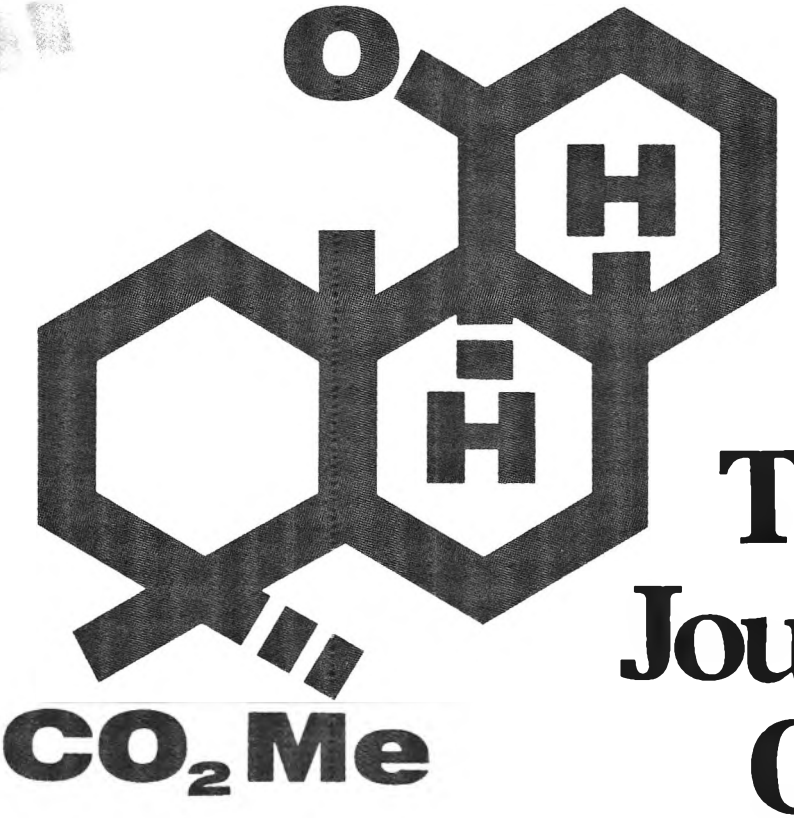

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THE JOURNAL OF Organic Chemistry®

VOLUME 42, NUMBER 13

JUNE 24, 1977

Polyphosphoric Acid Catalyzed Cyclization of Aralkenyl-Substituted Quaternary Ammonium Salts

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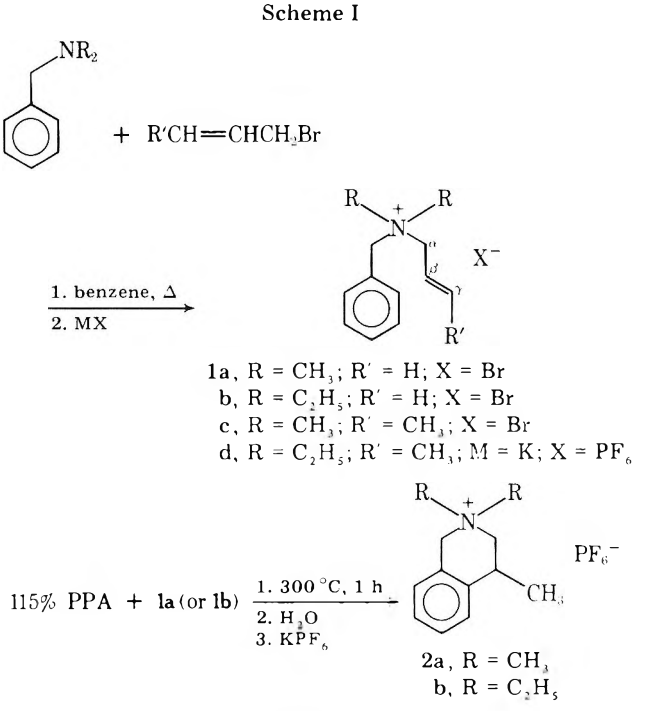
Received December 23, 1976

A simple method of wide scope for the synthesis of substituted indolium, quinolinium, isoquinolinium, and benzoazepinium salts has been developed from readily available starting materials. Quaternary ammonium compounds possessing a β-alkenyl substituent and an arylmethyl group readily cyclized in the presence of 115% polyphosphoric acid (PPA) at 300 °C for 1 h to furnish the substituted isoquinolinium and benzoazepinium salts in respectable yields (55–67%). On the other hand, alkenylanilinium salts cyclized at 130–140 °C for 1 h to give indolium and quinolinium salts in modest yields (18–38%). However, workup simply involved addition of the reaction mixture to ice–water to produce a homogeneous solution followed by the treatment with saturated aqueous KPF_6 and extraction of the salt formed with $HCCl_3$ or CH_2Cl_2. Spectral and elemental analyses supported the structures of the heterocyclic derivatives. A plausible mechanism involving the alkylation of a cation intermediate by the arene in a typical electrophilic substitution process is suggested for the salts carrying an arylmethyl group. In the case of the alkenylanilinium salts, the mechanism is not clear but rearrangements of the Claisen type appear to be operative.

Recently we reported[2] a facile ring closure of alkenylphosphonium salts containing an aryl or an arylmethyl group in the presence of 115% polyphosphoric acid (PPA) to furnish certain rare, difficultly accessible carbon–phosphorus heterocycles[3] in modest to good yields (24–82%). Likewise, treatment of arylmethylphosphonium salts having a β-carboxyl group produced functionalized C–P heterocycles in respectable yields.[4] The method appeared synthetically attractive from simplicity of experimental procedure alone which involved addition of the reaction mixture to ice–water followed by the treatment with aqueous saturated KPF_6 to precipitate the cyclic phosphonium salts often in a high state of purity.[2,4] Despite the widespread use of PPA as a cyclizing agent in organic synthesis for the obtention of a variety of ring systems,[5–7] quarternary ammonium compounds, via reaction with PPA, have not been fully explored as precursors to heterocyclic derivatives. However, related species may be expected to form from precursors containing heteroatoms in the cyclization reactions with PPA.[7] These considerations coupled with the observation[8,9] that arylphosphine oxides, with an appropriately oriented functionality, also cyclized smoothly in the presence of commercial 115% PPA[10] to give cyclic products, prompted us to extend the study to a few alkenyl substituted ammonium salts. We herein report the successful application of the technique to the synthesis of derivatives of indole, quinoline, isoquinoline, and benzoazepine from readily available, inexpensive reagents.

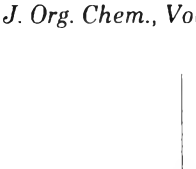
Allylbenzyldimethylammonium bromide (**1a**), the starting synthon, was prepared in near-quantitative yield by the quaternization of benzyldimethylamine with allyl bromide in benzene (Table I).[11] In the presence of 115% PPA at 300 °C for 1 h (Scheme I), salt **1a** cyclized to afford, after workup, the

Scheme I



crystalline 1,2,3,4-tetrahydro-2,2,4-trimethylisoquinolinium hexafluorophosphate (**2a**), mp 114.5–116.5 °C, in moderate yield (56%). ^1H NMR spectral analysis of the product **2a**, which contained the characteristic doublet for the C-methyl group at δ 1.41 (J_{HCCH} = 6 Hz), anchored the site of cyclization in **1a** at the β position (in relation to $>N^+<$ group). A gas, presumably HBr,[12] was evolved during the addition of the salt

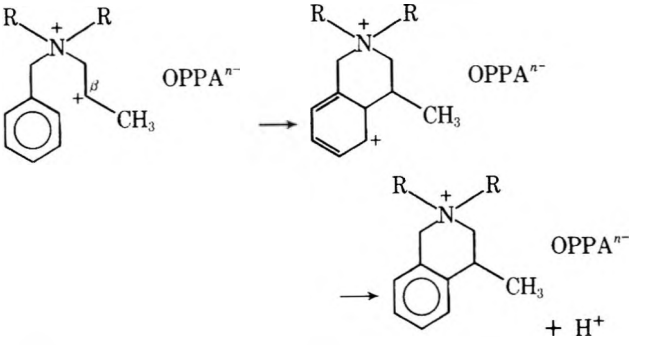
Table I



Compd	R	R′	X⁻	Mp, °C	Quaternizing solvent (reaction time, h)	Equiv of halide[a]	Yield, %[b]	Molecular formula		Anal., % C	H	N	P
1a[c]	CH_3	H	Br	99–100	Benzene (24)	1.16	97.7	$C_{12}H_{18}BrN$	Calcd	59.10	7.74	4.93	
1b	C_2H_5	H	Br	120–122	Benzene (24)	1.16	90.8	$C_{14}H_{22}BrN$	Found	58.87	8.07	5.00	
									Calcd	57.73	7.40	5.18	
1c	CH_3	CH_3	Br	128–129.5	Benzene (24)	1.10	93.3	$C_{13}H_{20}BrN$	Found	57.71	7.48	5.23	
									Calcd	49.59	6.61	3.86	8.54
1d[d]	C_2H_5	CH_3	PF_6	101–102	Benzene (26)	1.00	67	$C_{15}H_{24}F_6NP$	Found	49.39	6.63	3.80	8.51

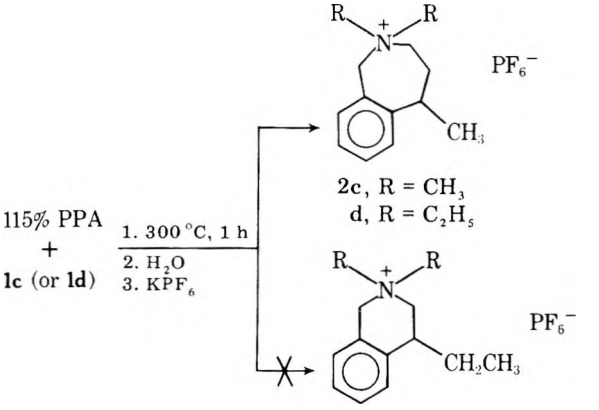
[a] Based on 1 equiv of amine. [b] Yield based on starting amine. [c] Previously reported in ref 11. [d] Isolated as the bromide and converted to the hexafluorophosphate derivative.

1a to PPA. Conceivably, the explusion of Br^- by PPA occurred during the reaction with simultaneous protonation of the olefinic bond in a preferred manner so as to produce a



cation at the β position.[2] Alkylation of the cation by the arene in a manner typical of an electrophilic substitution process followed by rearomatization would account for the observed product. Likewise, **1b** gave **2b** in good yield (67.6%). Interestingly, a seven-membered heterocyclic compound was *not* formed as judged from ^1H NMR analysis of the crude cyclized product obtained from **1a** or **1b**. In contrast, ammonium salts **1c** and **1d** possessing a crotyl chain, prepared by standard techniques (Table I) under identical reaction conditions, furnished the seven-membered cyclic salts **2c** and **2d**, respectively (Scheme II). No six-membered ring system was

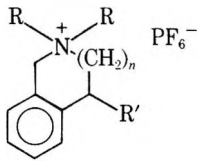
Scheme II



found. Here again, the position at which cyclization occurred was determined via ^1H NMR spectroscopy. Apparently, protonation of the olefinic bond must have occurred so as to produce a cation at the γ carbon (in relation to $>N^+<$) rather than a cation at the alternate β position. The results imply that (1) a cation intermediate is probably more stable at the γ position than a cation at the β position (hyperconjugative effect[2]); or (2) protonation is favored at the γ position in order to place the positive centers at the most remote positions. Unfortunately, lack of kinetic data with such ammonium salts or with related systems containing sulfur or phosphorus makes predictions extremely difficult.[13] An additional consideration must include the $>N^+<$ group which, although insulated from the aryl ring by the adjacent methylene, has been reported to deactivate the aromatic ring in electrophilic substitution reactions.[14] Nevertheless, the ring closure occurs in our systems.

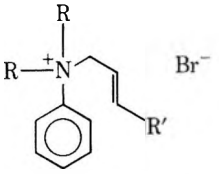
Very surprisingly the process was also found adaptable (although in low yields) for cyclization of anilinium salts possessing an alkenyl substituent. For example, treatment of allyldimethylanilinium bromide (**3a**)[15] in the presence of 115% PPA at 130–140 °C (Scheme III) gave the indolinium salt **4a** (after separation from a dark, viscous reaction mixture by column chromatography) only in low yield (18%). ^1H NMR analysis strongly suggested several components in the residual

Table II



Compd	R	R′	n	Mp, °C	Yield, %	Molecular formula	Anal., %	C	H	N	P
2a	CH_3	CH_3	1	114.5–116.5	56	$C_{12}H_{18}F_6NP$	Calcd	44.87	5.65	4.36	9.64
							Found	45.02	5.71	4.40	9.46
2b	C_2H_5	CH_3	1	131–132	67.6	$C_{14}H_{22}F_6NP$	Calcd	48.14	6.30	4.01	8.88
							Found	48.41	6.31	4.01	8.76
2c	CH_3	CH_3	2	122–123	62.5	$C_{13}H_{20}F_6NP$	Calcd	46.61	5.97	4.18	9.25
							Found	46.26	6.05	3.96	9.18
2d	C_2H_5	CH_3	2	128–129	55	$C_{15}H_{24}F_6NP$	Calcd	49.59	6.61	3.86	8.54
							Found	49.32	6.72	3.60	8.22

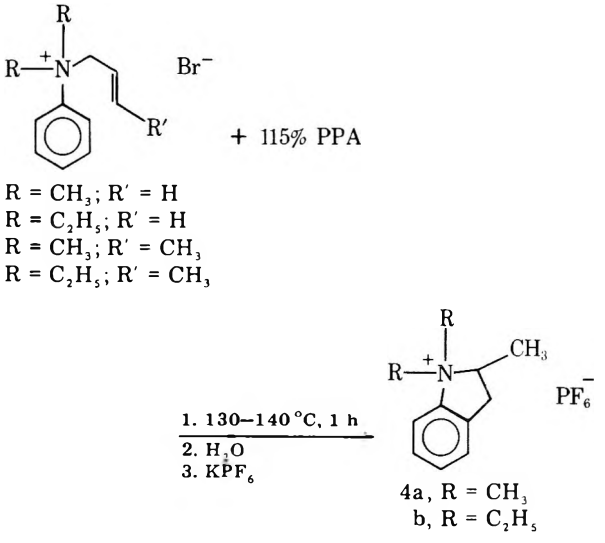
Table III



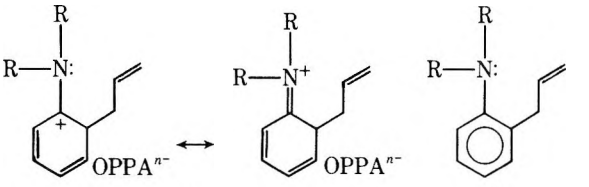
Compd	R	R′	Mp, °C	Quaternizing solvent (reaction time, h)	Equiv of halide[a]	Yield, %[b]
3a[c]	CH_3	H	123–124	Benzene (24)	1.32	96
3b[d]	C_2H_5	H	148–150	Neat (5 days)	1.24	75
3c[e]	CH_3	CH_3	123–125	Benzene (24)	1.00	54
3d	C_2H_5	CH_3	105–107	Neat (5 days)	1.26	90

[a] Based on 1 equiv of amine. [b] Yield based on starting amine. [c] Previously reported in ref 15 and 25. [The I^- and $(C_6H_5)_4B^-$ salts are reported in ref 19.] [d] Reported in ref 26 but no physical data were included. [e] Previously reported in ref 19 and 25 as the trans isomer, mp 143–144 °C. Our material is a mixture of cis and trans isomers in the ratio of 1:3.

Scheme III



mixture which, however, could not be readily separated. Repeated experiments aimed at improving the yield of the indolium salts utilizing the more abundant salt **3b** in the temperature range 150–300 °C gave only tarry material. At 100 °C, however, the starting material was recovered as the PF_6 salt, anion metathesis having occurred during the workup. Isolation of the cyclic products **4a** and **4b**, though in a low yield, is reasonable since the formation of the suspected intermediate **5** is like that found from an acid-catalyzed sigmatropic shift (Claisen type rearrangement) of allylaniline observed previously.[7] No such rearrangement has been reported from a quaternary salt, however. Solubility of the entire PPA reaction mixture in water and formation of the PF_6 salts upon addition of saturated aqueous KPF_6 to the resulting homogeneous solution is suggestive of stabilization of a cation intermediate by PPA anion ($OPPA^{n-}$). Recent mechanistic studies carried out in our laboratory[16] with structurally similar phosphonium salts via ^{31}P NMR spectroscopy support this hypothesis for the phosphorus system. In the present cases, the driving force for the reaction is probably the rapid loss of hydrogen from intermediate **5** (facilitated by the presence of the electron-deficient >N⁺< group)[14,17] to give **6** which cyclizes to **4a** or **4b**. Since salt **4a** was previously unreported, it was converted to the iodide, the properties of which were identical with those of that prepared by an alternative route (see Experimental Section).



5 6

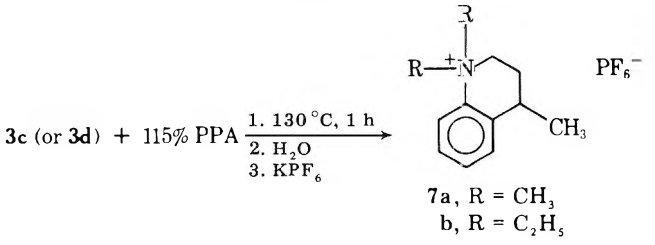
Anilinium salts **3c** and **3d** with a crotyl substituent also cyclized at 130 °C for 1 h in the presence of 115% PPA (Scheme IV) to give, surprisingly, the corresponding 4-alkylquinoline derivatives **7a** and **7b** as crystalline solids in low yields (21 and 29%). The position of the methyl group at C-4 rather than at C-2 in **7a** was confirmed by IR, ^1H NMR, elemental analysis, and by conversion to the iodide. The 4-isomeric iodide melted at 172–174 °C while the 2 isomer, which might result from **3c** by fragmentation and recombination of

Table IV. Physical Data for Indolium and Quinolinium Salts

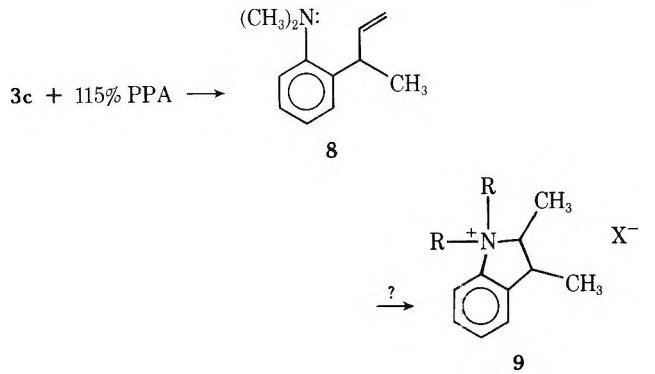
Compd	R	Mp, °C	Yield, %	Molecular formula	Anal., %	C	H	N	P
4a[a]	CH_3	140–141	18	$C_{11}H_{16}F_6NP$	Calcd	43.01	5.21	4.56	10.08
					Found	43.39	5.32	4.66	9.97
4b	C_2H_5	85–86	38	$C_{13}H_{20}F_6NP$	Calcd	46.61	5.97	4.18	9.25
					Found	46.67	6.10	4.16	8.98
7a[b]	CH_3	108–109	21	$C_{12}H_{18}F_6NP$	Calcd	44.87	5.65	4.36	9.64
					Found	44.68	5.68	4.29	9.73
7b	C_2H_5	150–152	29	$C_{14}H_{22}F_6NP$	Calcd	48.14	6.30	4.01	8.88
					Found	48.10	6.39	4.04	8.80

[a] Iodide; mp 208–210 °C. Anal. Calcd for $C_{11}H_{16}NI$: C, 45.71; H, 5.54; N, 4.84. Found: C, 45.65; H, 5.72; N, 4.90. [b] Iodide; mp 172–174 °C. Anal. Calcd for $C_{12}H_{18}NI$: C, 47.56; H, 5.94; N, 4.62. Found: C, 47.50; H, 6.12; N, 4.56.

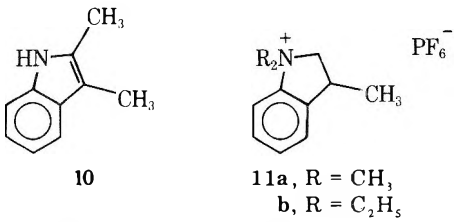
Scheme IV



the crotyl group, was reported to melt at 204 °C[18] and to have an ^1H NMR spectrum different from that of our isomer. Isolation and identification of **7a** was surprising in view of the predicted acid-catalyzed Claisen rearrangement of crotylaniline,[7,19] although admittedly the protonated form of the latter is not a quaternary salt. Since a complex mixture was formed from the PPA-catalyzed cyclizations leading to **7a** and **7b**, we cannot exclude the possibility that a Claisen-type intermediate (such as **8**) and product (such as **9**) are present in



low yields in the mixture. In fact, heating the $B(C_6H_5)_4$ salt of **3c** to 105 °C in HMPA has reportedly given **8**,[19] and heating crotylaniline in concentrated HCl reportedly gave the related product **10**.[7,19] In similar fashion, we cannot eliminate potential products **11a** or **11b** which, if present, are certainly in low yield in the mixture obtained from **3a** or **3b**, respectively.



In summary, the cyclization of allyl type, benzyl-substituted amines **1** proceeds well to give tetrahydroisoquinolines in modest yield but from stable, readily prepared synthons and under simple conditions. Although our approach does not supersede such methods as the classic Bischler–Napieralski,[20] Pictet–Spengler,[21] and Pomeranz–Fritsch[22] reactions, the use of quaternary salts does have the advantage that the immediate precursor can be made in large quantity and safely stored for long periods. On the other hand, the related quaternary anilinium salts **3** suffer some skeletal rearrangements during cyclization.

Experimental Section

General Data. Melting points were obtained with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-5A unit as KBr pellets. ^1H NMR spectra were recorded on a XL-100(15) Varian spectrometer equipped with a Nicolet TT-100 FT accessory and obtained with tetramethylsilane as the internal standard. Elemental analyses were carried out by Galbraith Laboratories, Knoxville, Tenn. Anhydrous solvents such as ether, petroleum ether (bp 40–60 °C), and benzene were dried over sodium and filtered prior to use. Neutral alumina (Brinkmann, activity I) supplied by Merck was employed for column chromatography.

Starting Materials. Allyl bromide, crotyl bromide, and the tertiary amines were all purchased from commercial sources and were purified by distillation prior to use. 2-Methylindole was purchased from Aldrich Chemical Co. The 115% PPA was obtained from FMC Corp.[10]

Allylbenzyldimethylammonium bromide (**1a**) was prepared from benzyldimethylamine and allyl bromide in benzene by the literature method.[11] Salt **1b** was prepared by a similar procedure. Anilinium salts **3a**[15] and **3c**[19,25] were prepared by known methods while the preparations of salts **3b** and **3d** followed a similar procedure and are reported in Table III.

Benzyl-2-butenyldimethylammonium Bromide (1c). A solution of benzyldimethylamine (13.5 g, 0.10 mol) and crotyl bromide (15.0 g, 0.11 mol) in dry benzene (175 mL) was boiled for 24 h (N_2). Rotoevaporation of the solvent left a viscous, brown oil which was boiled with ether (ca. 100 mL) for 3 h. The precipitated solid was filtered, washed with ether, and dried over P_2O_5 in vacuo (65 °C, 48 h) to give 25.2 g (93.3%) of **1c**, mp 128–129.5 °C. Infrared, ^1H NMR, and analytical data are given in Tables I and V.

Benzyl-2-butenyldiethylammonium Hexafluorophosphate (1d). A solution of benzyldiethylamine (8.0 g, 0.05 mol) and crotyl bromide (7 g, 0.05 mol) in dry benzene (150 mL) was boiled for 24 h (N_2) with the formation of a light brown oil. Benzene was removed in vacuo and the residual oil was boiled with ether (12 h) without solidification. The ether layer was decanted, the oil was dissolved in water (50 mL) and extracted with ether (2 × 100 mL), and the aqueous layer was treated with cold saturated solution of KPF_6 (50 mL). The cloudy solution was extracted with chloroform (4 × 200 mL), and the combined organic layers dried ($MgSO_4$). Evaporation of the solvent left an oil which, upon trituration with ether (200 mL), crystallized on standing. The filtered solid was dried over P_2O_5 in vacuo (70 °C, 72 h) to give 12.2 g (67%) of salt **1d**, mp 101–102 °C. Infrared, ^1H NMR, and analytical data are given in Table I and V.

Ring Closures to Produce the Isoquinolinium and Benzoazepinium Salts. The general procedure will be illustrated with the preparation of **2a.**

1,2,3,4-Tetrahydro-2,2,4-trimethylisoquinolinium Hexafluorophosphate (2a). In a 100-mL beaker was placed 60 mL of 115% PPA which was stirred with a mechanical stirrer and heated to 300 °C. Compound **1a** (2.0 g, 7.8 mmol) was added to the PPA in small

Table V. Spectral Data for the Starting Ammonium Salts and Reaction Products

Compd	IR absorption spectra in KBr,[a] selected bands, cm^{-1}	^1H NMR spectral assignments, chemical shifts, δ[b]
1a	1482 (m), 952 (m), 868 (vs), 782 (vs), 742 (vs), 703 (vs)	3.26 [s, $(CH_3)_2N^+<$, 6 H], 4.48 [d (J_{HCCH} = 6 Hz), $>N^+CH_2CH=$, 2 H], 5.12 (s, $ArCH_2N^+<$, 2 H), 5.56–6.40 (m, $-CH=CH_2$, 3 H), 7.30–7.90 (m, ArH, 5 H)
1b	1460 (m), 972 (m), 760 (vs), 722 (m), 708 (s)	1.47 [(J_{HCCH} = 7 Hz), $(CH_3CH_2)_2N^+<$, 6 H], 3.34–3.58 [q (J_{HCCH} = 7 Hz), $(CH_3CH_2)_2N^+<$, 4 H], 4.18 [d (J_{HCCH} = 6 Hz), $>^+NCH_2CH=$, 2 H], 4.84 (s, $ArCH_2N^+<$, 2 H), 5.48–6.38 (m, $-CH=CH_2$, 3 H), 7.22–7.82 (m, ArH, 5 H)
1c	1478 (m), 978 (m), 858 (s), 768 (m), 732 (m)	1.82 (d, $CH_3CH=$, 3 H), 3.22 [s, $(CH_3)_2N^+<$, 6 H], 4.42 (d, $>^+NCH_2CH=$, 2 H), 5.06 (s, $ArCH_2N^+<$, 2 H), 5.52–5.92 (m, $-CH=$, 1 H), 6.06–6.52 (m, $-CH=$, 1 H), 7.26–7.58 (m, ArH, 3 H), 7.60–7.88 (m, ArH, 2 H)
1d[c]	1460 (m), 982 (m), 835 (vs), 764 (s), 712 (s)	1.40 [t (J_{HCCH} = 7 Hz), $(CH_3CH_2)_2N^+<$, 6 H], 1.83 [d (J_{HCCH} = 6 Hz), $CH_3CH=$, 3 H], 3.03–3.28 [q (J_{HCCH} = 7 Hz), $(CH_3CH_2)_2N^+<$, 4 H], 3.68 [d (J_{HCCH} = 6 Hz), $>^+NCH_2CH$, 2 H], 4.28 (s, $ArCH_2N^+<$, 2 H), 5.38–5.80 (m, $-CH=$, 1 H), 5.80–6.36 (m, $-CH=$, 1 H), 7.22–7.60 (m, ArH, 5H)
2a	1490 (s), 835 (vs), 768 (s), 736 (m)	1.41 [d (J_{HCCH} = 6 Hz), CH_3CH, 3 H], 3.06 and 3.29 [s, $(CH_3)_2N^+<$, 6 H], 3.12–3.54 (m, $>N^+CH_2CH$, 2 H), 3.60–3.84 (m, $ArCH<$, 1 H), 4.24–4.68 (m, $ArCH_2N^+<$, 2 H), 7.02–7.50 (m, ArH, 4 H)
2b[c]	1485 (s), 838 (vs), 768 (s)	1.24–1.56 [m, $(CH_3CH_2)_2N^+<$ and $>CHCH_3$, 9 H], 2.90–3.58 [m, $(CH_2)_3N^+<$, 6 H], 3.58–3.84 (m, $ArCHCH_3$, 1 H), 4.20 (m, $ArCH_2N^+<$, 2 H), 7.00–7.46 (m, ArH, 4 H)
2c[c]	1482 (s), 838 (vs), 764 (s)	1.40 [d (J_{HCCH} = 6 Hz), CH_3CH, 3 H], 1.60–2.32 (m, $>CHCH_2$, 2 H), 2.82 and 3.17 [s, $(CH_3)_2N^+<$, 6 H], 2.50–3.80 (m, $>CHCH_3$ and $>^+NCH_2$, 3 H), 4.10–4.80 (m, $ArCH_2N^+<$, 2 H), 6.98–7.56 (m, ArH, 4 H)
2d[c]	1475 (m), 836 (vs), 768 (m)	1.06–1.56 [m, $(CH_3CH_2)_2N^+<$, 6 H], 1.43 [d (J_{HCCH} = 7 Hz), CH_3CH, 3 H], 1.62–2.36 (m, ring CH_2, 2 H), 2.80–3.66 [m, $(CH_2)_3N^+<$ and $ArCH<$, 7 H], 4.20–4.70 (m, $ArCH_2N^+<$, 2 H), 7.10–7.60 (m, ArH, 4 H)
3a[d]	1464 (m), 962 (m), 766 (s), 694 (s)	4.0 [s, $(CH_3)_2N^+<$, 6 H], 5.18 (m, $>N^+CH_2-$, 2 H), 5.36–5.96 (m, $-CH=CH_2$, 3 H), 7.40–7.78 (m, ArH, 3 H), 8.04–8.24 (m, ArH, 2 H)
3b	1485 (s), 1460 (s), 960 (s), 768 (s), 710 (s), 692 (s)	1.26 [t (J_{HCCH} = 7 Hz), $(CH_3CH_2)_2N^+<$, 6 H], 4.00–4.44 [m, $(CH_3CH_2)_2N^+<$, 4 H], 4.82 (m, $>N^+CH_2-$, 2 H), 5.48–5.94 (m, $-CH=CH_2$, 3 H), 7.40–7.82 (m, ArH, 3 H), 8.10–8.36 (m, ArH, 2 H)
3c[d]	1486 (s), 965 (m), 850 (m), 760 (m), 692 (s)	1.62 [d (J_{HCCH} = 6 Hz), trans CH_3], 1.80 [d (J_{HCCH} = 7 Hz), cis CH_3] (trans 66.7% and cis 33.3%), 3.94, 4.07 [s, $(CH_3)_2N^+<$, 6 H], 5.11 (m, $>N^+CH_2-$ and $-CH=$, 3 H), 6.22 (m, $-CH=$, 1 H), 7.38–7.76 (m, ArH, 3 H), 7.98–8.20 (m, ArH, 2 H)
3d	1482 (s), 972 (m), 895 (m), 848 (m), 780 (s), 772 (s), 696 (s)	1.22 [t (J_{HCCH} = 7 Hz), $(CH_3CH_2)_2N^+<$, 6 H], 1.74 [d (J_{HCCH} = 6 Hz), $CH_3CH=$, 3 H], 3.94–4.46 [m, $(CH_3CH_2)_2N^+<$, 4 H], 4.56–4.86 (m, $>N^+CH_2-$, 2 H), 5.20–5.60 (m, $CH=$, 1 H), 6.04–6.46 (m, $CH=$, 1 H), 7.34–7.80 (m, ArH, 3 H), 8.04–8.36 (m, ArH, 2 H)
4a[c]	1465 (s), 838 (vs), 765 (m), 724 (m)	1.70 [d (J_{HCCH} = 7 Hz), $>CHCH_3$, 3 H], 3.12 and 3.48 [s, $(CH_3)_2N^+<$, 6 H], 2.94–3.62 (m, benzylic CH_2, 2 H), 4.14–4.40 (m, CH_3CH, 1 H), 7.40–7.62 (m, ArH, 4 H)
4b[c]	1476 (s), 840 (vs), 770 (m), 722 (m)	1.10–1.30 [t of t (J_{HCCH} = 7 Hz), $(CH_3CH_2)_2N^+<$, 6 H], 1.70 [d (J_{HCCH} = 6 Hz), $>CHCH_3$, 3 H], 2.94–4.04 [m, $(CH_3CH_2)_2N^+<$ and benzylic CH_2, 6 H], 4.30–4.60 (m, $CHCH_3$, 1 H), 7.32–7.58 (m, ArH, 4 H)
7a[c]	1474 (s), 840 (vs), 766 (s), 764 (m)	1.40 [d (J_{HCCH} = 8 Hz), CH_3CH, 3 H], 1.78–2.62 (broad m, ring CH_2, 2 H), 3.04–3.30 (m, $>CHCH_3$, 1 H), 3.52 and 3.58 (s, $(CH_3)_2N^+<$, 6 H), 3.76–3.92 (m, $>N^+CH_2-$, 2 H), 7.36–7.66 (m, ArH, 4 H)
7b[c]	1462 (m), 842 (vs), 762 (s)	1.25–1.48 [m, $(CH_3CH_2)_2N^+<$ and CH_3CH, 9 H], 1.80–2.66 (m, ring CH_2, 2 H), 3.06–3.30 (m, $>CHCH_3$, 1 H), 3.56–4.04 [m, $(CH_3CH_2)_2N^+<$ and benzylic CH_2, 6 H], 7.30–7.54 (m, ArH, 4 H)

[a] The spectra were obtained on samples (2–4 mg) with KBr (400 mg) pellets. All the PF_6 salts showed very strong absorption in the region 830–840 cm^{-1}; see L. C. Thomas, "Interpretation of the Infrared Spectra of Organophosphorus Compounds", Heyden, London, 1974, Chapter 7. [b] Spectra obtained on $DCCl_3$ solution of each compound with Me_4Si as internal standard; peak positions quoted in the case of doublets are measured from the approximate center, and relative peak areas are given as whole numbers. [c] ^1H NMR spectra obtained in $DCCl_3$ with added trifluoroacetic acid to give a clear solution. [d] IR and ^1H NMR of $(C_6H_5)_4B$ salt reported in ref 19.

portions over a 10-min period followed by additional heating and stirring for 1 h. During the addition, a gas (presumably HBr[12]) was evolved. The dark brown solution was cooled to 90–100 °C and slowly poured onto 300 mL of ice–water with swirling, a process which resulted in formation of a *homogeneous solution* upon stirring for 15 min. The solution was filtered to remove black particles and the brown filtrate was treated with saturated KPF_6 (75 mL) in the cold to the formation of cloudiness. This mixture was concentrated in a rotary evaporator to about 200 mL until excess KPF_6 precipitated and repeatedly extracted with chloroform (6 × 200 mL). The organic layer was dried ($MgSO_4$), filtered, and treated with carbon black which, when filtered hot, left a colorless filtrate. Evaporation of the solvent

gave a brown oil which, when triturated with ether (100 mL), solidified. The solid was collected and recrystallized twice from CH_2Cl_2–ether to afford 1.4 g (56%) of salt **2a**, mp 114.5–116.5 °C. Infrared, ^1H NMR, and analytical data are given in Tables II and V.

Ring Closures to Produce the Indolium Salts. The general procedure will be illustrated with the preparation of **4a**.

2,3-Dihydro-1,1,2-trimethylindolium Hexafluorophosphate (4a). To 60 mL of 115% PPA mechanically stirred and heated to 140 °C, salt **3a** (2.0 g, 7.41 mmol) was added during a 10-min period, followed by an additional period of heating for 1 h. Workup was as described for **2a** to afford a dark brown oil (1.9 g). The oil was dissolved in a minimum amount of CH_2Cl_2 and eluted through an alumina column (60 g) with CH_2Cl_2. Evaporation of the solvent to a small volume, followed by the dropwise addition of ether to produce turbidity, afforded, upon standing in the refrigerator, salt **4a**. Crystallization (twice) from CH_2Cl_2–ether afforded pure **4a** (430 mg, 18%) as a white, crystalline solid, mp 140–141 °C. The identity of **4a** was established by conversion to the known iodide, mp 208–210 °C (methanol–ethyl acetate, lit.[23] 208–210 °C), by metathesis of the anion of **4a** with potassium iodide in CH_3CN/H_2O. A more direct proof that the product isolated in the above reaction was the 2-methylindolium salt rather than the 3-methylindolium hexafluorophosphate was obtained as follows.

2-Methylindole was reduced by the known method[24] to 2,3-dihydro-2-methylindoline which gave the following spectral data: IR (film) ν 3330, 1640, 1448, 1435, 1250, 752 cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.14 [d (J_{HCCH} = 6 Hz), CH_3CH, 3 H], 2.38–3.13 (pair of quartets, benzylic CH_2, 2 H), 3.62 (s, >NH, 1 H, which disappeared on shaking with D_2O), 3.66–3.88 (m, –CH, 1 H), and 6.45–7.04 (m, ArH, 4 H). Alkylation with methyl iodide by the reported procedure[23] gave the methiodide as a white, crystalline solid, mp 208–210 °C (methanol–ethyl acetate, lit.[23] 208–210 °C), with the following spectral properties: IR (KBr) ν 1475, 1450, 1230, 1024, 982, 762, 718 cm^{-1}; ^1H NMR (F_3CCO_2D) δ 1.81 [d (J_{HCCH} = 7 Hz), >CHC**H**$_3$, 3 H], 3.28 and 3.64 [s, >N$^+$(C**H**$_3$)$_2$, 6 H], 3.00–3.70 (m, benzylic CH_2, 2 H), 4.34–4.60 (m, >C**H**CH$_3$, 1 H), and 7.55–7.76 (m, ArH, 4 H). The iodide was transformed to the PF_6 salt, mp 140–141 °C (CH_2Cl_2–ether), by the same procedure in CH_3OH/H_2O with KPF_6. The melting points of the PF_6 salt and the iodide from the PPA cyclization reaction were not depressed on admixture with authentic samples of the PF_6 salt and the iodide, respectively. Furthermore, infrared and ^1H NMR of both the PF_6 salt and the iodide were identical with those of authentic samples. Infrared, ^1H NMR, and analytical data are given in Tables II and V.

Ring Closures to Produce Quinolinium Salts. The general procedure will be illustrated with the preparation of **7a**.

1,2,3,4-Tetrahydro-1,1,4-trimethylquinolinium Hexafluorophosphate (7a). To a well-stirred sample of 115% PPA maintained at 130 °C salt **3c** (2 g, 7.80 mmol) was added during a 10-min period and heating was continued for 1 h. Workup of the reaction mixture was carried out as described previously for **2a**. The resulting dark-colored gum (1.65 g) was chromatographed over neutral alumina (45 g). Elution with hexane and subsequent purification by short-path distillation afforded a light brown oil (0.49 g), bp 85 °C (0.25 mm), which appeared to be a mixture of several products on analysis by ^1H NMR. Further elution with $HCCl_3$ and CH_2Cl_2 afforded a white solid, after solvent evaporation, which was crystallized twice from CH_2Cl_2–ether to afford the crystalline salt **7a** (0.53 g, 21%), mp 108–109 °C. Infrared, ^1H NMR, and analytical data are given in Tables II and V. The corresponding iodide, prepared by the general metathesis reaction, melted at 172–174 °C (CH_2Cl_2–ether), and had the following spectral data: IR (KBr) ν 1495, 1440, 1052, 948, 850, 772 cm^{-1}. ^1H NMR (F_3CCO_2D) δ 1.50 [d (J_{HCCH} = 7 Hz, >CHC**H**$_3$, 3 H], 1.86–2.72 (broad m, ring CH_2, 2 H), 3.10–3.32 (m, benzylic >CH–, 1 H), 3.62 and 3.66 [s, >N$^+$(C**H**$_3$)$_2$, 6 H], 3.88–4.10 (m, >N$^+$C**H**$_2$, 2 H), and 7.48–7.74 (m, ArH, 4 H). A report[18] of the 2 isomer gives a mp of 204 °C along with an ^1H NMR spectrum different from that of our product.

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Registry No.—**1a**, 22100-10-3; **1b**, 62076-98-6; **1c**, 62058-78-0; **1d**, 62058-80-4; **2a**, 62058-82-6; **2b**, 62058-84-8; **2c**, 62058-86-0; **2d**, 62077-00-3; **3a**, 16370-22-2; **3b**, 62058-87-1; *cis*-**3c**, 62058-88-2; *trans*-**3c**, 62058-89-3; **3d**, 62058-90-6; **4a**, 62058-92-8; **4a** iodide, 62058-93-9; **4b**, 62058-95-1; **7a**, 62058-97-3; **7a** iodide, 62058-98-4; **7b**, 62059-00-1; benzyldimethylamine, 103-83-3; crotoyl bromide, 4784-77-4; benzyldiethylamine, 772-54-3; methylindole-2, 95-20-5; 2,3-dihydro-2-methylindoline, 6872-06-6; methyl iodide, 74-88-4.

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Ring-Opening Reactions. 1. Decomposition of Some Quaternary Ammonium Ions with Sodium Methoxide in Methanol

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Product analysis and partial rate coefficients have been obtained for the reaction of five- and six-membered cyclic ammonium ions with sodium methoxide in methanol. The overall process consists of three competing reactions, two of which involve ring opening and are controlled by steric and stereochemical factors as functions of ring structure and reaction type; related data for the dibutyldimethylammonium ion have also been obtained for comparison.

The olefin-forming decomposition of quaternary ammonium salts and of the related amine *N*-oxides has drawn the attention of several groups[1-4] and owes much of its importance to the structure elucidation of alkaloids by the well-known Hofmann exhaustive methylation procedure.[5]

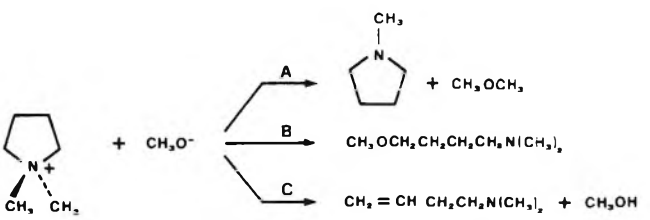
The reaction is generally accompanied by nucleophilic substitution at the nitrogen-bonded saturated carbon.[5,6] Starting from cyclic ammonium ions both olefin-forming β-elimination and endocyclic substitution lead to ring opening. The relative importance of the competitive changes is expected to depend on the conformational and other structural features of the ring as well as on the anionic reagent, reactant concentrations, and other experimental conditions. Although several studies have dealt with the product composition of these reactions under varying conditions, no rate study is available for use in reactivity–structure correlations.

Knowledge of the diverse response of ring opening to competitive reactions having different mechanistic requirements should throw light on the nature of the major factors involved in reactivity parameters. In connection with our current interest in ring-forming and ring-opening reactivity,[7,8] we have undertaken quantitative investigations on the degradation of cyclic quaternary ammonium salts. In this paper we wish to report on the product analyses and partial rate factors for the reaction of *N,N*-dimethylpyrrolidinium (I) and *N,N*-dimethylpiperidinium (II) iodides and, for comparison, the open-chain dibutyldimethylammonium iodide (III) with sodium methoxide in methanol.

Results and Discussion

The reactions were carried out in 0.05–0.10 M solution and followed to complete conversion at 130 °C in sealed ampules. Product analyses were performed by a VPC method and reaction rates measured by acid–base potentiometric titration of the total amine product formed. The results are reported in Table I. The overall process for the cyclic substrates consists of three competing reactions, A, B, and C, that are shown typically for compound I in Scheme I. The reactions observed

Scheme I



for the open-chain compound are the demethylation (A), the debutylation (B), and the olefin-forming elimination (C) (see Experimental Section). The observed product composition data are in agreement with known trends caused by the influence of reactant concentrations[5,9] and of the base/solvent system.[5,10,11] At concentrations as low as those used in this work β-elimination from compounds I and II and sodium methoxide occurs to a much lesser extent than from the corresponding hydroxides under typical Hofmann exhaustive methylation concentrations.[1] In contrast, when the PhS^-/HMPT system is used[12] no β-elimination product is formed at all.

The degradation followed second-order kinetics and was assumed to consist of three bimolecular components (A, B, and C) whose rate constants were calculated by combining the overall rate constant value (k_T) with the composition data (Table I). The k_A, k_B, k_C are partial rate coefficients that are related to free energies of activation for changes having substantially similar ground states and differing by their transition states. The diverse factors[13] related to the ring structure of substrates I and II, such as ring strains and ease of approach of the reagent, are expected to influence such transition states in different ways and, therefore, to yield useful information on their relative importance.

The reactivities of compounds I and II toward the exocyclic displacement (A) are essentially the same and similar to that of the open-chain compound III. It is of interest that the quaternization of cyclic amines by methyl iodide,[13] which involves a reversal of the change experienced at the nitrogen atom and an increase in coordination number from 3 to 4, shows some selectivity when the five- and six-membered rings are compared, the five-ring/six-ring reactivity ratio being about 4. In both reactions a transition state of the type $[N^{\delta+}\cdots CH_3\cdots X^{\delta-}]$ is involved. Apparently C–N bond breaking for the demethylation reaction (X = CH_3O) is less important than C–N bond making for the quaternization reaction (X = I), largely as a consequence of the nature of X.

The strain energy is known to be higher for a five-membered than for a six-membered ring.[14] Consequently, the ease of ring opening should be greater in the former case. This is consistent with the fact that the endocyclic displacement (B) is faster than reaction A for compound I, whereas it is markedly slower for compounds II and III, by factors of 24 and 32, respectively. In the former case the rate-depressing steric effect expected for the "more branched" alkyl group (k_B) is presumably more than offset by ring strain relief. However, the relatively high k_B value for I may also be partly caused by a reduced steric requirement of the transition state for reaction B due to the different geometry of the five-membered ring as compared to the six-membered ring.[12]

The results on reaction C show a major point of stereochemical interest; the reaction rate for compound I is 75-fold lower than that of reaction B, whereas it is 3- and 15-fold higher for compounds II and III, respectively. As models indicate, compound II is expected to attain a more closely anti-periplanar conformation than the five-membered ring in the transition state of the E2 mechanism, whereas syn elimination can be excluded. As a result of the competition

Table I. Product Analysis and Second-Order Rate Constants (M^{-1} s^{-1}) for the Reaction of Some Quaternary Ammonium Iodides with Sodium Methoxide in Methanol at 130 °C[a]

	I	II	III
10^4k_T	3.80	0.702	1.40
Reaction A, %	16.4	86.0	67.0
10^4k_A	0.623	0.604	0.938
Reaction B, %	82.5	3.6[b]	2.1
10^4k_B	3.14	0.0251	0.0294
Reaction C, %	1.1[c]	10.4	30.9
10^4k_C	0.0418	0.0729	0.433

[a] The precision in the product analysis was better than ±3% unless stated otherwise; that in the overall rate constants was better than ±2%. [b] ±6%. [c] ±7%.

between the ring-opening reactions B and C elimination is more important than substitution for the more flexible structures II and III, whereas the opposite is true for compound I. Also, the more flexible structure III (open chain) is more prone to elimination than II (six-ring) by a rate factor of about 6. A still more marked drop in rate of elimination would be expected in going from II to I (five-ring). A rate depression of only 1.7 is found, however, and can be consistently explained by the intervention of some steric strain relief which would accompany the opening of the five-membered ring in both reactions C and B.

It should be noted that, although conclusions similar to the above discussion can be drawn from the composition data of Table I, on comparing different substrates they are fortuitous unless reaction rates are obtained. Such information has been provided here for the first time. Another example of composition data which can be correctly interpreted in terms of reactivity comes from the decomposition of the spiro-*N,N*-tetramethylenepiperidinium ion[15,16] where five- and six-membered rings compete for the same reaction in the same molecule. The results, though qualitative, are in essential agreement with the present data since only the five-membered ring of the spiro ion is reported to undergo cleavage for the endocyclic displacement whereas for the β-elimination reaction both rings are cleaved in approximately equal amounts.

We plan to extend this investigation to other cyclic ammonium ions in the small- and medium-ring region and to other base–solvent media.

Experimental Section

Proton magnetic resonance spectra were obtained in $CDCl_3$ solution on a JEOL JNM-C60HL spectrometer, using Me_4Si as the internal standard. Mass spectra were performed either on a AEI MS12 at 70 eV or Varian MAT 111 spectrometer at 80 eV. The preparative VPC experiments were carried out on a Carlo Erba Fractovap Model B instrument. For the VPC analyses and the potentiometric microtitrations see the appropriate section.

Materials. *N*-Methylpyrrolidine (Schuchardt), *N*-methylpiperidine (Schuchardt), butyl methyl ether (Fluka), *n*-butylamine (Erba), and dibutylamine (Fluka) were commercial samples.

N,N-Dimethylpyrrolidinium iodide (I) and *N,N*-dimethylpiperidinium iodide (II) were prepared as described in the literature,[17] in 96 and 92% yields, respectively. Iodide ion content was checked by potentiometric titration and indicated a purity of 100% for both salts.

Dibutyldimethylammonium iodide (III) was prepared according to the procedure used for the preceding salts. It was purified by recrystallization from ethanol–ethyl acetate to give white crystals in 76% yield, mp 148–149 °C (lit.[18] 149–150 °C). Iodide ion analysis indicated a purity of 99%.

4-Dimethylamino-1-butene and 5-dimethylamino-1-pentene were prepared as described in the literature,[19] in 26 and 57% yields, respectively.

Butyldimethylamine was obtained in 86% yield by methylation of butylamine by the Clarke–Eschweiler method,[20] bp 93–95 °C (lit.[21] 94 °C). Dibutylmethylamine was similarly obtained in 80% yield, bp 56–57 °C (18 mm) [lit.[18] 49–51 °C (10 mm)].

The purity and structure of the synthesized amines were thoroughly checked by gas chromatography and ^1H NMR spectrometry.

Kinetics. The overall rates were measured by acid–base potentiometric titration of the total amine product formed. A solution of dried (Adberhalden) ammonium iodide in anhydrous methanol was mixed with the required volume of a stock solution of sodium methoxide in the same solvent. The resulting mixture, 0.1 M in methoxide and 0.05 M in the ammonium salt, was transferred in 1.3-mL aliquots, by an automatic pipet, to dried ampules which were flushed with dry nitrogen and sealed. Two ampules were kept for blank determination. A set of 15–20 ampules was placed in a thermostat at 130 °C, and zero time started 5 min after immersion. A 1-mL aliquot of solution was transferred with a pipet from the ampule to a titration vessel containing 20 mL of acetone and an excess of *p*-toluenesulfonic acid (1 mL, added from a stock methanolic solution), and titrated with 0.05 M tetrabutylammonium hydroxide in MeOH/*i*-PrOH using Radiometer glass G202C and calomel K401 electrodes. Microtitrations were performed with a Radiometer SBR2c-TTT1c-ABU1b apparatus, fitted with a 2.50-mL microburet. End points were determined graphically from the recorded titration curves. Blank determinations were carried out by the same procedure and the value of the actual determination was corrected accordingly. The extent of reaction at infinity time was determined either by potentiometric titration or by VPC measurement (with an internal standard) and found to be no less than 92% for a reaction range wider than 2 half-lives.

Runs were made on the ammonium salts in the absence of sodium methoxide, in order to check the occurrence of solvolyses and of any attack by iodide ion. All such reactions were negligibly slow in comparison with the reaction with methoxide (VPC analysis).

The rate constant of the overall process, k_T, has been evaluated from the integrated second-order rate equation. A least-squares treatment, as carried out with the aid of a Hewlett-Packard 9820A calculator, gave the slope (k_T).

Product Analysis and Partial Rate Coefficients. A. Preparative scale experiments were carried out for the identification of the reaction products. A methanolic solution, 0.5 M in methoxide and 0.25 M in the ammonium iodide, was prepared in a 200-mL Carius tube by adding the required volume of stock methanolic sodium methoxide to a solution of dried ammonium iodide. The tube was sealed and heated in an oven at 130 °C for 48–72 h, than cooled and opened. The content was transferred into a flask, acidified with concentrated HCl, and evaporated to dryness on a rotary evaporator. The solid residue was dissolved in water and the organic bases set free with 18 M NaOH. The aqueous layer was extracted with pentane, and the extract was separated, dried over anhydrous Na_2CO_3, and concentrated. The latter was shown to consist of three compounds by TLC, which were purified by column chromatography on grade II–III alumina (Merck) using petroleum ether (bp 40–60 °C) with an increasing concentration of ether. The three bases thus separated were recovered by removal of the solvents, purified by preparative gas chromatography, and identified by ^1H NMR, mass spectrum, and C, H, N analysis, unless direct VPC comparison was made possible with the aid of an authentic sample.

In the reaction of I two of the components were identified as 4-dimethylamino-1-butene and *N*-methylpyrrolidine by VPC comparison with authentic samples. The third component was identified as 4-dimethylamino-1-butyl methyl ether from the following data: ^1H NMR δ 3.2–3.5 (m, 5 H, CH_2OCH_3 protons), 2.1–2.4 [m, 8 H, $CH_2N(CH_3)_2$ protons], 1.3–1.8 (m, 4 H, "central" methylene protons). In the mass spectrum the product showed a molecular peak at *m/e* 131 (calcd 131) together with a base peak at *m/e* 58, probably due to the fragment $(CH_3)_2{}^+N{=}CH_2$.

Anal. Calcd for $C_7H_{17}NO$: C, 64.07; H, 13.06; N, 10.67. Found: C, 63.91; H, 13.00; N, 10.64.

In the reaction of II two of the components were identified as 5-dimethylamino-1-pentene and *N*-methylpiperidine by comparison with authentic samples. The third component was identified as 5-dimethylamino-1-pentyl methyl ether from the following data: ^1H NMR δ 3.2–3.5 (m, 5 H, CH_2OCH_3 protons), 2.0–2.4 [m, 8 H, $CH_2N(CH_3)_2$ protons], 1.2–1.8 (m, 6 H, "central" methylene protons). In the mass spectrum the product showed a molecular peak at *m/e* 145 (calcd 145), together with a base peak at *m/e* 58, probably due to the fragment $(CH_3)_2{}^+N{=}CH_2$.

In the reaction of III all the components were identified by VPC comparison with authentic samples as butyl methyl ether, butyldimethylamine, and dibutylmethylamine.

B. The rate constants for the individual reactions A, B, and C (Table I) were calculated from the overall rate constant and the composition data. To this end the product composition was determined under kinetics conditions. Four ampules from each set of rate measurements were kept at 130 °C for a time interval corresponding to 80–100% reaction. The content of the ampules (5 mL) was transferred into a 10-mL flask, acidified with 0.2 M HCl, and evaporated to dryness on a rotary evaporator at 40 °C. The solid residue was treated with 5 M NaOH (2 mL) and the organic bases extracted with pentane (3 mL). The pentane extract was analyzed by gas chromatography which was carried out with a Carlo Erba Fractovap Model GI instrument, fitted with a 20% Carbowax 20M on a firebrick (pretreated with sodium hydroxide) column operating in the range 70–180 °C. In the case of compound III a portion of the content (2–3 μL) of the ampules was directly injected into the gas chromatograph. The peaks were identified by comparison with authentic specimens of the compounds. The areas were measured and the molar ratios among the various components were determined by internal calibration based on the analysis of "synthetic" mixtures. Correction factors used for the quantitative evaluation of peak areas were obtained by subjecting standard mixtures of the three reaction products (prepared by accurately mixing weighed amounts of the three products) to the operations involved in the actual isolation procedure. For the cyclic ammonium salts I and II, the percentage found for each tertiary amine in the reaction mixture was the actual percentage of the corresponding reaction; for the open-chain ammonium salt III, the tertiary amine $CH_3CH_2CH_2CH_2N(CH_3)_2$ was produced by both reactions B and C. The contribution of reaction B was evaluated by the VPC determination of the content of $CH_3CH_2CH_2CH_2OCH_3$.

Registry No.—I, 872-44-6; II, 3333-08-2; III, 61134-94-9; sodium methoxide, 124-41-4; methanol, 67-56-1; 4-dimethylamino-1-butene, 55831-89-5; *N*-methylpyrrolidine, 120-94-5; 4-dimethylamino-1-butylmethyl ether, 33962-95-7; 5-dimethylamino-1-pentene, 1001-91-8; *N*-methylpiperidine, 626-67-5; 5-dimethylamino-1-pentylmethyl ether, 58390-18-4; butyl methyl ether, 628-28-4; butyldimethylamine, 927-62-8; dibutylmethylamine, 3405-45-6.

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Synthesis and Structure of Alloxazine 5,10-Dioxides

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Various alloxazine 5,10-dioxides (**7**–**9**) have been synthesized by direct H_2O_2/trifluoroacetic acid oxidation and their structures proven to consist preferentially in the 1H tautomeric lactam configuration. The three methyl blocked tautomeric forms **12**–**14** of 3-methylalloxazine 5,10-dioxide (**8**) could be obtained by diazomethane methylation of **8**. Comparisons of the UV spectra are used for the structural assignments.

The first alloxazine *N*-oxide was prepared by Petering,[1,2] who oxidized 8-chloroalloxazine with 30% H_2O_2 in 88% formic acid at 65–95 °C and believed that the 5,10-dioxide was synthesized. In trying to repeat this procedure Berezovskii et al.[3–5] claimed to have obtained only the 10-oxides when oxidizing alloxazine and its methyl derivatives with H_2O_2 in formic acid, with peracetic acid, and with monopersulfuric acid. However, Gladys and Knappe[6] were unable to confirm this.

There is some agreement that the conditions used by Petering will lead to mono-*N*-oxides, specifically the *N*-10-oxide if the N-1 is unsubstituted and the *N*-5-oxide if there is an alkyl substituent in the 1-position. This sensitivity toward steric (peri) hindrance parallels the findings with lumazine *N*-oxides by Pfeiderer and Hutzenlaub.[7] In related studies, alloxazine 5-oxides were prepared by the "indirect" cyclization methods[8–14] which permitted unambiguous placement of the *N*-oxide grouping in the 5-position. Alloxazine 5,10-dioxides have not yet been synthesized via this route.

Since close relationships can be expected between the published structures of lumazine 5,8-dioxides and its alloxazine analogues, we decided to study the structure of alloxazine 5,10-dioxides. These compounds can exist mainly in two energetically favored tautomeric forms, where A would be con-

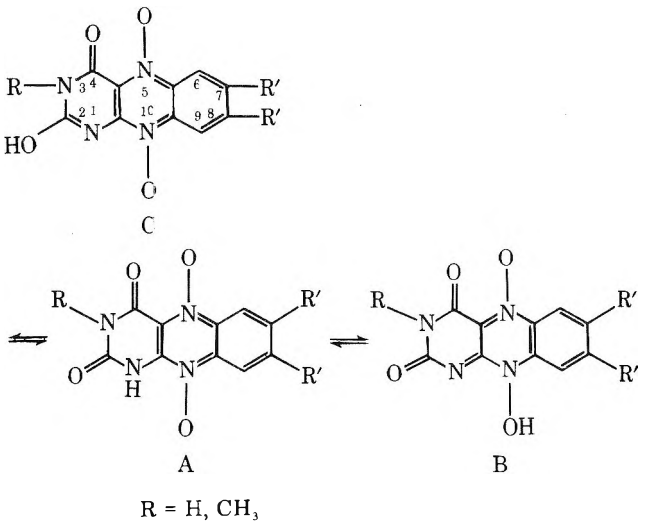


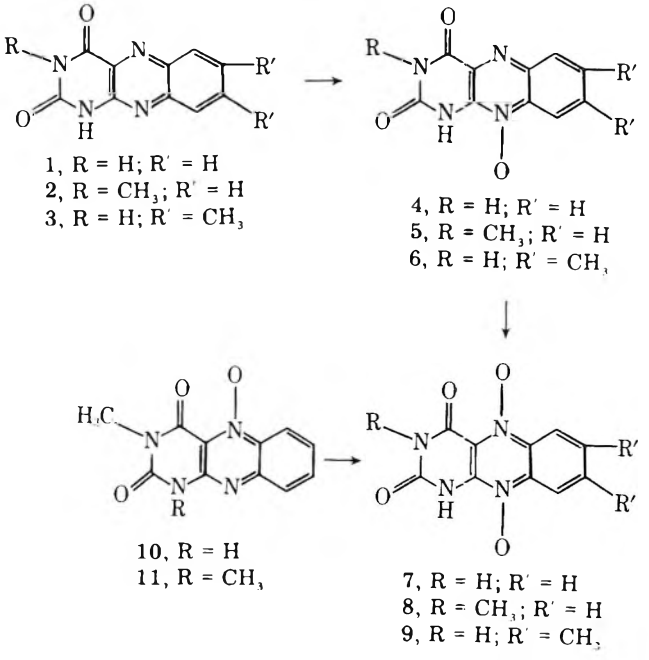
Table I. 90-MHz NMR Spectra of Alloxazine *N*-Oxides in $CDCl_3$[a]

	Aromatic protons	*O*-CH_3 (3)	*N*-CH_3
1,3-Dimethylalloxazine 5-oxide (11)	8.29 m (1), 7.86 m (2), 7.64 m (1)		3.79 s (3) 3.50 s (3)
1,3-Dimethylalloxazine 5,10-dioxide (13)	8.55 m (2), 7.84 m (2)		4.00 s (3) 3.44 s (3)
3,2-*O*-Dimethylalloxazine 5,10-dioxide (12)	8.69 m (2), 7.82 m (2)	4.35 s	3.57 s (3)
3-Methyl-10-methoxyalloxazine 5-oxide (14)	8.49 m (1), 7.89 m (2), 7.60 m (1)	4.31 s	3.45 s (3)

[a] δ values in parts per million, Me_4Si internal standard; s = singlet, m = multiplet, number of protons in parentheses.

sidered as a true di-*N*-oxide and B as a vynclogous cyclic hydroxamic acid. The lactim form, C, is another disfavored tautomer of less importance. It was necessary to prepare in addition to the alloxazine di-*N*-oxides their methyl blocked tautomers for spectral comparison in order to differentiate between these forms.

When alloxazine (1), its 3-methyl (2), and 7,8-dimethyl derivative (lumichrome) (3) were oxidized at room temperature with a large excess of H_2O_2 in trifluoroacetic acid for several days, the corresponding 5,10-dioxides 7–9 were formed via the *N*-10-monooxides 4–6. We then prepared 1,3-dimethylalloxazine 5-oxide (11) using the procedure of Goldner



1, R = H; R′ = H
2, R = CH_3; R′ = H
3, R = H; R′ = CH_3

4, R = H; R′ = H
5, R = CH_3; R′ = H
6, R = H; R′ = CH_3

10, R = H
11, R = CH_3

7, R = H; R′ = H
8, R = CH_3; R′ = H
9, R = H; R′ = CH_3

12

+

13

+

14

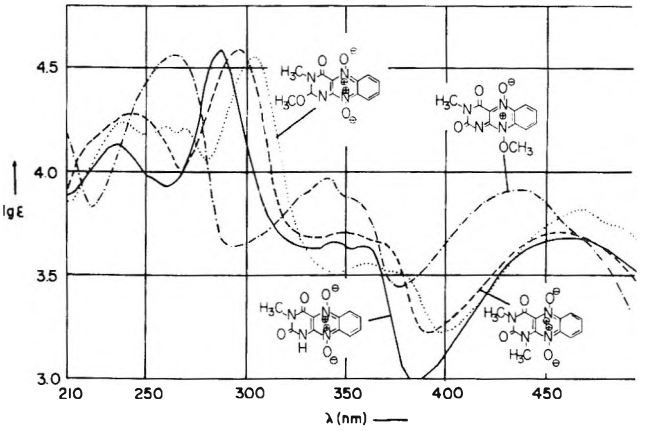


Figure 1. UV spectra of 3-methyl- (8) —, 1,3-dimethyl- (13) - - -, 2,3-*O*-dimethylalloxazine 5,10-dioxide (12) · · ·, and 3-methyl-10-methoxyalloxazine 5-oxide (14) - · - · - in methanol.

et al.[9] and when this was treated with the H_2O_2 (in trifluoroacetic acid) only unchanged starting material was recovered.

An alternative pathway to 13 appeared to be through the methylation of 3-methylalloxazine 5,10-dioxide (8), which was obtained by H_2O_2 oxidation of 3-methylalloxazine (2) and its 5-oxide (10), respectively, in trifluoroacetic acid: Treatment of 8 in methanol with ethereal diazomethane gave a complex mixture of at least six compounds which were separated by thick layer chromatography on silica gel with $CHCl_3$/acetone (9:1). The well separated bands were eluted and the substances isolated and crystallized. The fastest moving component was 1,3-dimethylalloxazine 4-oxide (11), which must have been formed by deoxygenation at N-10 and subsequent methylation. The other three compounds which were purified appeared to be isomeric dimethyl derivatives on the basis of C, H, and N elementary analysis. Two also showed the presence of methoxy group by Zeisel determination under conditions where the main product of the reaction was almost inert. We therefore assigned the 1,3-dimethylalloxazine 5,10-dioxide structure (13) to the main reaction product. The structural assignment of the two other methoxy derivatives has been based on NMR studies where one shows in analogy to 13 a symmetrical splitting of the aromatic protons is two multiplets of 2 H each. The other isomer is characterized by a more complicated pattern illustrating a unsymmetrical neighborhood of the benzene ring. This information supports the structure 12 for the former isomer and 14 for the latter isomer (Table I).

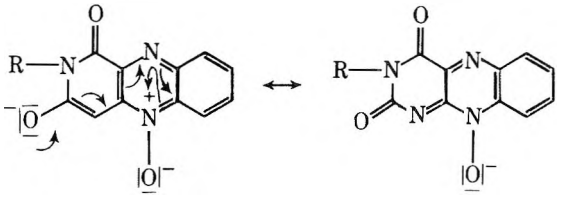
A comparison of the UV spectra of 3-methylalloxazine 5,10-dioxide (8) with the 3-methyl blocked tautomers 12–14 in methanol (Figure 1) clearly demonstrates that the predominant tautomeric form of alloxazine 5,10-dioxides is represented by the 1*H*,3*H*-2,4-dioxotetrahydro structure (7–9) and not a N-10 or C-2–OH tautomer.

Table II. Physical Data of Alloxazine *N*-Oxides

	pK_a value in H_2O	UV absorption spectra[a] ϵ_{max}, nm	Log ϵ	pH	Molecular form[b]
3-Methylalloxazine (2)	8.31 ± 0.08	212, 42, [252], 331, 377, 219, 258, [280], 330, 420	4.53, 4.54, [4.47], 3.93, 3.87, 4.49, 4.66, 3.72, 3.89	6.0 11.0	0 −
3-Methylalloxazine 5-oxide (10)	7.95 ± 0.1	[238], 263, 296, 305, 338, 402, [243], 266, [305], [313], 342, 455	[4.17], 4.49, 3.73, 3.73, 3.77, 3.60, [4.07], 4.59, [3.77], [3.73], 3.68, 3.58	2.2 10.0	0 −
1,3-Dimethylalloxazine 5-oxide (11)		266, [305], 323, 337, 402	4.62, [3.81], 3.88, 3.91, 3.68	MeOH	0
3-Methylalloxazine 10-oxide (5)	6.00 ± 0.1	226, 262, [330], 345, 395, 228, 270, 285, [338], 352, 447	4.11, 4.77, [3.89], 4.06, 3.79, 4.14, 4.56, 4.49, [3.75], 3.86, 3.87	4.0 9.0	0 −
Alloxazine 5,10-dioxide (7)	5.30 ± 0.05 11.42 ± 0.1	228, 253, 283, [344], 367, 440, 222, 234, 257, 294, [350], 363, 495, 235, 286, [352], 367, 503	4.22, 4.01, 4.70, [3.77], 3.76, 3.78, 4.07, 4.08, 4.17, 4.59, [3.79], 3.81, 3.78, 3.98, 4.71, [3.84], 3.94, 3.85	3.0 8.0 14.0	0 − 2−
7,8-Dimethylalloxazine 5,10-dioxide (9)	5.60 ± 0.1 11.54 ± 0.1	232, 287, [359], 371, 440, 232, 258, 301, [362], 375, 492, 236, 255, 292, [360], 374, 500	4.21, 4.69, [3.81], 3.89, 3.71, 4.08, 4.11, 4.65, [3.75], 3.82, 3.72, 4.02, 3.92, 4.85, [3.83], 3.93, 3.82	3.0 8.0 11.0	0 − 2−
3-Methylalloxazine 5,10-dioxide (8)	5.02 ± 0.1	230, 254, 282, 343, 358, 442, 223, 235, 257, 286, [351], 365, 503, 233, [253], 288, 344, 358, 462	4.21, 4.00, 4.72, 3.79, 3.83, 3.81, 4.02, 4.03, 4.09, 4.58, [3.78], 3.85, 3.79, 4.13, [3.97], 4.58, 3.66, 3.64, 3.69	2.0 8.0 MeOH	0 − 0
1,3-Dimethylalloxazine 5,10-dioxide (13)		239, 296, 351, [362], 460	4.28, 4.59, 3.71, [3.67], 3.71	MeOH	0
3,2-*O*-Dimethylalloxazine 5,10-dioxide (12)		237, 260, 269, 304, 358, [373], 468	4.24, 4.22, 4.20, 4.56, 3.56, [3.52], 3.82	MeOH	0
3-Methyl-10-methoxyalloxazine 5-oxide (14)		265, [325], 340, [355], 440	4.57, [3.88], 3.97, [3.87], 3.81	MeOH	0

[a] Values in brackets denotes a shoulder. [b] 0 = neutral form, − = monoanion, 2− = dianion.

A determination of the pK_a values of the different alloxazine *N*-oxides showed (see Table II) that all compounds with the *N*-10-oxide function are stronger acids than the *N*-5-oxides. (This is in good agreement with observations with the lumazine series.[7]) These observations can be explained by the



hypothesis that the anion of the *N*-10-oxide can be stabilized through a mesomeric effect, while in the case of the 5-oxides only an inductive influence is possible.

The UV spectra indicate that the introduction of a *N*-oxide function in position 5 or 10 is associated with a bathochromic shift of the longwave absorption band of 30–40 nm and the monoanion formation, by deprotonation at N-1, causes in all mentioned compounds another red shift of about 50 nm independent of their oxidation state.

Experimental Section

NMR spectra were determined in deuteriochloroform with a Bruker HFX-90 spectrometer and the UV spectra with a Cary recording spectrometer, Model 1115/15 (Applied Physics Corp.). The pK_a values are based on the spectrophotometric method.[15] Chromatographic studies were carried out using precoated cellulose and silica gel plates (Schleicher and Schüll). Merck silica gel PF_{254} thick plates (2 mm) were used for the preparative separations. All melting points are uncorrected.

Alloxazine 5,10-Dioxide (7). Alloxazine (1) (1 g) was dissolved by warming in 60 mL of trifluoroacetic acid. H_2O_2 (30%, 4 mL) was added dropwise (with stirring) at room temperature and stirring was continued for 24 h. An additional 4 mL of 30% H_2O_2 was then added and the mixture stirred for another 24 h. The deep yellow solution was then poured onto ice and the resulting orange precipitate filtered by suction and washed with water and ethanol. After drying at 100 °C 0.6 g (52% yield) of yellow crystalline powder with mp 300 °C was obtained. Recrystallization from dimethyl sulfoxide/water solution gave a yellow powder which dissolves in 0.1 N NaOH to give a deep red color and shows a positive dark blue color with 1% $FeCl_3$ solution in water/methanol mixture.

Anal. Calcd for $C_{10}H_6N_4O_4$: C, 48.79; H, 2.46; N, 22.76. Found: C, 48.60; H, 2.54; N, 22.42. Mol wt 246.18 (mass spectrum *m/e* 246).

3-Methylalloxazine 5,10-Dioxide (8). A mixture of 3-methylalloxazine (2) and its 5-oxide (10) (2 g) prepared according to the Goldner et al. procedure[9] was dissolved in 30 mL of trifluoroacetic acid and treated with three 3-mL portions of 30% hydrogen peroxide as described above to give 1.8 g of yellow crystalline powder of mp 320–325 °C dec. The chromatographically pure material can further be purified by recrystallization from Me_2SO/water or glacial acetic acid.

Anal. Calcd for $C_{11}H_8N_4O_4$: C, 50.77; H, 3.10; N, 21.53. Found: C, 50.68; H, 3.07; N, 21.06. Mol wt 260.2 (mass spectrum *m/e* 260).

7,8-Dimethylalloxazine 5,10-Dioxide (9). 7,8-Dimethylalloxazine (1 g) in 35 mL of trifluoroacetic acid was treated in four portions with a total of 12 mL of 30% peroxide in the same way as described for 8. Recrystallization of the crude reaction product from glacial acetic acid gave 0.8 g (71%) of yellow crystalline powder of mp 330 °C.

Anal. Calcd for $C_{12}H_{10}N_4O_4$: C, 52.56; H, 3.78; N, 20.50. Found: C, 52.37; H, 3.68; N, 20.43. Mol wt 274.2 (mass spectrum *m/e* 274).

Methylation of 3-Methylalloxazine 5,10-Dioxide (8). To a suspension of 0.3 g of finely ground 8 in 20 mL of absolute methanol was added with stirring an ethereal solution of diazomethane (prepared from 5 g of *N*-nitroso-*N*-methylurea). The yellow solution changed gradually to an orange-red precipitate after stirring for 1 day at room temperature. The reaction mixture was evaporated to dryness, the residue dissolved in a small amount of chloroform, and applied to five preparative silica gel plates (40 × 20 × 0.2 cm) for separation. The plates were developed twice, first with a chloroform/acetone mixture 9:1 and the second time with a 9:2 mixture. There was good separation into four main bands of yellow and orange fluorescence which consisted of increasing R_f values of **14**, **12**, **13**, and **11**. The bands were cut out and eluted with acetone and evaporated to dryness to give chromatographically pure amorphous solids.

1,3-Dimethylalloxazine 5-Oxide (11). Crude product of the above separation (30 mg) was recrystallized from 5 mL of water/ethanol (1:1) yielding 12 mg of yellow needles with mp 216 °C (lit. mp 237 °C)[9,14] (authentic sample mp 218 °C, no depression).

Anal. Calcd for $C_{12}H_{10}N_4O_3$: C, 55.81; H, 3.90; N, 21.70. Found: C, 55.79; H, 3.88; N, 21.39. Mol wt 258.2.

2,3-Dimethylalloxazine 5,10-Dioxide (12). Orange colored eluate (40 mg) was purified by recrystallization from 10 mL of ethanol to give 20 mg of orange crystals with mp 236–238 °C.

Anal. Calcd for $C_{12}H_{10}N_4O_4$: C, 52.55; H, 3.68; N, 20.43; OCH_3, 11.3. Found: C, 52.85; H, 3.67; N, 20.20; OCH_3, 9.8.

1,3-Dimethylalloxazine 5,10-Dioxide (13). Crude reaction product (0.1 g) was recrystallized from a mixture of 5 mL of water and 2 mL of ethanol to give 0.076 g of shiny crystals, mp 194 °C.

Anal. Calcd for $C_{12}H_{10}N_4O_4$: C, 52.55; H, 3.68; N, 20.43. Found: C, 52.81; H, 3.67; N, 20.10. Mol wt 274.2.

3-Methyl-10-methoxyalloxazine 5-Oxide (14). Crude material (40 mg) was recrystallized from 10 mL of ethanol to give 20 mg of orange crystals with mp 196–198 °C.

Anal. Calcd for $C_{12}H_{10}N_4O_4$: C, 52.55; H, 3.68; N, 20.43; OCH_3, 11.3. Found: C, 52.39; H, 3.71; N, 20.22; OCH_3, 11.7.

Biological Activity of Alloxazine Di-*N*-oxide. Assays were performed under the supervision of the Drug Research and Development Section, Division of Cancer Treatment, National Cancer Institute, U.S. Public Health Services by the procedures described in Geran et al.[16] A compound is considered to show significant in vivo activity against the Walker 256 tumor system if it causes reduction of tumor weight in the treated rats to 42% or less of the tumor weight in the control animals. In this test system the alloxazine di-*N*-oxide at 60 mg/kg showed an 80% reduction in tumor weight. In other tests using mouse leukemia L-1210 no life prolongation was noted. The alloxazine di-*N*-oxide inhibited the growth of *Lactobacillus casei* (ATCC 7469) growing in folic acid limited medium at 20 mcg/mL, and this inhibition was not reversed by citrovorum factor, thymidine, or riboflavin.

Registry No.—**1**, 490-59-5; **2**, 2891-59-0; **3**, 1086-80-2; **5**, 22525-79-7; **7**, 50628-74-5; **8**, 54011-43-7; **9**, 39132-80-4; **10**, 4897-17-0; **11**, 2962-89-2; **12**, 62015-56-9; **13**, 32706-14-2; **14**, 62015-57-0.

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(17) We thank Mrs. M. Bischler and Mr. E. Krienitz, Department of Chemistry, University of Konstanz, for the determination of the physical data, and Professor D. Perlman, School of Pharmacy, for assistance with the bioassay determinations.

Structural Studies of Organosulfur Compounds.[1] 3. Stereochemistry and Conformational Distortions in *trans*-Hexahydro-1,4-benzoxathiane *S*-Oxides

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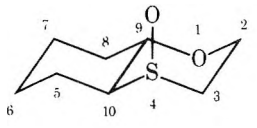
trans-Hexahydro-1,4-benzoxanthiane and the 4-oxides have been prepared and the stereochemistry of the sulfinyl derivatives determined. Acid-catalyzed equilibration of the sulfoxides indicate that the axial sulfoxide is more stable than the equatorial by 0.85 ± 0.07 kcal/mol. Application of the *R*-value method indicates that the axial sulfoxide is severely flattened when compared to the equatorial diastereomer.

In a recent report[1] we had established the preferred conformation of the sulfinyl oxygen atom in the 1,4-oxathiane system **1** in the absence of other substituents[2] as predominantly *axial* by low temperature ^{13}C NMR techniques. This result was found to be in keeping with a number of previous reports describing sulfinyl oxygen conformations with other heteroatoms within the six-membered ring or as substituents,[3] but yet contrary to a number of other studies describing the conformational characteristics of sulfoxides.[4] We reasoned that the calculated conformational free energy difference, $\Delta\Delta G° \simeq 0.4$ kcal/mol, for the sulfinyl oxygen atom in thiane 1-oxide (**2**) and 1,4-oxathiane 4-oxide (eq ⇌ ax; $\Delta G° = -0.17$ kcal/mol for thiane 1-oxide[3b] and $\Delta G° = -0.68$ kcal/mol for 1,4-oxathiane 4-oxide[1]) results, in part, from the presence of an attractive intramolecular electrostatic interaction in 1,4-oxathiane 4-oxide which is absent in the pentamethylene sulfoxide, **2**. This may be viewed as a 1,4-attractive interaction between the negatively charged oxygen of the sulfoxide and the positive carbon atoms (and perhaps hydrogens) at C2 and C6.[5] Intramolecular dipole–dipole interactions appear to be dominant features in a number of heterosubstituted sulfoxides. In fact, a recent report describing the results of empirical force field (molecular mechanics[6]) calculations on six-membered ring sulfoxides[7] suggests that the conformations of the sulfinyl oxygen atom are controlled largely by dipolar considerations which exist between a ring heteroatom and the sulfinyl oxygen atom.

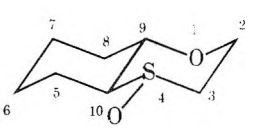
An attractive or repulsive interaction, which might result in a decrease or increase in the distance between the axial sulfinyl oxygen and the C2, C6 carbons and hydrogens, would be expected to induce either mild puckering or flattening of the central ring of **1** when compared to a system without an axial sulfinyl oxygen.[8] This distortion could be identified from precise determinations of vicinal coupling constants which could ultimately be translated into torsional angles.[9,10]

In this report, we have examined the conformational distortions caused by the sulfinyl and sulfonyl oxygens in the 4-oxides of *trans*-hexahydro-1,4-benzoxathiane (**6**). We view

6 and its 4-oxides as excellent choices since the trans ring-fused decalin analogues would ensure conformational rigidity of the chair conformation of the basic 1,4-oxathiane ring thus preventing conversion to boat or twist-boat conformations but providing allowances for minor conformational distortions. We, of course, recognize that the sulfoxides, 13 and 14, do not exactly simulate the chair conformations of sulfoxide 1 because there is one additional 1,3-syn-axial sulfinyl oxygen–carbon hydrogen interaction in 13 involving C5.[11] However, we have assumed that this interaction is effectively neutralized by an essentially equivalent interaction involving the equatorial sulfinyl oxygen atom and the C5 carbon and hydrogen in 14.



13



14

Results and Discussion

Syntheses. We prepared the model systems, 6, 13, 14, and 15, by the series of reactions described in Chart I. As reported in previous studies,[12] *trans*-2-mercaptocyclohexanol (3) was obtained from the reaction of cyclohexene oxide with thiourea in acidic media. This mercapto alcohol 3 was reacted with bromoacetaldehyde diethyl acetal and potassium hydroxide to give the open-chain acetal[13] which spontaneously cyclized on standing or could be condensed with boron trifluoride etherate to afford a ca. 1:1 mixture of the cyclic acetals, 4 and 5. Attempted reductive cleavage of the ethoxyl group in the mixture of 4 and 5 with lithium aluminum hydride–aluminum chloride[14] gave essentially starting material and small quantities of saturated and unsaturated oxathianes, 6 and 7, respectively. *trans*-Hexahydro-1,4-benzoxathiin (7) was easily hydrogenated with hydrogen over palladium on carbon in ethanol[15] to give pure 6 after sublimation. The yields of 7 and eventually 6 could be significantly improved by converting the acetals 4 and 5 into lactols (9 and 10) with 4–6% sulfuric acid at reflux for 48 h.[16] The lactols, 9 and 10, were acylated with acetic anhydride in pyridine[17] to give a mixture of acetates (11, 12) which was pyrolyzed[17] (180 °C) to give 7 in nearly quantitative yield. Oxidation of 6 with *m*-chloroperoxybenzoic acid (MCPBA)[3h] or sodium metaperiodate ($NaIO_4$)[3h] gave good yields of the sulfoxides 13 and 14 but significantly different isomeric distributions (see Experimental Section). Sulfone 15 was prepared by oxidation of 6 with excess hydrogen peroxide in acetic acid at reflux or with 2 equiv of MCPBA at ambient temperature. The sulfone was also prepared by oxidation of 7 with H_2O_2–HOAc[16] followed by reduction with hydrogen over palladium on carbon in ethanol.[16]

Stereochemical Assignments. The stereochemistry of sulfoxides 13 and 14 was determined by ^1H and ^{13}C NMR spectroscopy and from the degree of stereoselectivity resulting from oxidation of 6 to 13 and 14.

Recently, considerable interest has centered on the application of ^{13}C NMR as a tool for stereochemical assignments of cyclic organosulfur compounds. A useful feature of ^{13}C NMR is the substantial upfield shifts observed for carbons which are syn-clinal[1,3e,f,18,19] and anti-periplanar[20] to a substituent on sulfur. In the syn-clinal arrangement, the upfield shifts are thought to arise from steric interactions resulting from congestion of atoms involving carbon,[21,22] while the upfield shifts in the anti-periplanar array may be best viewed as a hyperconjugative transfer of charge from the free-electron pairs on a second-row heteroatom (e.g., N, O, or F) to the anti-periplanar carbon[20] or a σ-inductive effect when ammonium and sulfonium ion substituents are γ-anti to the carbon.[20,23]

The initial assignments of the C2, C3, C9, and C10 atoms in 6 were based on the expected electronegative influence of the heteroatoms (oxygen and sulfur)[24] α to the carbons and off-resonance decoupling which served to unequivocally assign the bridgehead carbons (C9, C10).[25] The C2 atom in sulfoxide 13 (δ 57.14 ppm) is 5.96 ppm to higher field than C2 of sulfoxide 14 and C9 of 13 (δ 70.12 ppm) also experiences an upfield shift of 7.16 ppm relative to C9 in 14 (δ 77.28 ppm). See Table I for the relevant ^{13}C NMR data. Similar observations describing this upfield shift effect of carbon when proximal (syn-clinal) to the sulfinyl oxygen have been reported for a number of conformationally homogeneous systems[26] and

Chart I

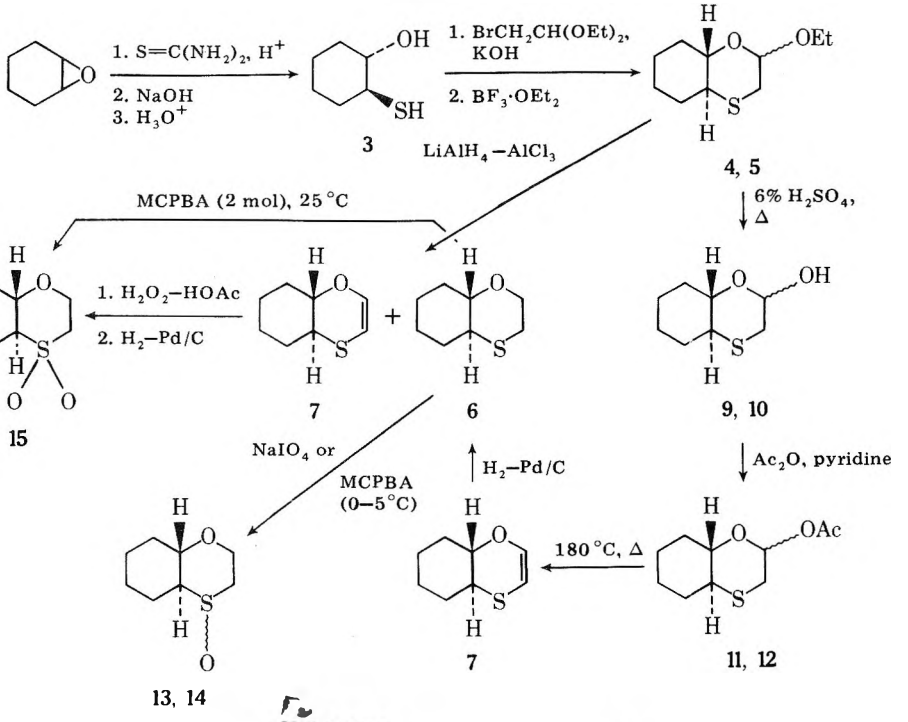
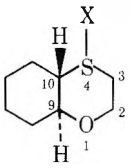


Table I. Carbon Chemical Shifts of *trans*-Hexahydro-1,4-benzoxathiane and *S*-Oxides[a]



Carbon atom	Sulfide 6 (X = lone pair)	Axial sulfoxide 13 (X = oxygen atom)	Sulfone 15 (X = O_2)	Equatorial sulfoxide 14 (X = oxygen atom)
2	68.78	57.14	65.03	63.10
3	32.74	45.99	52.61	51.77
10	43.96	57.30	65.75	66.58
9	82.57	70.12	78.94	77.28

[a] ^{13}C NMR shifts are reported in parts per million (δ) downfield from internal tetramethylsilane and are considered accurate to ± 0.01 ppm. See Experimental Section for details.

Table II. ^1H NMR Data of *trans*-Hexahydro-1,4-benzoxathiane and 4-Oxides[a]

NMR parameter[b,c]	Axial sulfoxide (13)	Sulfone (15)	Sulfide (6)	Equatorial sulfoxide (14)
$^3J_{2e,3a}$	4.0	5.30	3.43	4.08
$^3J_{2e,3e}$	2.50	2.60	2.10	3.00
$^3J_{2a,3a}$	9.0	10.90	11.55	12.20
$^3J_{2a,3e}$	5.00	2.83	2.20	1.30
$^2J_{2ae}$	12.70	12.80	11.60	13.30
$^2J_{3ae}$	11.0	13.60	13.60	12.15
δ_{2e}	3.98	4.28	4.18	4.20
δ_{2a}	4.43	4.12	3.74	3.71
δ_{3e}	2.87	3.07	2.35	3.38
δ_{3a}	2.82	3.28	3.05	2.96

[a] See Experimental Section for additional NMR data. [b] Coupling constants are given as hertz. [c] Proton chemical shifts are given in parts per million (δ) downfield from tetramethylsilane (Me_4Si).

based on comparison with these observations we assign sulfoxide **13** as the one possessing the axial sulfinyl oxygen and **14** with the equatorial one.

It is noteworthy that the C2 and C9 atoms in **6** are deshielded relative to the same atoms in **14** by 5.68 and 5.29 ppm, respectively. These are among the largest γ-anti-periplanar shifts currently known[19b] and their magnitudes indicate that they are comparable to the γ-gauche or syn-clinal effect in other systems. The relatively large differences between the two sets of carbons in **6** and **14** may arise from a composite effect involving hyperconjugative transfer of charge[20] and a σ-inductive effect[23] to the γ-anti carbons since the sulfur atom has both residual positive character and an oxygen substituent with electron pairs.

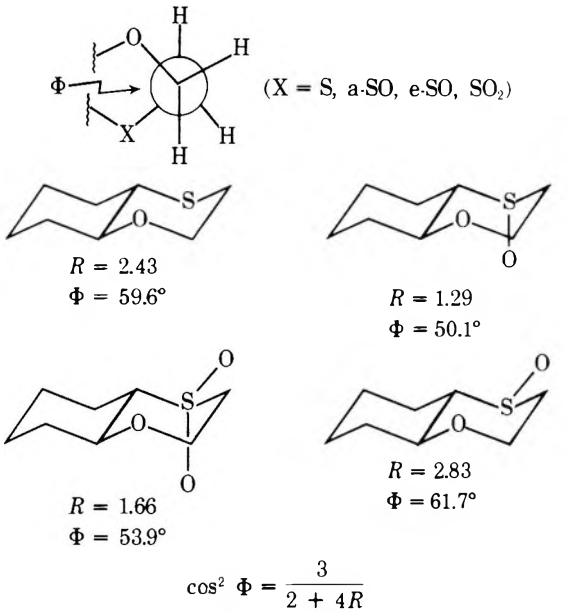
The configurational assignments are further corroborated by the observed downfield shifts of the axial C2 and C9 protons on the introduction of an axial oxygen at sulfur (e.g., **6** → **13**). See Table II for the appropriate proton chemical shifts.[28] This paramagnetic shift is presumably due to an anisotropic deshielding effect,[28] van der Waals steric effect, and/or an electric field effect[29] of the S–O group on the C2 and C9 protons in the 1,3-diaxial conformation.

Oxidation of 4-*tert*-butylthiane with a number of oxidants including $NaIO_4$ and MCPBA has been extensively investigated[3h] and a useful degree of selectivity per oxidant has been established.[3h,30a] For instance, oxidation of 4-*tert*-butylthiane with $NaIO_4$ give 75% cis (axial sulfoxide) and 25% trans while oxidation with MCPBA affords only 36% cis and 64% trans isomer. For *trans*-hexahydro-1,4-benzoxathiane (**6**), we have assumed that the ring oxygen is sufficiently removed from the immediate environment of the sulfur so as not to influence the mode of oxidation and the subsequent product distribution. Oxidation of **6** with $NaIO_4$ gives a mixture of sulfoxides containing 65% of **13** (axial sulfoxide) and 35% of **14** while oxidation with MCPBA gives 26% of **13** and 74% of **14** (equatorial sulfinyl oxygoen). These results are in good agreement with those previously reported for 4-*tert*-butylthiane[3h,30a] and serve to confirm by extrapolation the stereochemistry of sulfoxides **13** and **14**.

Conformational Distortions. All of the ^1H NMR parameters have been determined for all of the *trans*-hexahydro-1,4-benzoxathiane derivatives by comparison of computer simulations with experimental spectra. Thus, excellent use could be made of the *R*-value method[9] with proper extensions to torsional angle determinations[10] to assess the relative magnitude(s) of any conformational distortions. It has been previously demonstrated that the ratio, *R*, of the average $^3J_{trans}$ to $^3J_{cis}$ couplings in six-membered rings is a direct function of conformational distortions within the ring,[9] but relatively independent of the electronegativities of the substituents.[31] Thus, for molecules in the perfect chair conformation, $R \cong 2.0$, while *R* values greater than 2.75 characterize puckered chair forms and those values approximating 1.2 describe molecules in the flexible or flattened conformation.[9] The qualitative nature of the *R*-value method has largely been removed by the demonstration of a satisfactory correlation between dihedral angles determined by x-ray methods[10] and those calculated from *R* values. The calculated *R* values and torsional angles are given in Chart II. From the data it is apparent that the torsional angles for sulfide **6** and equatorial sulfoxide **14** are quite similar, suggesting (as perhaps expected) that the 1,4-oxathiane ring in both systems is not appreciably distorted. The relatively large torsional angle about O–C2–C3–S in **6** is virtually equivalent to that found in 1,4-oxathiane, $\phi = 60°$.[9] However, in the axial sulfoxide **13** and the sulfone **15** the relatively smaller torsional angles indicate that these molecules are slightly flattened about O–C2–C3–S with **13** experiencing the greatest perturbation. This distortion may be viewed as an attempt to relieve repulsive 1,3-syn-axial (nonbonding) interactions between the sulfinyl oxygen (or sulfonyl oxygen) and the C2, C9 carbons and hydrogens. The difference in torsional angles between the sulfone and the axial sulfoxide (ca. 5°) is due, at least in part, to different degrees of hybridization and the effective steric demands of the S→O bond in each compound while the difference in the diastereoisomeric sulfoxides (ca. 10°) is largely due to their respective steric environments.

The conformational free energy of the sulfinyl group ($\Delta G_{S\rightarrow O}$) was determined from acid-catalyzed (HCl–dioxane–water) equilibration[32,33] of both the axial and equatorial isomers. The equilibrium composition obtained from at least

Chart II. *R* Values and Calculated Torsional Angles of *trans*-Hexahydro-1,4-benzoxathiane Derivatives



$$\cos^2 \Phi = \frac{3}{2 + 4R}$$

five determinations from each side gave $\Delta G°_{30.0} = 0.85 \pm 0.07$ kcal/mol for the axial $\rightleftarrows$ equatorial sulfinyl oxygen equilibrium *favoring the axial S → O group* which is in good agreement with the low temperature determination ($\Delta G°_{-80} = 0.68$ kcal/mol)[1] involving 1,4-oxathiane 4-oxide considering the slight differences in the system and the solvent media. From this it is clear that energy minimization in the axial sulfoxide is accompanied by flattening; however, **13** still assumes a ground-state energy considerably lower than that of **14**. These observations, in some respects, support the recent conclusions drawn from molecular mechanics calculations[7] where the suggestion is made that there is only minor repulsion in the axial form of thiane 1-oxide when compared to the major repulsive nonbonding interactions between the equatorial sulfinyl oxygen and the four vicinal hydrogens. The design and results of our experiments do not allow for an assessment of steric perturbations which might be evident in **14**. It is conceivable that severe flattening of the ring in **13** is partially attenuated by an intramolecular electrostatic attraction without which one might expect an even larger perturbation in the form of ring deformation.

Experimental Section

Melting points were obtained in a Mel-Temp melting point apparatus with an open capillary tube and are uncorrected.

Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and Integral Microanalytical Laboratories, Inc., Raleigh, N.C.

^{1}H NMR spectra were recorded on JEOL Model C-60 HL and Varian Model XL-100-12 NMR spectrometers. ^{13}C NMR FT spectra were recorded on a Varian Model XL-100-12 NMR spectrometer controlled by a 620/f computer. All FT spectra were obtained at ambient temperature (ca. 30 °C) and Fourier transforms were based upon 8K data points with off-resonance and noise decoupling. The proton and carbon chemical shifts of samples as 5–15 (w/w %) deuteriochloroform ($CDCl_3$) solutions are presented in parts per million (δ) downfield from internal tetramethylsilane (Me_4Si) and these values are considered accurate to ±0.01 ppm unless otherwise indicated. The coupling constants are given in hertz and are accurate to ±0.1–0.2 Hz unless otherwise specified. All relevant experimental proton signals were simulated with an in-house modification of LAOCOON III capable of handling eight spins. ^{1}H NMR coupling patterns are designated as s = singlet, d = doublet, m = multiplet, q = quartet, and t = triplet.

Infrared spectra were obtained from samples as neat films and solutions and were recorded on Perkin-Elmer Models 257 and 421 spectrophometers with polystyrene (1601.4 cm^{-1}) as reference. Absorption intensities are shown as s = strong, w = weak, m = medium, vs = very strong, and vw = very weak.

Gas–liquid partition chromatography (GLC) analyses were performed on Hewlett-Packard Models 5750 and 5754 research gas chromatographs. A Varian Aerograph Series 2700 instrument was used for preparative separations. *trans*-2-Mercaptocyclohexanol (**3**) was prepared from the procedure described by Bordwell and Andersen.[12]

***trans*-2-(Thioacetaldehyde diethyl acetal)cyclohexanol.** A solution of *trans*-2-mercaptocyclohexanol (11.75 g, 90.0 mmol) in 30 mL of 95% ethanol was added to a solution of potassium hydroxide (7.0 g, 125 mmol, assuming 85% purity) in 100 mL of 95% ethanol and stirred at ambient temperature for 15 min. A solution of bromoacetaldehyde diethyl acetal (18.0 g, 90.0 mmol) in 30 mL of ethanol was added to the mercaptide solution and the resulting orange solution was refluxed for 22 h. Potassium bromide was removed by filtration and the resulting ethanolic solution was concentrated to dryness (rotary evaporator) to afford a red residue. This material was dissolved in 100 mL of ether and the ethereal solution was washed with water (100 mL), dried (anhydrous magnesium sulfate), and concentrated (rotary evaporator) to give a yellow oil. Distillation under reduced pressure gave 12.9 g (58%) of a colorless oil: bp 113–117 °C (0.125 Torr); IR (neat film) 3442 (broad band, OH), 2990 (m), 2940 (s), 2860 (m), 1450 (m), 1351 (w), 1128 (s), 1068 (vs), 1018 (m), and 917 cm^{-1} (w). This material slowly cyclized to give a mixture consisting of a 1:1 ratio of **4** and **5**.

2-Ethoxy-*trans*-hexahydro-1,4-benzoxathianes (4 and 5). A solution of *trans*-2-(thioacetaldehyde diethyl acetal)cyclohexanol (12.9 g, 52.0 mmol) in 100 mL of dry ether was treated with 1 mL of boron trifluoride etherate at room temperature for 48 h. The resulting solution was washed with water (100 mL) and twice with a saturated solution of sodium carbonate (100 mL). The ethereal solution was dried (anhydrous magnesium sulfate) and concentrated to dryness (rotary evaporator) to afford an oil. Distillation under reduced pressure gave 5.95 g (57%) of a clear oil of two components which was otherwise homogeneous by GLC: bp 65–72 °C (0.02 Torr); IR (neat film) 2979 (m), 2940 (s), 2870 (m), 1456 (m), 1378 (w), 1343 (m), 1210 (m), 1160 (m), 1132 (s), 1076 (s), 1018 (m), 990 (m), and 856 cm^{-1} (w). Anal. Calcd for $C_{10}H_{18}O_2S$: C, 59.37; H, 8.97. Found: C, 58.90; H, 9.07.

***trans*-Hexahydro-1,4-benzoxathiane (6).** *trans*-Hexahydro-1,4-benzoxathiin (**7**, 10.0 g, 64 mmol) in 50 mL of absolute ethanol was reduced with hydrogen (50 psi) over 10% palladium on carbon (10.0 g) for 13 h. The catalyst was removed by filtration and the ethanol solution was concentrated to dryness (rotary evaporator) to give an oily material which gave after sublimation (37 °C, 0.25 Torr) 8.7 g (71%) of an oily, crystalline substance. Recrystallization of this material from petroleum ether (bp 30–60 °C) gave 5.7 g (47%) of a colorless, crystalline solid: mp 40.5–41.5 °C; IR (CCl_4) 2940 (s), 2860 (m), 1450 (m), 1302 (m), 1196 (m), 1109 (s), 1062 (m), and 1018 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 0.93–2.08 (m, 8 H, CH_2), 2.35 (d of t, J_{gem} = 13.6, J_{ea} = 2.2, J_{ee} = 2.1 Hz, 1 H, SCH_e), 2.65 (m, 1 H, SCH), 3.05 (t of d, J_{gem} = 13.6, J_{aa} = 11.55, J_{ae} = 3.43 Hz, 1 H, SCH_a), 3.28 (m, 1 H, OCH), 3.74 (t of d, J_{gem} = 11.6, J_{aa} = 11.55, J_{ae} = 2.2 Hz, 1 H, OCH_a), and 4.18 ppm (d of q, J_{gem} = 11.6, J_{ea} = 3.43, J_{ee} = 2.1 Hz, 1 H, OCH_e). Anal. Calcd for $C_8H_{14}SO$: C, 60.71; H, 8.92. Found: C, 60.94; H, 8.84.

2-Hydroxy-*trans*-hexahydro-1,4-benzoxathianes (9 and 10). The 2-ethoxy-*trans*-hexahydro-1,4-benzoxathiane mixture of **4** and **5** (41.6 g, 200 mmol) was poured into a solution of 4–6% sulfuric acid (300 mL) and refluxed for 40 h, cooled to ambient temperature, and neutralized with sodium bicarbonate. The solid material was dissolved in ether and the solution dried (magnesium sulfate), then concentrated to dryness (rotary evaporator) to afford a solid. Recrystallization from a methylene chloride–hexane solution gave 12.5 g (36%) of colorless crystals, mp 97–100 °C. Anal. Calcd for $C_8H_{14}SO_2$: C, 55.14; H, 8.09. Found: C, 55.25; H, 8.88. The mother liquor from the recrystallization contained unreacted starting material (**4** and **5**).

2-Acetyl-*trans*-hexahydro-1,4-benzoxathianes (11 and 12). The mixture of acetols **9** and **10** (18.0 g, 103 mmol), 75 mL of acetic anhydride, and 75 mL of pyridine was heated to reflux for ca. 20 min and then reduced in volume to about 30 mL (rotary evaporator). The remaining solution was cooled to ambient temperature and 150 mL of water was added to hydrolyze the residual anhydride. The mixture was neutralized with a saturated solution of sodium bicarbonate and extracted with ether (2 × 100 mL) and the ethereal solution was dried (magnesium sulfate) and concentrated to dryness (rotary evaporator). The product was distilled under reduced pressure to afford a colorless oil (20.1 g, 90%), bp 75–76 °C (0.04 Torr). Anal. Calcd for $C_{10}H_{16}SO_3$: C, 55.57; H, 7.40. Found: C, 55.49; H, 7.76.

***trans*-Hexahydro-1,4-benzoxathiin (7).** The mixture of 11 and 12 (19.2 g, 128 mmol) was heated in an oil bath to 180 °C at atmospheric pressure. The heating was continued until acetic acid had ceased distilling over. The resulting oil was distilled under reduced pressure (0.04 Torr) to afford essentially quantitative yield of the olefin 7 (14.0 g, 99.2%): bp 36–37 °C (0.04 Torr); ^{13}C NMR δ 139.31 (=CHO)and 93.52 ppm (=CHS); ^1H NMR δ 5.03 (d, 1 H, J = 6.3 Hz, (=CHS)and 6.56 ppm (d, 1 H, J = 6.3 Hz, =CHO).

***trans*-Hexahydro-1,4-benzoxathiane 4,4-Dioxide (15).** A solution of *trans*-hexahydro-1,4-benzoxathiane (300 mg, 2.84 mmol) in 5 mL of glacial acetic acid and 3 mL of hydrogen peroxide (excess) was heated to reflux for 20 min, then cooled to ambient temperature. The cooled solution was diluted with water (30 mL) and extracted with chloroform (2 × 20 mL). The chloroform solution was washed with a saturated solution of sodium bicarbonate (2 × 20 mL), water (20 mL), and finally with a saturated sodium chloride solution (20 mL). The resulting solution was dried (magnesium sulfate) and concentrated to dryness (rotary evapoartor) to give 308 mg (86%) of a colorless, crystalline powder which was recrystallized from hexane: mp 120–121 °C; IR ($CHCl_3$) 2946 (s), 2865 (m), 1444 (m), 1308 (s), 1292 (m), 1278 (m), 1270 (m), 1172 (m), 1126 (vs), 1110 (s), 1024 (m), 1008 (m), and 960 cm^{-1} (w); ^1H NMR ($CDCl_3$) δ 0.97–2.45 (m, 8 H, CH_2), 2.85 (m, 1 H, SCH), 3.07 (d of t, J_{gem} = 13.6, J_{ea} = 2.83, J_{ee} = 2.6 Hz, 1 H, SCH_e), 3.28 (d of q, J_{gem} = 13.6, J_{aa} = 10.9, J_{ae} = 5.3 Hz, 1 H, SCH_a), 3.67 (m, 1 H, OCH), 4.12 (d of t, J_{gem} = 12.8, J_{aa} = 10.9, J_{ae} = 2.83 Hz, 1 H, OCH_a), and 4.28 ppm (d of q, J_{gem} = 12.8, J_{ee} = 2.6, J_{ea} = 5.3, 1 H, OCH_e). Anal. Calcd for $C_8H_{14}O_3S$: C, 50.43; H, 7.45. Found: C, 50.50; H, 7.42.

***trans*-Hexahydro-1,4-benzoxathiane 4-Oxides (13 and 14) from $NaIO_4$.** A solution of*trans*-hexahydro-1,4-benzoxathiane (3.0 g, 19 mmol) in 50% methanol (200 mL) and dioxane (3 mL) was reacted with sodium metaperiodate (4.0 g, 19.0 mmol) at 0–5 °C (ice bath) for 6 h and at room temperature overnight (14 h). Sodium iodate was removed by filtration and the resulting aqueous layer was extracted with chloroform (3 × 100 mL). The organic layer was dried (anhydrous magnesium sulfate) and concentrated to dryness (rotary evaporator) to afford 2.96 g (90%) of a colorless, crystalline solid: mp 89–92 °C; IR ($CHCl_3$) 1448 (m), 1092 (s), 1038 (s), 1012 (vs), and 997 cm^{-1} (s). TLC (silica gel, chloroform–petroleum ether as eluent) indicated the presence of starting sulfide 6 and two other components. The crude mixture was separated by column chromatography (silica gel with chloroform–petroleum ether as eluent) to give a pure mixture of sulfoxides (2.46 g, 75%) with the axial sulfoxide 13 predominating in the mixture (axial, 65%; equatorial 35%) as determined by GLC.

***trans*-Hexahydro-1,4-benzoxathiane 4-Oxides (13 and 14) from MCPBA.** A solution of mCPBA (400 mg, 2.0 mmol) in 25 mL of anhydrous methylene chloride was added dropwise over a period of 1 h to a solution of *trans*-tetrahydro-1,4-benzoxathiane (330 mg, 2.10 mmol) in anhydrous methylene chloride (25 mL) at 0–5 °C (ice bath). The solution was stirred for 12 h, then allowed to come to ambient temperature overnight (ca. 15 h). The solution was cooled (ice water), filtered to remove the chlorobenzoic acid, washed with a saturated solution of sodium bicarbonate (3 × 25 mL), and finally dried (magnesium sulfate). Removal of the solvent (rotary evaporator) gave 296 mg (82%) of a colorless product, mp 74–76 °C. GLC indicated the presence of 6 and the sulfoxides 13 and 14. The mixture of sulfoxides contained 74% equatorial isomer and 26% axial.

Separation of the Diastereoisomeric Sulfoxides. Separation of 13 and 14 was accomplished on a silica gel column (1 × 18 in., 70–325 mesh, EM Reagents) eluting with a 60:40 (v/v %) chloroform–petroleum ether solution and collecting 40-mL fractions. The diastereoisomeric sulfoxides were obtained analytically pure by this procedure.

4a-*trans*-Hexahydro-1,4-benzoxathiane 4-Oxide (13): mp 105.5–107.0 °C; ^1H NMR ($CDCl_3$) δ 1.04–2.2 (m, 8 H, CH_2), ca. 2.28 (m, 1 H, SCH), 2.82 (m, J_{gem} = 11.0, J_{aa} = 9.0, J_{ae} = 4.0 Hz, 1 H, SCH_a), 2.87 (m, J_{gem} = 11.0, J_{ea} = 5.0, J_{ee} = 2.5 Hz, 1 H, SCH_e), 3.98 (m, J_{gem} = 12.70, J_{ea} = 3.5, J_{ee} = 2.9 Hz, 1 H, OCH_e), 4.03 (m, 1 H, OCH), and 4.43 ppm (d of q, J_{gem} = 12.70, J_{aa} = 9.0, J_{ae} = 5.0 Hz, 1 H, OCH_a). Anal. Calcd for $C_8H_{14}O_2S$: C, 55.14; H, 8.09. Found: C, 54.99; H, 8.25.

4e-*trans*-Hexahydro-1,4-benzoxathiane 4-Oxide (14): mp 116.0–117.0 °C; ^1H NMR ($CDCl_3$) δ 1.04–2.25 (m, 8 H, CH_2), 2.53 (m, 1 H, SCH), 2.96 (t of q, J_{gem} = 12.15, J_{aa} = 12.2, J_{ae} = 4.08 Hz, 1 H, SCH_a), 3.27 (m, 1 H, OCH), 3.38 (d of q, J_{gem} = 12.15, J_{ea} = 1.3, J_{ee} = 3.0 Hz, 1 H, SCH_e), 3.71 (t of d, J_{gem} = 13.3, J_{aa} = 12.2, J_{ae} = 1.3 Hz, 1 H, OCH_a), and 4.20 ppm (d of q, J_{gem} = 13.3, J_{ea} = 4.08, J_{ee} = 3.0 Hz, 1 H, OCH_e). Found: C, 55.00; H, 8.20.

Equilibrations. Equilibrium concentrations of 13 and 14 were obtained by equilibrating weighted mixtures of 13 and 14 from both sides at 300 K in a hydrochloric acid–dioxane–water solution.[33] The reaction mixtures were diluted with water and extracted with methylene chloride and the methylene chloride solutions were neutralized with a saturated solution of sodium bicarbonate, dried (sodium sulfate), and concentrated to dryness (rotary evapoartor) to give crystalline material. Gas–liquid partition chromatographic analyses were performed on samples of the solid material dissolved in chloroform on 6 and 12 ft × 0.125 in. (i.d.) stainless steel columns with 10% XE-60 nitrile on Chromosorb W-HP-AW-DMCS (100–120 mesh) at 200–210 °C. Response ratios were measured from the areas obtained from weighed samples. Equilibrium compositions were usually attained after 2 h and after 8–22 h major decomposition (or rearrangement) products were observed by GLC.

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Registry No.—3, 60861-06-5; 4, 62015-70-7; 5, 62057-83-4; 6, 62015-71-8; 7, 62015-72-9; 9, 62015-73-0; 10, 62057-84-5; 11, 62015-74-1; 12, 62057-85-6; 13, 62015-75-2; 14, 62057-86-7; 15, 62015-76-3; *trans*-2-(thioacetaldehyde, diethyl acetal)cyclohexanol, 62015-77-4; bromoacetaldehyde diethyl acetal, 2032-35-1.

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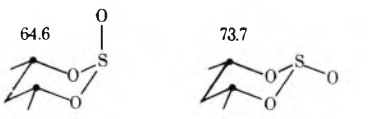
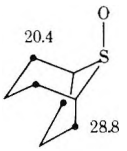


4-trans,6-trans 4-cis,6-cis

the carbons shown as darkened circles.) The chemical shift difference between the γ-gauche (δ 20.4 ppm) and γ-anti (δ 28.8 ppm) carbons in 9-thiabicyclo[3.3.1]nonane *S*-oxide compares favorably with previous reports.[18b]



(27) On tabulating the C2 and C3 proton chemical shifts (Table II), we noted that a comparison of these shifts lends support to the suggestion of Khan et al.[4c] in that the bonc anisotropies of the C–S and C–S(O_2) bonds are opposite in sign to those of C–C, C–O, and C–S(O).[4c] If we use the $+\Delta\delta$ representation for cases where the C3 axial proton resonates at higher field than the C3 equatorial and $-\Delta\delta$ for examples where the C3 equatorial proton comes to higher field than C3 H_a (following the scheme introduced by Khan et al.[4c] for convenience), it is clear that sulfone **15** ($\Delta\delta = -0.21$ ppm) and sulfide **6** ($\Delta\delta = -0.70$ ppm) show the same overall pattern of shifts supporting, at least in principle, the identify of sign for C–S and C–S(O_2) bond anisotropies. On the other hand, the sign of the chemical shift difference between the axial and equatorial protons α to the sulfinyl group in **13** ($\Delta\delta = +0.05$ ppm) and **14** ($\Delta\delta = +0.42$ ppm) and the ones α to the ring oxygen in **6** ($\Delta\delta = +0.44$ ppm), **15** ($\Delta\delta = +0.16$ ppm), and **14** ($\Delta\delta = +0.49$ ppm) suggest that the C–O and C–S(O) bond anisotropies are also of the same sign. As expected the positive sign of $\Delta\delta$ was not observed for the C2 methylene group of **13** because the axial sulfinyl group exerts a substantial deshielding effect on the 1,3-syn-axial C2 proton.[29]
(28) It has been suggested from calculation that the S=O bond anisotropy probably resembles that of a carbonyl bond rather than that of an acetylenic bond.[3j]
(29) (a) C. H. Green and D. G. Hellier, *J. Chem. Soc., Perkin Trans. 2*, 458 (1972); (b) R. Leff and A. Marquet, *Tetrahedron*, **30**, 3379 (1974).
(30) (a) For a brief but recent summary, see L. van Acker and M. Anteunis, "Organic Sulphur Chemistry", C. J. M. Stirling, Ed., Butterworths, Reading, Mass., 1975, p 358. (b) The results of the degree of stereoselectivity from oxidation of substituted thianes by a number of different oxidants have been interpreted in terms of "product development" and "steric approach" controls.[3h] In addition, it has been postulated that electrophilic reactions involving thianes will proceed by equatorial attack. See J. Klein and H. Stollar, *Tetrahedron*, **30**, 2541 (1974).
(31) See T. P. Forrest, *J. Am. Chem. Soc.*, **97**, 2628 (1975).
(32) (a) K. Mislow, T. Simmons, J. T. Melillo, and A. L. Ternay, Jr., *J. Am. Chem. Soc.*, **86**, 1452 (1964); (b) G. Modena, *Int. J. Sulfur Chem., Part C*, **7**, 95 (1972).
(33) Details of the equilibration studies are given in the Experimental Section.

Quinazolines and 1,4-Benzodiazepines. 77.[1] Reaction of 2-Amino-1,4-Benzodiazepines with Bifunctional Acylating Agents

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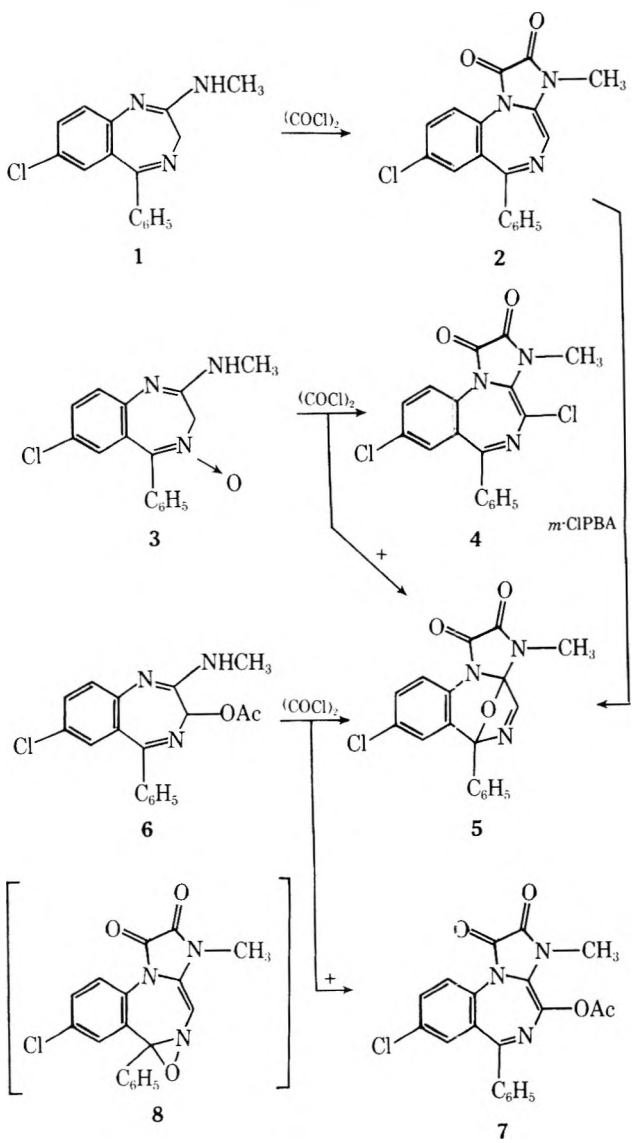
Treatment of 2-amino-1,4-benzodiazepines with acylating agents such as oxalyl chloride, ethyloxalyl chlorooxalate, and phosgene gave a variety of condensed ring products depending on the reagent used and the substituents present on the diazepine ring.

A major thrust in benzodiazepine chemistry in recent years has centered on compounds possessing an additional heterocyclic ring fused to the heterocyclic nucleus.[2] As part of this widespread research effort, we have investigated the reaction of 2-amino-1,4-benzodiazepines with bifunctional acylating reagents and found that a variety of condensed ring systems can be obtained.

The presence of reactive substituents at the 3 position of the diazepine ring can markedly influence the reaction course. Thus, while treatment of **1** (Scheme I) with oxalyl chloride gave the expected imidazolinedione **2**,[3] treatment of the *N*-oxide derivative **3** gave a mixture of two products, compounds **4** and **5**, both of which, while containing the anticipated new ring formed between the 1 and 2 positions of the benzodiazepine ring, were further modified as indicated by the structures shown. Treatment of the 3-acetoxy benzodiazepine **6** under the same conditions also gave a mixture of two products, compounds **5** and **7**.

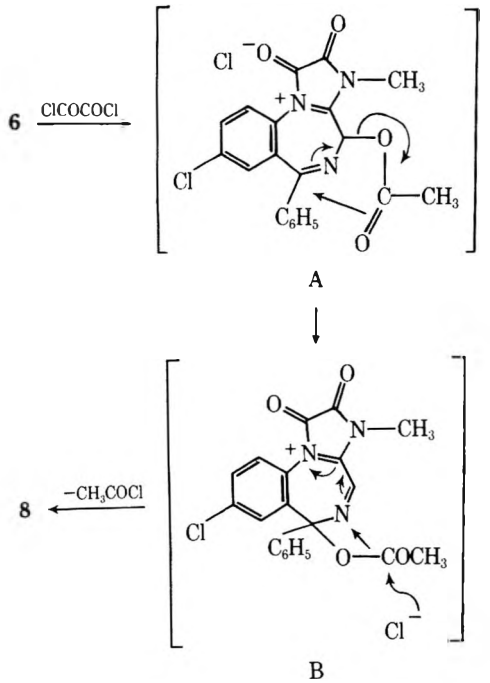
Scheme I



m-ClPBA = *m*-chloroperbenzoic acid

The formation of the imidazole ring in compounds **2**, **4**, **5**, and **7** is straightforward and it is readily apparent that the 4-chloro substituent in compounds **4** can be derived from a type of Polonovski rearrangement of the nitrone followed by a displacement of the resulting –OCOCOCl group by chloride ion.[4] The formation of compound **5** almost certainly proceeds via the tautomeric structure **8** since **5** can also be prepared from **2** by oxidation with *m*-chloroperbenzoic acid. In fact, on the basis of spectral data, we were unable to distinguish between structures **5** and **8** and therefore the compound was submitted for single crystal x-ray analysis. Figure 1 shows a stereodrawing for structure **5**.

A possible mechanism for the formation of **8** (i.e., **5**) is shown below.



Initial attack of the acid chloride on the amidine would lead to the imidazolinedione intermediate A. In a reverse of the allylic rearrangement observed in the Polonovski, the acetate could migrate to the 6 position as shown in B which could then undergo attack by chloride ion to give the oxaziridine **8**, tautomeric with compound **5**.

Treatment of **5** with ethanol leads to the hydroxy ether **9**, probably formed by the addition of ethanol to the Schiff base,

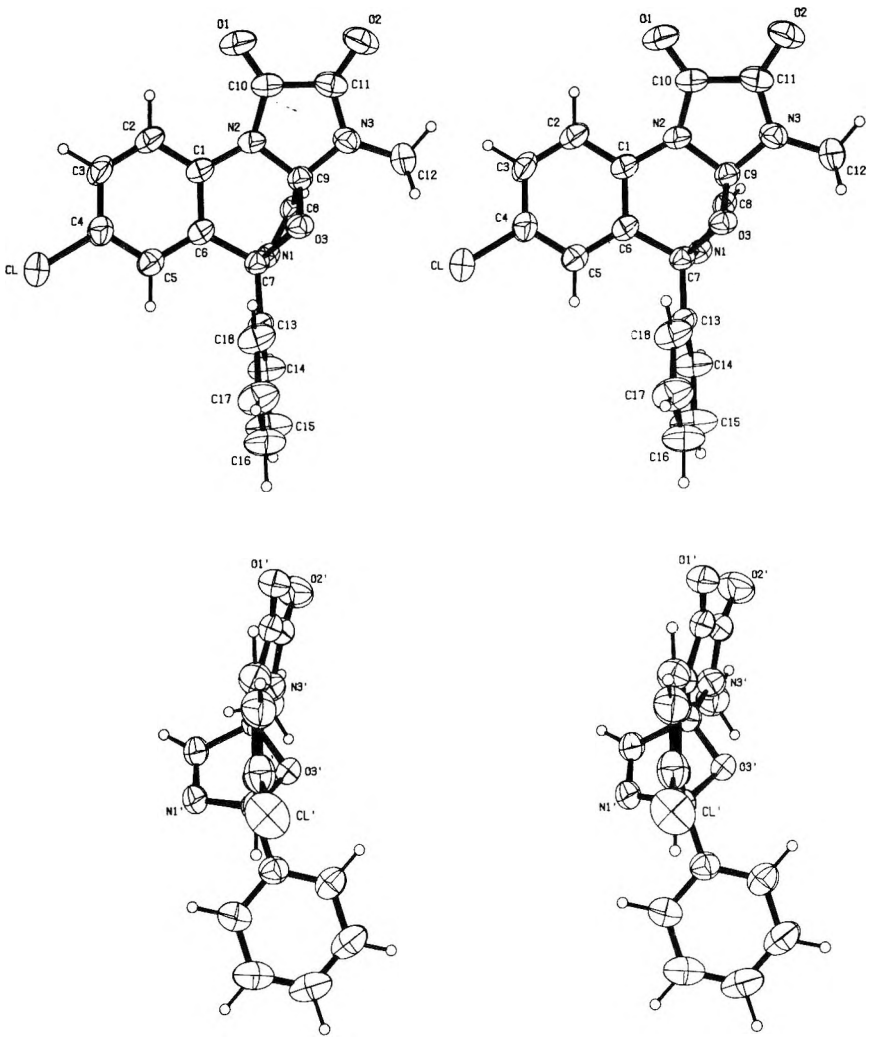


Figure 1. Stereodrawings of the two independent molecules of **5**. Two different views are shown because the conformations of the two independent molecules are essentially the same. The molecule in the lower view has been rotated 90° about the vertical axis from the orientation shown in the upper drawing.

followed by opening of the ether. The structure of **9** was established by ammonolysis of the imidazolindione ring to give the known 3-ethoxy compound **10**[4] (Scheme II). When compound **9** was treated first with thionyl chloride and then with ethanol, the diether, compound **11**, was obtained.

When **5** was treated with ammonia, the only product isolated was the diamide, compound **14**. The structure of **14** was assigned as shown, based on the NMR signal obtained for the $NHCH_3$ group (3 H doublet which collapses to a singlet in D_2O), and on the UV spectrum. Subsequently the structure of **14** was confirmed by single crystal x-ray analysis. Once again ammonolysis of the diamide would lead to an intermediate such as **12**, which could then give the tricyclic intermediate **13**. As in the case of compound **9** the hydrated amidine in **13** would cleave under the reaction conditions to afford the observed product, compound **14**.

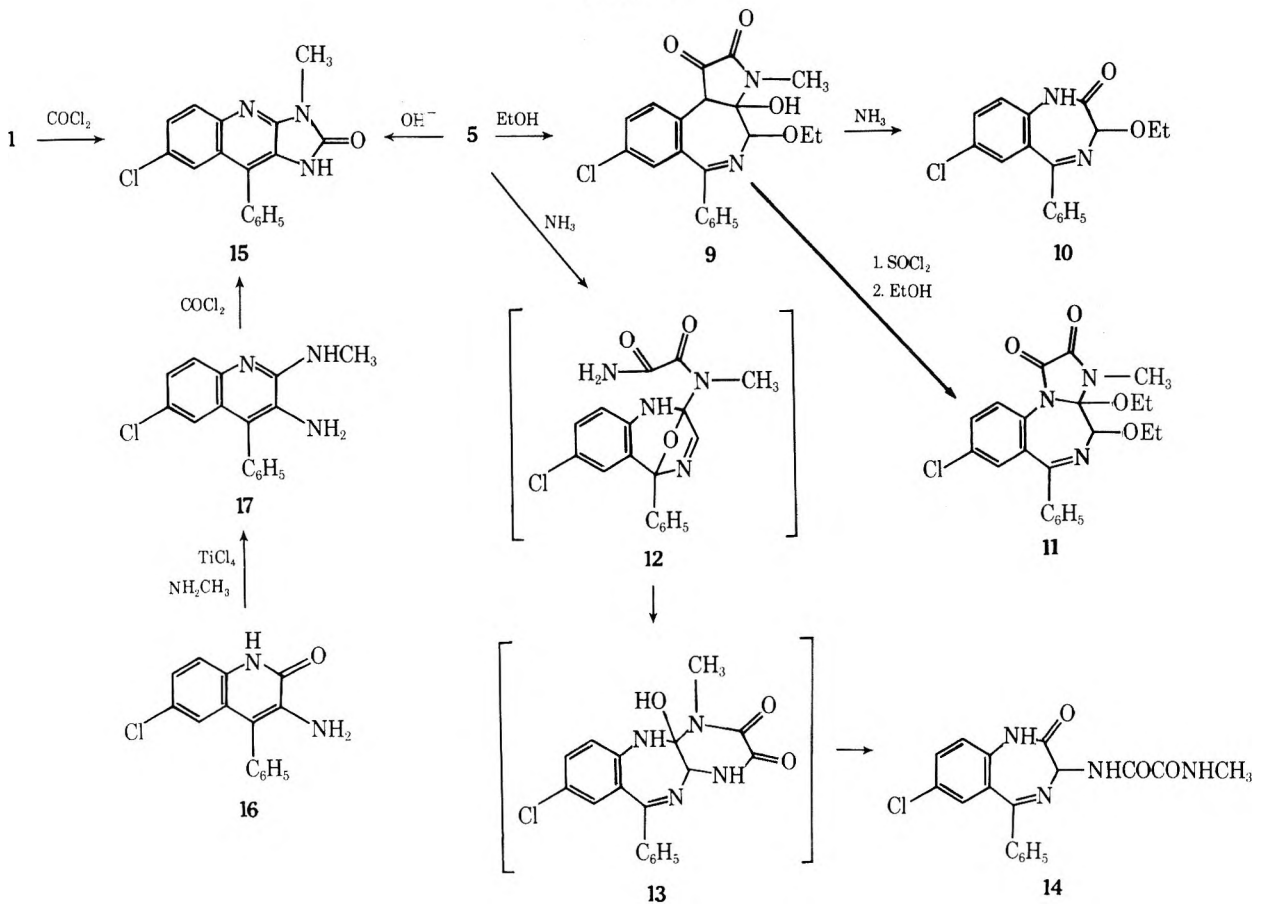
A rather unusual rearrangement was observed when the oxaziridine **5** was treated with base. In this instance the quinoline derivative **15** was isolated. The same product was also prepared by treatment of the amidine **1** with phosgene. The structure of **15** was confirmed by an alternative synthesis from the known carbostyril **16**.[6] Treatment of **16** with titanium tetrachloride and methylamine[7] afforded the 2-methylaminoquinoline **17** which was then cyclized to **15** using phosgene.

The formation of compound **15** from **1** is readily explained on the basis of the mechanism described in an earlier publication which reported the rearrangement of a benzodiazepin-2-one to a related oxazoloquinoline.[9] The mechanism for the formation of **15** from **5** is not so readily apparent, but might possibly be explained as indicated in Scheme III. Attack of hydroxide ion on the amide as shown, with concomitant formation of the amidine, cleavage of the oxide, and ring opening, would lead to an intermediate such as **18**. Cyclization could then occur to give the five-membered ring, structure **19**. Decarboxylation of **19** to the anion followed by an aldol type of cyclization would lead to **20**, dehydration of which would afford the observed product, compound **15**.

Treatment of compound **3** with ethyloxalyl chloride (Scheme IV) afforded a mixture of **4** and the interesting N-demethylated product, compound **21**. Compound **21** was also obtained either directly from **22** or again with N-demethylation from **23** by treatment with ethyloxalyl chloride. Deacylation of **21** with hydrazine gave compound **24**. Both **21** and and **24** gave compound **22** on treatment with aqueous sodium hydroxide. Treatment of compound **23** with phosgene afforded the expected oxazolone **25**.

A possible common intermediate in the cyclization of compounds **3**, **11**, and **23** to compound **21** could be the diester **26**. Whether or not a mono- or diamide is then formed is not significant since the next important intermediate would be a quaternary salt such as **27**. Where R = CH_3 and in the presence of chloride ion, **27** would readily demethylate to give compound **21**, after amide formation at the 1 nitrogen. Apart

Scheme II



from the demethylation step the reaction products shown in Scheme IV are similar to those obtained by the acetylation of compound **22** with acetic anhydride.[9]

Treatment of the 3-chloro benzodiazepine, compound **4**, with ammonia (Scheme V) afforded a mixture of the three compounds **28**, **29**, and **30**. The stereochemistry of the two spiro compounds is unknown and the structures are arbitrarily assigned. The mass spectra of **29** and **30** were identical and both exhibited a molecular ion indicative of loss of ammonia and a parent ion of *m/e* 241 which corresponds to 6-chloro-4-phenylquinazoline. It was not surprising, therefore, that both compound **29** and compound **30** underwent a thermal rearrangement with ring contraction to give the single quinazoline **31** whose mass spectrum was indistinguishable from those of compounds **29** and **30**. In order to exclude the possibility that compound **31** was a six-seven-six ring system, its structure was confirmed by single crystal x-ray analysis. Such a six-seven-six ring system, related to compound **34**, could be derived from spiro ring opening, loss of ammonia, and recyclization of the diamide onto the 3 position of the benzodiazepine.

With the definitive assignment of structure **31** as a quinazoline, doubts existed as to the authenticity of the unusual ortho-amide structures **29** and **30**. Spectral data were, at best, equivocal and therefore it was decided to prepare a related compound in which stereoisomers were eliminated and which would contain a methylene group at the 3 position of the benzodiazepine. Such a derivative would be amenable to ^{13}C NMR spectroscopic analysis and would distinguish the spiro benzodiazepine from the alternate dihydroquinazoline

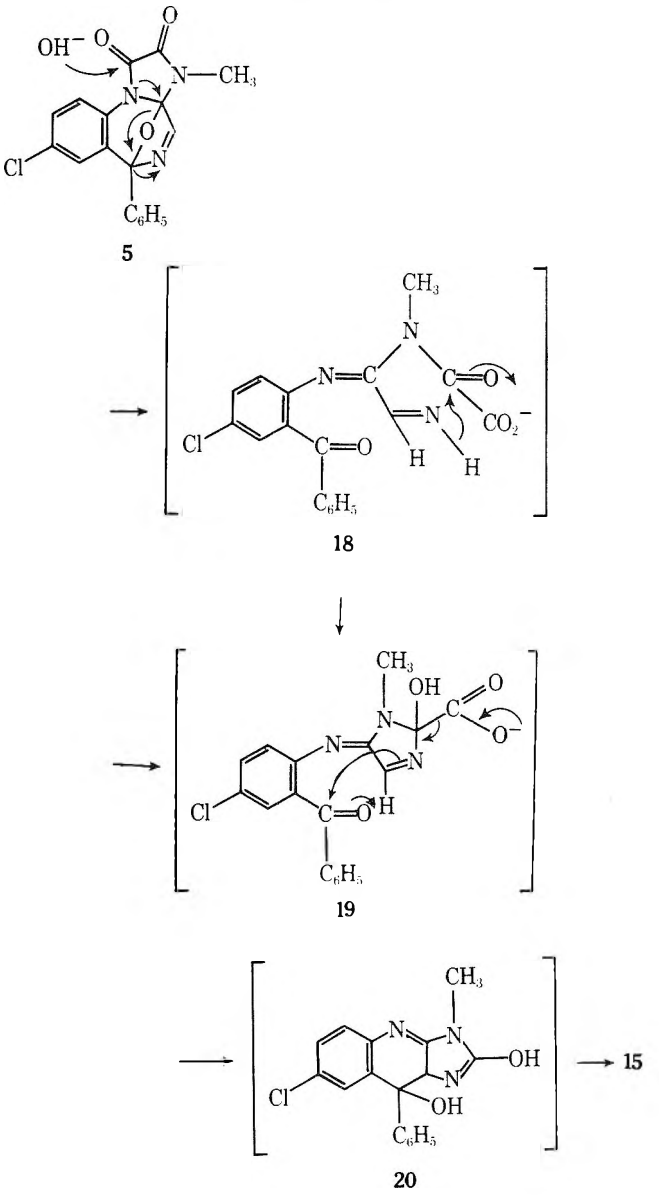
Table I. Crystal Data

Compd	5	14	31
Formula	$C_{18}H_{12}N_3O_3$	$C_{18}H_{15}ClN_4O_3$	$C_{18}H_{13}ClN_4O_2$
Formula weight	353.76	370.80	352.78
Space group	$P\bar{1}$	$Pbca$	$P2_1/n$
a, Å	8.865 (3)	9.570 (5)	9.598 (2)
b, Å	12.524 (3)	10.028 (7)	18.562 (4)
c, Å	15.352 (4)	37.449 (14)	9.264 (3)
α, deg	79.93 (2)		
β, deg	74.10 (2)		101.55 (2)
γ, deg	85.94 (2)		
Z	4	8	4
d_{calcd}, g cm^{-3}	1.455	1.370	1.448
μ(Cu Kα), cm^{-1}	23.1	21.2	22.8

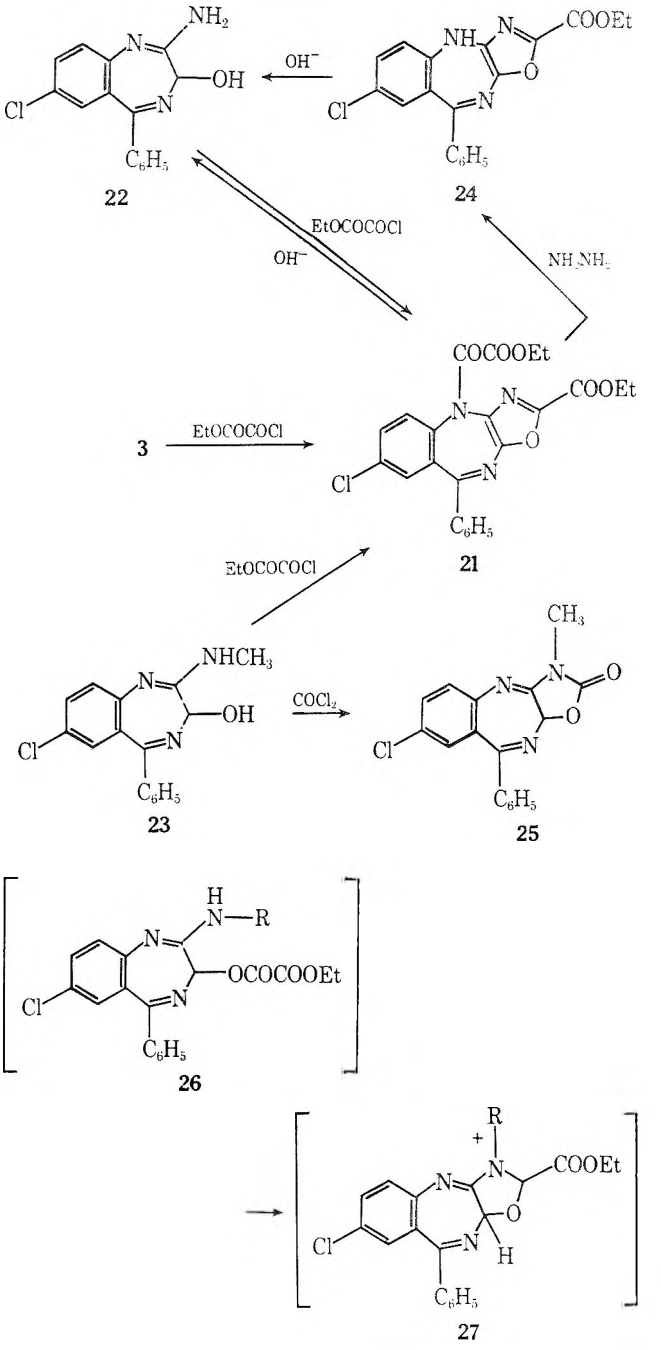
Table II. Experimental Details

Compd	5	14	31
Crystal size, mm	0.05 × 0.20 × 0.35	0.03 × 0.10 × 0.60	0.03 × 0.10 × 0.30
Maximum θ, deg	76	53.5	76
Number of reflections	6735	2128	3050
Absorption correction	Yes	Yes	Yes
Least-squares refinement	block diagonal (two blocks)	Full matrix	Full matrix
Heavier atoms	Anisotropic	Anisotropic	Anisotropic
Hydrogen atoms	Iso (fixed)	Iso (fixed)	Iso (fixed)
Final R	0.049	0.056	0.052
Rinal wR	0.075	0.051	0.045
Final difference map—largest peak (e A^{-3})	<±0.2	<±0.1	<±0.1

Scheme III



Scheme IV



structure A. For this reason then, compound **2** was treated with methylamine and afforded, after workup, a mixture of the hydrolysis product, compound **1**, together with the expected spiro derivative **32**. The ^{13}C NMR spectrum of **32** shows a singlet for the quaternary carbon and a triplet for the methylene carbon. This excludes structure A as a possibility and is compatable with the spiro structure as shown.

A related type of ammonolysis of compound **4** was observed when ethylenediamine was substituted for ammonia in the reaction. In this instance the two products isolated were the spiro derivative, compound **33**, and the piperazinobenzodiazepine, compound **34**. Compound **33** was converted to **34** in high yield by treatment with an organic base in methanol solution. Compound **34** exhibited the characteristic UV spectrum of a 3*H*-1,4-benzodiazepine and there was no fragmentation observed in the mass spectrum which could be attributable to a quinazoline structure.

Crystallography. Crystals of **5**, **14**, and **31** were obtained from acetone and dichloromethane/methanol, respectively. All intensity data were measured on Hilger-Watts four-circle diffractometers (Ni filtered Cu Kα radiation, θ–2θ scans, pulse height discrimination). The crystal data are given in Table I. A multiple solution procedure[10] was used to solve the three structures. The experimental details are summarized in Table II.

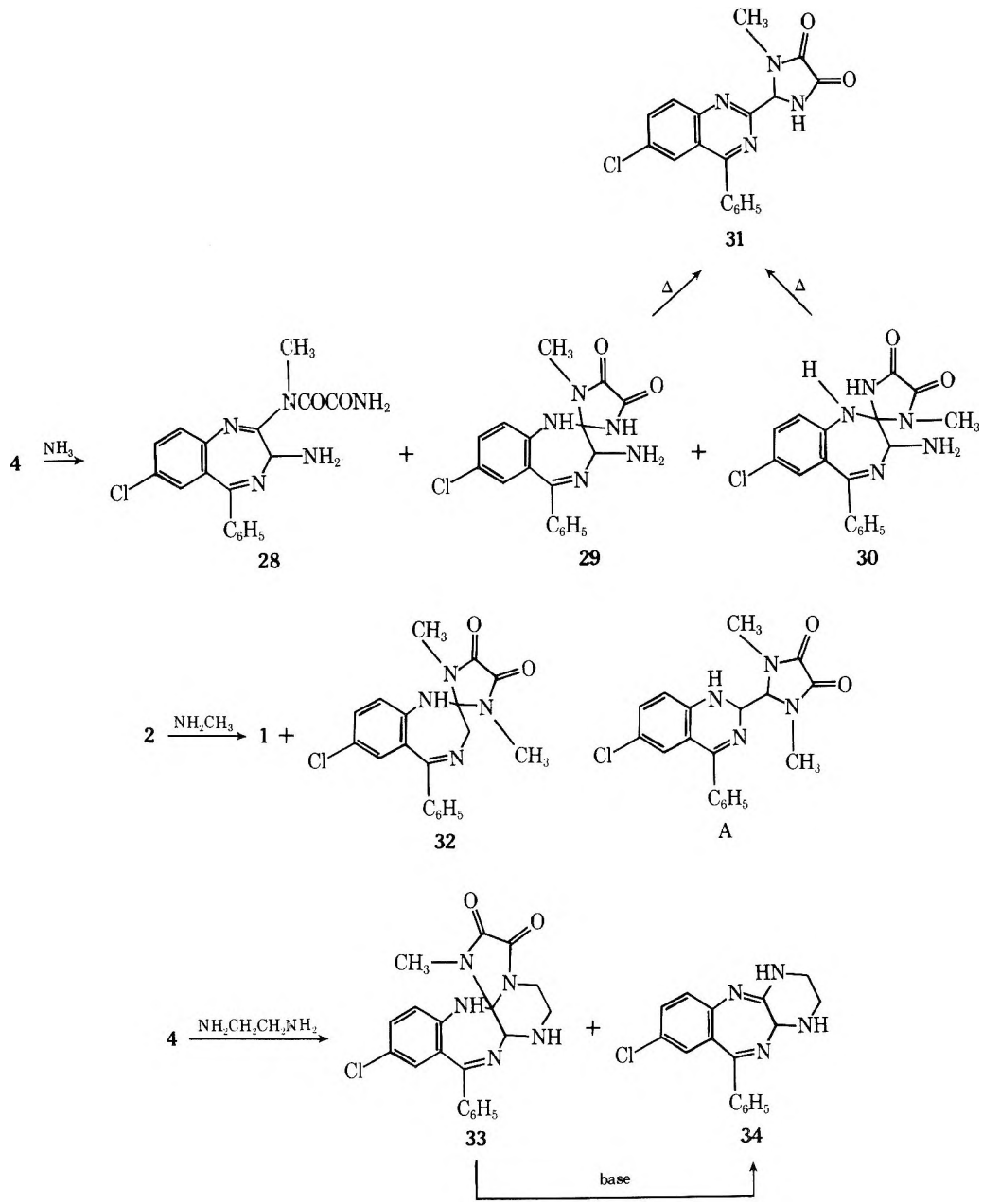
Experimental Section[11]

8-Chloro-3-methyl-6-phenyl-3*H*-imidazo[1,2-*a*][1,4]benzodiazepine-1,2-dione (2). A solution of 40 g (0.141 mol) of 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine (**1**)[12] in 500 mL of dry benzene was treated with 21.5 g (0.17 mol) of oxalyl chloride. The reaction mixture was refluxed and stirred for 5 h, and then cooled and filtered. The filtrates were concentrated and crystallized from a mixture of dichloromethane and ether to give 11.4 g of product. The initial precipitate was extracted with a mixture of 100 mL of dichloromethane and dilute potassium carbonate solution and filtered. The organic layer was separated, dried, and added to the mother liquors from the first crop. The solution was concentrated, cooled, and filtered to yield 4 g of starting material. The filtrates were evaporated, dissolved in dichloromethane, and chromatographed through 200 g of Florisil. Elution with 1.5 L of dichloromethane gave, after evaporation and crystallization from a mixture of dichloromethane and ether, an additional 5 g (combined yield 16.4 g) of product. A sample was recrystallized from a mixture of dichloromethane and ether to give **2** as orange rods, mp 200–202 °C.

Anal. Calcd for $C_{18}H_{12}ClN_3O_2$: C, 64.01; H, 3.58; N, 12.44. Found: C, 63.98; H, 3.43; N, 12.47.

4,8-Dichloro-3-methyl-6-phenyl-3*H*-imidazo[1,2-*a*][1,4]-

Scheme V



benzodiazepine-1,2-dione (4) and 8-Chloro-3a,6-epoxy-1,2,3a,6-tetrahydro-3-methyl-6-phenyl-3*H*-imidazo[1,2-*a*]-[1,4]benzodiazepine-1,2-dione (5). A suspension of 40 g (0.133 mol) of 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**3**)[12] in 500 mL of benzene was treated with 40 g (0.315 mol) of oxalyl chloride. The reaction mixture was refluxed for 3.5 h, and then evaporated to dryness. The residue was dissolved in 300 mL of dichloromethane, washed with 150 mL of 10% potassium carbonate solution, dried over sodium sulfate, and concentrated to 200 mL. This solution was filtered through 600 g of Florisil in a sintered glass funnel and eluted with 2 L of chloroform. The eluent was concentrated, cooled, and filtered to give 19.4 g of **4** as orange prisms, mp 252–260 °C. A second crop of 20 g was obtained from the mother liquors to give a combined yield of 39.4 g (79%). An analytical sample (mp 258–262 °C) was obtained by recrystallization from a mixture of dichloromethane and ether.

Anal. Calcd for $C_{18}H_{11}Cl_2N_3O_2$: C, 58.08; H, 2.98; N, 11.29; Cl, 19.05. Found: C, 57.82; H, 2.81; N, 11.27; Cl, 19.23.

In a reaction carried out as described for the preparation of compound **4**, using 5.0 g of **3** as starting material, the residue obtained after extraction, washing, and drying was carefully chromatographed over 150 g of Florisil. Using benzene as the eluent removed all of **4**. The eluent was then changed to a mixture of 10% ether in benzene. Removal of solvent from these fractions afforded 0.8 g of an oil. The oil was crystallized from ether and the product was recrystallized from a mixture of dichloromethane and ether to give 0.5 g (8%) of **5** as white needles, mp 165–175 °C, resetting to needles, mp 238–242 °C.

Anal. Calcd for $C_{18}H_{12}ClN_3O_3$: C, 61.10; H, 3.42; N, 11.88. Found: C, 61.00; H, 3.03; N, 11.97.

8-Chloro-3a,6-epoxy-1,2,3a,6-tetrahydro-3-methyl-6-phenyl-3*H*-imidazo[1,2-*a*][1,4]benzodiazepine-1,2-dione (5) and 4-Acetoxy-8-chloro-3-methyl-6-phenyl-3*H*-imidazo[1,2-*a*]-[1,4]benzodiazepine-1,2-dione (7). A solution of 10 g (0.0293 mol) of 3-acetoxy-7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine (**6**)[13] in 200 mL of benzene was treated with 8 g (0.064 mol) of oxalyl chloride, and the reaction mixture was refluxed for 5 h and then evaporated to dryness. The residue was dissolved in 75 mL of dichloromethane and filtered through 100 g of Florisil in a sintered glass funnel. Elution with dichloromethane followed by 10% ether in dichloromethane gave, after removal of solvents, 5 g of an oil. This was crystallized from a mixture of dichloromethane and ether to give 3.3 g (32%) of **5** as white needles, mp and mmp 238–243 °C.

The filtrates were concentrated and cooled. The precipitate was collected and recrystallized from a mixture of dichloromethane and ether to give 0.6 g (5%) of **7** as orange rods, mp 206–208 °C.

Anal. Calcd for $C_{20}H_{14}ClN_3O_4$: C, 60.69; H, 3.57; N, 10.62. Found: C, 60.41; H, 3.49; N, 10.55.

From Compound 2. A cold solution of 16 g (0.0473 mol) of **2** in 400 mL of dichloromethane was treated with 11.5 g (0.057 mol) of 85% *m*-chloroperbenzoic acid. After 18 h at room temperature the reaction

mixture was washed with dilute ammonium hydroxide (2 × 150 ml), dried over anhydrous sodium sulfate, and filtered through 100 g of Florisil in a sintered glass funnel. The product was eluted with 500 mL of dichloromethane and then 500 mL of a 10% solution of ether in dichloromethane. The eluents were combined and concentrated to give 14 g of crude oil. Crystallization from ether and recrystallization from a mixture of dichloromethane and ether gave 9.7 g (58%) of **5** as white prisms, mp and mmp 237–241 °C.

8-Chloro-4-ethoxy-3a-hydroxy-3-methyl-6-phenyl-2,3,3a,4-tetrahydro-1*H*-imidazo[1,2-*a*][1,4]benzodiazepine-1,2-dione (9). A solution of 0.3 g (0.848 mmol) of **5** in 25 mL of absolute ethanol was heated under reflux for 18 h and then evaporated to dryness. The residue was dissolved in 10 mL of dichloromethane and filtered through 25 g of Florisil. The column was eluted with 100 mL of dichloromethane and then with 300 mL of ethyl acetate. The ethyl acetate fraction was evaporated, and the product was crystallized from ether and recrystallized from a mixture of tetrahydrofuran and hexane to give 0.2 g (60%) of **9** as white prisms, mp 190–198 °C.

Anal. Calcd for $C_{20}H_{18}ClN_3O_4$: C, 60.08; H, 4.54; N, 10.51. Found: C, 60.03; H, 4.35; N, 10.37.

7-Chloro-3-ethoxy-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (10). A solution of 0.1 g (0.25 mmol) of **9** in 20 mL of dioxane was added to 80 mL of liquid ammonia, and after 18 h the solution was evaporated under vacuum. The residue was dissolved in 20 mL of dichloromethane, washed with 10 mL of water, dried with sodium sulfate, and evaporated to dryness. The residue was crystallized from ether and recrystallized from a mixture of dichloromethane and ether to give 40 mg (44%) of **10** as off-white prisms, mp and mmp with an authentic sample prepared as described in the literature[4] 222–225 °C: UV λ_{max} (Me_2CHOH) 230 nm (ϵ 40 800), 318 (2830), infl 250 (16 000).

Anal. Calcd for $C_{17}H_{15}N_2O_2Cl$: C, 64.87; H, 4.80. Found: C, 64.76; H, 4.67.

8-Chloro-3a,4-diethoxy-3-methyl-6-phenyl-2,3,3a,4-tetrahydro-1*H*-imidazo[1,2-*a*][1,4]benzodiazepine-1,2-dione (11). A solution of 0.1 g (0.25 mmol) of **9** in 20 mL of dichloromethane was treated with 1 mL (0.0134 mol) of thionyl chloride, and heated under reflux for 10 min. The solution was evaporated under reduced pressure and the residue was immediately dissolved in 10 mL of absolute ethanol and heated under reflux for 3 h. The ethanol was removed under reduced pressure and the product was dissolved in 20 mL of dichloromethane. The solution was washed with 10 mL of dilute ammonium hydroxide and brine, dried over sodium sulfate, filtered, and evaporated. The residue was crystallized from ether and recrystallized from a mixture of dichloromethane and ether to give 50 mg (47%) of **11** as white prisms, mp 259–262 °C.

Anal. Calcd for $C_{22}H_{22}ClN_3O_4$: C, 61.75; H, 5.18; N, 9.82. Found: C, 61.95; H, 5.13; N, 9.83.

(7-Chloro-1,3-dihydro-2-oxo-5-phenyl-2*H*-1,4-benzodiazepin-3-yl)oxamic Acid *N*-Methylacetamide (14). A solution of 1.0 g (0.0028 mol) of **5** in 50 mL of dichloromethane was added to 50 mL of liquid ammonia. After standing for 4 h, 40 mL of water was added and the precipitate was recovered by filtration. Recrystallization from a mixture of dichloromethane and methanol gave 0.2 g (20%) of **14** as white prisms, mp 307–313 °C: NMR (Me_2SO-d_6) δ 11.19 (s, 1, NH), 8.91 (d, 1, J = 8 Hz, OH), 8.84 (b, 1, NH), 5.26 (d. 1, J = 8 Hz, CH), 2.76 (d, 3, J = 5 Hz, NCH_3), 5.26 and 2.76 collapse to singlets on exchange with D_2O; UV λ_{max} (Me_2CHOH) 229 nm (ϵ 39 600), 316 (2330), infl 250 (15 800); mass spectrum m/e 370 (M^+).

Anal. Calcd for $C_{18}H_{15}ClN_4O_3$: C, 58.31; H, 4.08; N, 15.11. Found: C, 58.17; H, 3.89; N, 14.88.

7-Chloro-3-methyl-9-phenyl-1,3-dihydro-2*H*-imidazo[4,5-*b*]quinolin-2-one (15). A. From Compound 5. A solution of 0.8 g (2.26 mmol) of **5** in 20 mL of dioxane was treated with 5 mL (0.015 mol) of 3 N sodium hydroxide. After standing for 2 h at room temperature, the reaction mixture was poured into 100 mL of water. The solution was extracted with 150 mL of dichloromethane, which was washed with brine, dried over sodium sulfate, and evaporated to dryness. The residue was crystallized from a mixture of dichloromethane, methanol, and ether to give 0.5 g (71%) of **15** as white needles, mp 312–313 °C: NMR (Me_2SO-d_6) δ 11.2 (s, 1, NH), 3.49 (s, 3, NCH_3); UV λ_{max} (Me_2CHOH) 205 nm (ϵ 23 300), 235 (50 600), 310 (9500), 325 (13 000), 340 (16 700); mass spectrum m/e 309 (M^+).

Anal. Calcd for $C_{17}H_{12}ClN_3O$: C, 65.90; H, 3.90; N, 13.57. Found: C, 66.11; H, 3.88; N, 13.82.

B. From Compound 17. A solution of 0.1 g (0.353 mmol) of **17** in 10 mL of dry benzene was treated with 0.32 mL (0.4 mmol) of a 12.5% solution of phosgene in benzene. The mixture was refluxed for 2 h and evaporated and the residue crystallized from methanol. Recrystallization from a mixture of dichloromethane and ether gave 40 mg (36%) of **15** as white plates which reset to needles at 290–300 °C and melted at 310–313 °C, mmp with a sample obtained from A 310–313 °C.

C. From Compound 1. A suspension of 6.0 g (0.0211 mol) of **1** in 100 mL of dry benzene was treated with 30 g (0.0375 mol) of a 12.5% solution of phosgene in benzene and the reaction mixture was refluxed for 7 h. The mixture was filtered and the filtrates were evaporated to dryness. The precipitate and the residue obtained from the filtrates were each dissolved in 100 mL of dichloromethane, washed with 40 mL of 10% potassium carbonate solution, dried over sodium sulfate, and evaporated to dryness. The fraction obtained from the precipitate was recrystallized from a mixture of dichloromethane and ether to give 1.5 g of starting material. The mother liquors were evaporated and the residue was combined with that obtained from the original filtrates. The oil was dissolved in 50 mL of dichloromethane and chromatographed through 200 g of Florisil. Elution with a 10% solution of ether in benzene, followed by ether and finally by ethyl acetate, gave, after removal of solvents, fractions of 0.5 and 1.0 g, respectively. The ethyl acetate fraction was crystallized from a mixture of dichloromethane and ether to give 0.8 g (12.3%) of **15** as white prisms, mp and mmp with the product obtained from A 310–313 °C.

3-Amino-6-chloro-2-methylamino-4-phenylquinoline (17). A solution of 3.0 g (11.1 mmol) of 3-amino-6-chloro-4-phenylcarbostyril (**16**)[6] in 250 mL of dry xylene was saturated with methylamine, and then 3.8 g (20 mmol) of titanium tetrachloride in 20 mL of xylene was added. After stirring and refluxing for 18 h, an additional 3.8 g of titanium tetrachloride was added, and the reaction mixture was again saturated with methylamine. The reaction mixture was then refluxed for 24 h, and the same amount of the two reagents was again added followed by 80 h of refluxing and stirring. After the reaction mixture was cooled to room temperature, concentrated ammonium hydroxide was added until the precipitate turned almost white. The precipitate was removed by filtration and washed with ethyl acetate, and the combined filtrates were dried with sodium sulfate and concentrated to dryness.

The residual oil was crystallized from ether to give 1.2 g of starting material. The filtrates were concentrated and dissolved in dichloromethane and the solution was chromatographed through a column of Florisil, eluting with 1 L of benzene, 1.5 L of dichloromethane, and 1 L of ether. From the combined dichloromethane and ether fractions, a total of 0.6 g of crude product was obtained. Recrystallization from a mixture of ether and petroleum ether gave 0.4 g (21%) of **17** as off-white prisms, mp 118–120 °C.

Anal. Calcd for $C_{16}H_{14}ClN_3$: C, 67.72; H, 4.97; N, 14.81. Found: C, 67.85; H, 5.09; N, 14.95.

7-Chloro-2-ethoxycarbonyl-9-phenyl-4*H*-oxazolo[4,5-*b*]-[1,4]benzodiazepine-4-glyoxylic Acid Ethyl Ester (21). A. From Compound 3. A solution of 5.0 g (16.7 mmol) of **3** in 200 mL of benzene was treated with 5.0 g (36.5 mmol) of ethyloxalyl chloride and heated under reflux for 16 h. The reaction mixture was evaporated to dryness and the residue was dissolved in 100 mL of dichloromethane. The solution was washed with 50 mL of 10% potassium carbonate solution, dried over sodium sulfate, and evaporated to dryness. The residue was recrystallized from a mixture of dichloromethane and ether to give 4.2 g (54%) of **21** as yellow rods, mp 198–207 °C.

Anal. Calcd for $C_{23}H_{18}ClN_3O_6$: C, 59.05; H, 3.88; N, 8.98. Found: C, 58.69; H, 3.85; N, 8.91.

B. From Compound 22. A solution of 0.2 g (0.7 mmol) of 2-amino-7-chloro-3-hydroxy-5-phenyl-3*H*-1,4-benzodiazepine (**22**)[12] in 20 mL of benzene and 0.4 g (2.8 mmol) of ethyl oxalyl chloride was heated on the steam bath for 1 h and evaporated to dryness and the residue was crystallized from ether. Recrystallization of the product from a mixture of dichloromethane and ether gave 0.2 g (60%) of **21** as yellow rods, mp and mmp with the product obtained from A 195–205 °C.

C. From Compound 23. A mixture of 5.0 g (0.0167 mol) of 7-chloro-2-methylamino-3-hydroxy-5-phenyl-3*H*-1,4-benzodiazepine (**23**)[13] in 200 mL of benzene was treated with 5.0 g (0.0365 mol) of ethyloxalyl chloride and the reaction mixture was refluxed for 18 h and then evaporated to dryness. The residue was dissolved in 75 mL of dichloromethane, which was washed with a 10% solution of potassium carbonate, dried over sodium sulfate, and concentrated. The residue was crystallized from a mixture of dichloromethane and ether to give 4.1 g (53%) of **21** as yellow rods, mp and mmp 197–207 °C.

7-Chloro-9-phenyl-4*H*-oxazolo[4,5-*b*][1,4]benzodiazepine-2-carboxylic Acid Ethyl Ester (24). A solution of 1.0 g (2.13 mmol) of **21** in a mixture of 40 mL of tetrahydrofuran and 10 mL of methanol was treated with 2 g of an 85% solution of hydrazine hydrate in water, and after 1 h the solvent was removed under vacuum. The residue was warmed with 50 mL of methanol and filtered and the precipitate was

recrystallized from a mixture of *N*,*N*-dimethylformamide, methanol, and water to give 0.6 g (75%) of **24** as reddish-brown rods, mp 244–249 °C.

Anal. Calcd for $C_{19}H_{14}ClN_3O_3$: C, 62.05; H, 3.83; N, 11.43. Found: C, 61.78; H, 3.73; N, 11.56.

2-Amino-7-chloro-3-hydroxy-5-phenyl-3*H*-1,4-benzodiazepine (22). A. From Compound 21. A solution of 1.0 g (2.13 mmol) of **21** in 100 mL of methanol was treated with 10 mL of 10 N sodium hydroxide and the mixture was heated under reflux for 15 min. Solvents were removed by evaporation and the residue was dissolved in 100 mL of dichloromethane. The solution was washed with 50 mL of dilute acetic acid. The organic layer was separated, dried over sodium sulfate, and filtered through 100 g of Florisil. The Florisil was eluted first with 600 mL of a mixture of 10% ether in dichloromethane and then with 800 mL of ethyl acetate. Evaporation of the ethyl acetate fractions gave 0.5 g of an oil which was crystallized from a mixture of dichloromethane and ether and then recrystallized from a mixture of dichloromethane and methanol to give 0.4 g (37%) of **22** as white rods, mp and mmp with an authentic sample 177–185 °C dec.

B. From Compound 24. A solution of 0.1 g (0.27 mmol) of **24** in 10 mL of ethanol and 2 mL of 3 N sodium hydroxide was refluxed for 14 min and then evaporated to dryness. The residue was dissolved in 50 mL of dichloromethane, which was washed with 30 mL of water, dried over sodium sulfate, and evaporated to dryness. Recrystallization of the residue from a mixture of dichloromethane and ether gave 40 mg (50%) of **22** as white rods, mp and mmp with an authentic sample 178–182 °C dec.

7-Chloro-3-methyl-9-phenyl-10a*H*-oxazolo[4,5-*b*][1,4]benzodiazepin-2(3*H*)-one (25). A solution of 5.0 g (0.0167 mol) of **23** in 20 mL of pyridine and 40 mL of tetrahydrofuran was cooled in an ice bath and was treated with 26.1 g (0.033 mol) of a 12.5% solution of phosgene in benzene. After 20 h at room temperature, the solution was evaporated to dryness and the residue was dissolved in 100 mL of dichloromethane which was washed with 75 mL of a 5% solution of sodium bicarbonate, dried over sodium sulfate, and filtered through 100 g of Florisil. The Florisil was eluted with 500 mL of benzene and 750 mL of dichloromethane which were combined and concentrated. The residue was crystallized from a mixture of ether and petroleum ether and recrystallized from a mixture of dichloromethane and petroleum ether to give 3.9 g (72%) of **25** as white rods, mp 208–212 °C.

Anal. Calcd $C_{17}H_{12}ClN_3O_2$: C, 62.68; H, 3.71; N, 12.90. Found: C, 62.58; H, 3.54; N, 12.88.

3-Amino-7-chloro-2-(*N*¹-methyloxamido)-5-phenyl-3*H*-1,4-benzodiazepine (28), 3-Amino-7-chloro-5-phenyl-2,3-dihydro-3′-methylspiro[1*H*-1,4-benzodiazepine-2,2′-imidazolidine]-4′,5′-dione (29), and 3-Amino-7-chloro-5-phenyl-2,3-dihydro-1′-methylspiro[1*H*-1,4-benzodiazepine-2,2′-imidazolidine]-4′,5′-dione (30). A solution of 15 g (0.0402 mol) of **4** in 400 mL of dry dichloromethane was added to 300 mL of liquid ammonia. After standing for 2 h, 200 mL of water was added, and the reaction mixture was filtered. The filter cake was refluxed in a mixture of chloroform and ethanol (50/50) for 5 min, cooled, and filtered to give 9.1 g (61%) of **30** as pale yellow prisms. An analytical sample was recrystallized from a mixture of dichloromethane and methanol to give **30** as pale yellow prisms, mp 186–187 °C: IR (KBr) 3400, 3385, 3370 (NH, NH_2), 1740 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 9.73 (s, 1, NH), 6.65 (s, 1, NHC=O), 5.27 (s, 1, CH), 3.19 (s, 2, NH_2), 2.85 (s, 3, NCH_3); UV λ_{max} (Me_2CHOH) 232 nm (ϵ 33 000), 395 (1300); mass spectrum *m/e* 352 ($M^+ - 17$), 240 (base peak).

Anal. Calcd for $C_{18}H_{16}ClN_5O_2$: C, 58.46; H, 4.36; N, 18.94. Found: C, 58.41; H, 4.30; N, 19.18.

The dichloromethane/water filtrates from above were separated and the organic layer was dried over sodium sulfate, filtered, and concentrated to 100 mL. The solution was cooled and filtered. The solid residue was recrystallized from a mixture of dichloromethane and methanol to give 2.5 g (17%) of **29** as yellow rods, mp 183–187 °C: IR (KBr) 3420, 3315 (NH, NH_2), 1758, 1720 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 9.75 (s, 1, NH), 6.57 (s, 1, NHC=O), 5.36 (d, 1, J = 2 Hz, CH), 2.98 (s, 2, NH_2), 2.87 (s, 3, NCH_3); UV λ_{max} (Me_2CHOH) 230 nm (ϵ 34 200), 397 (1300); mass spectrum *m/e* 352 ($M^+ - 17$), 240 (base peak).

Anal. Calcd for $C_{18}H_{16}ClN_5O_2$: C, 58.46; H, 4.36; N, 18.94. Found: C, 58.47; H, 4.05; N, 19.00.

The filtrates from **29** were concentrated and the residue was crystallized from dichloromethane. The solid was recrystallized from a mixture of dichloromethane and finally from a mixture of dichloromethane and ether to give 0.3 g (2%) of **28** as white prisms, mp 280–284 °C: IR (KBr) 3380 (NH_2), 1720, 1675 cm^{-1} (C=O); NMR (CF_3COOD) δ 6.85 (s, 1, CH), 3.50 (s, 3, NCH_3); UV λ_{max} (Me_2CHOH) 240 nm (ϵ 28 000), 265 (20 000), 350 (2500); mass spectrum *m/e* 369 (M^+).

Anal. Calcd for $C_{18}H_{16}ClN_5O_2$: C, 58.46; H, 4.36; N, 18.94. Found: C, 58.52; H, 4.46; N, 18.69.

1-Methyl-2-(6-chloro-4-phenyl-2-quinazolinyl)-4,5-imidazolidinedione (31). A. From Compound 29. A 1-g (0.0027 mol) sample of **29** was heated to 200 °C under nitrogen in an oil bath for 5 min. After cooling, the residue was dissolved in 25 mL of dichloromethane which was then washed with 20 mL of dilute ammonium hydroxide, dried over sodium sulfate, and chromatographed through 100 g of silica gel. The column was eluted with dichloromethane, dichloromethane and ether (10/1), and then with ether. The ether fraction was evaporated and the residue was crystallized from ethyl acetate and recrystallized from a mixture of dichloromethane and ether to give 0.35 g (37%) of **31** as white prisms, mp 205–235 °C: IR (KBr) 3395, 3330 (NH), 1750, 1720 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 6.09 (s, 1, CH), 2.88 (s, 3, NCH_3); UV λ_{max} (Me_2CHOH) 237 nm (ϵ 54 000), 273 (9300), 328 (6500); mass spectrum *m/e* 352 (M^+), 240 (base peak).

Anal. Calcd for $C_{18}H_{13}ClN_4O_2$: C, 61.28; H, 3.71; N, 15.88. Found: C, 61.12; H, 3.50; N, 15.76.

B. From Compound 30. Compound **31** was also prepared by heating 0.1 g (0.27 mmol) of **30** at 205 °C for 10 min under nitrogen in an oil bath. The residue was crystallized from a mixture of dichloromethane and ether and recrystallized from methanol to give 30 mg (32%) of **31** as white prisms, mp and mmp with a sample prepared as in A 205–238 °C.

7-Chloro-2,3-dihydro-1′,3′-dimethylspiro-5-phenyl[1*H*-1,4-benzodiazepine-2,2′-imidazolidine]-4,5′-dione (32). A solution of 1.2 g (0.00355 mol) of **2** in 20 mL of dry tetrahydrofuran was treated with a saturated solution of methylamine in dry tetrahydrofuran cooled in an ice bath. After 2.5 h at room temperature the mixture was concentrated to a small volume and hexane was added. The precipitate was filtered and recrystallized from the same solvents to give 0.5 g (38%) of **32** as white rods, mp 340–342 °C: IR (KBr) 3390 (NH), 1750, 1720 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 6.96 (s, 1, NH), 4.02 (s, 2, CH_2), 2.80 (s, 6, 2 NCH_3); ^{13}C NMR (Me_2SO-d_6) δ 95.7 (s, 1, CN_3), 56.1 (t, 1, CH_2), 26.5 (q, 2, 2 NCH_3); UV λ_{max} (Me_2CHOH) 221 nm (ϵ 29 000), 234 (31 300), 332 (2610).

Anal. Calcd for $C_{19}H_{17}ClN_4O_2$: C, 61.87; H, 4.65; N, 15.19. Found: C, 62.03; H, 4.91; N, 15.02.

The mother liquors obtained from the above reaction were concentrated to dryness. The residue was crystallized from methanol, and recrystallized from a mixture of dichloromethane and petrol to give 0.2 g of **1** as white prisms, mp and mmp with an authentic sample 246–249 °C.

11-Chloro-1,5-6,7,7a,14-hexahydro-1-methyl-9-phenylimidazo[1,2-*b*][1,2]pyrazino[2,3-*b*][1,4]benzodiazepine-2,3-dione (33) and 8-Chloro-2,3,4,4a-tetrahydro-6-phenyl-1*H*-pyrazino[2,3-*b*][1,4]benzodiazepine (34). A suspension of 10 g (0.0269 mol) of **4** in 400 mL of dry benzene was treated with 4 g (0.0667 mol) of ethylenediamine and the reaction mixture was stirred at room temperature for 18 h. The solution was then warmed to 60 °C for 1 h and cooled in an ice bath and 100 mL of water was added. The solution was filtered, and the layers were separated. The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. The residue was dissolved in benzene and chromatographed through 600 g of Florisil using benzene (1.5 L), ether (1.5 L), ethyl acetate (2 L), and methanol (1 L) as the eluents. The ethyl acetate fraction was evaporated to give 1.5 g of oil which was crystallized and recrystallized from a mixture of dichloromethane and ether to give 0.8 g (7.5%) of **33** as white prisms, mp 290–292 °C: IR (KBr) 3300 (NH), 1750 cm^{-1} (C=O); NMR ($CDCl_3$) δ 4.86 (d, 1, CH), 2.93 (s, 3, CH_3), 2.00 (s, 1, NH); UV λ_{max} (Me_2CHOH) 241 nm (ϵ 32 000), 265 (14 800), 350 (2800); mass spectrum *m/e* 395 (M^+), 241.

Anal. Calcd for $C_{20}H_{18}ClN_5O_2$: C, 60.68; H, 4.58; N, 17.69. Found: C, 60.60; H, 4.60; N, 17.60.

The methanol fraction was evaporated to give 4 g of oil which was crystallized from a mixture of dichloromethane and ether and recrystallized from methanol to give 0.3 g (3.6%) of **34** as pale yellow rods, mp 194–198 °C dec: IR (KBr) 3250 (NH), 1620 cm^{-1} (C=N); NMR (Me_2SO-d_6) δ 4.04 (s, 1, CH), 2.80–3.65 (m, 6, CH_2CH_2 + 2 NH); UV λ_{max} (Me_2CHOH) 229 nm (ϵ 27 200), 273 (16 000) 347 (2500); mass spectrum *m/e* 310 (M^+).

Anal. Calcd for $C_{17}H_{15}ClN_4$: C, 65.70; H, 4.87; N, 18.03. Found: C, 65.32; H, 4.94; N, 17.81.

A solution of 0.1 g (0.271 mmol) of **33** in 40 mL of methanol and 2 mL of diethylamine was heated under reflux for 7 h. Solvents were evaporated, and the residue was dissolved in 25 mL of dichloromethane, which was washed with 15 mL of water, dried over sodium

sulfate, and evaporated to dryness. Crystallization from methanol gave 0.05 g (60%) of **34** as pale yellow rods, mp and mmp with a sample prepared as above 192–195 °C.

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Registry No.—**1**, 4393-72-0; **2**, 41963-51-3; **3**, 58-25-3; **4**, 62167-14-0; **5**, 62167-11-7; **6**, 5969-98-2; **7**, 62167-15-1; **9**, 62167-16-2; **10**, 4951-07-9; **11**, 62167-17-3; **14**, 62167-12-8; **15**, 62167-18-4; **16**, 5220-83-7; **17**, 62167-19-5; **21**, 62167-20-8; **22**, 4647-62-5; **23**, 3489-63-2; **24**, 62167-21-9; **25**, 62167-22-0; **28**, 62167-23-1; **29**, 62197-70-0; **30**, 62197-71-1; **31**, 62167-13-9; **32**, 62167-24-2; **33**, 62167-25-3; **34**, 62197-72-2.

Supplementary Material Available. Table of the positional and thermal parameters for **5**, **14**, and **31** (8 pages). Ordering information is given on any current masthead page.

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Synthesis and Acylation of Pyrrolinones

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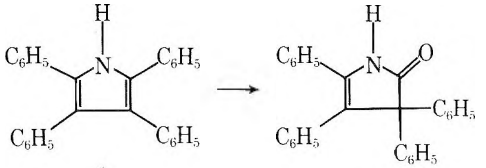
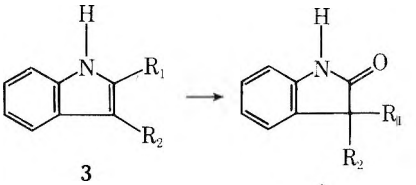
Ethyl 5-acetyl-2,4-dimethylpyrrole-3-carboxylate (**5a**) reacted with concentrated nitric acid to give pyrrolinone **6a** and nitropyrrole **7**. Several pyrroles related to **5a** were also oxidized to pyrrolinones. Diethyl 2-acetyl-3-methylsuccinate reacted with ammonia to give a mixture of ethyl 4,5-dihydro-2,4-dimethyl-5-oxo-1*H*-pyrrole-3-carboxylate (**13b**) and its Δ^3 isomer (**14b**). Acylation of **13b** and its *N*-methyl analogue **13a** with various reagents was studied. The reaction products were formulated as pyrrolinones or 5-acyloxypyrroles on the basis of spectral (^{1}H and ^{13}C NMR, UV, and IR) properties.

Wasserman and Liberles have described the oxidation of tetraphenylpyrrole (**1**) to pyrrolinone **2**;[1] related reactions



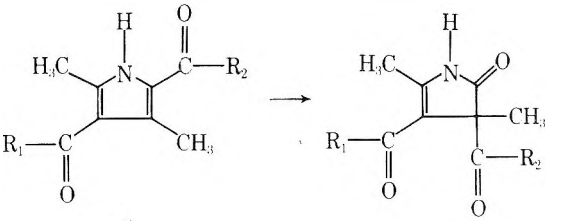
1 **2**



3 **4**

a, $R_1 = R_2 = C_6H_5$
b, $R_1 = COOC_2H_5$; $R_2 = CH_3$

leading to indolinones **4a** and **4b** have also been described.[2-4] In this paper we report additional examples of this oxidative rearrangement in which the migrating group is acetyl, carboalkoxy, or dialkylcarbamoyl. We have found that pyrroles **5a–i** react rapidly with concentrated nitric acid to give pyrrolinones **6a–i**. We have synthesized related 4,4-disubstituted pyrrolinones by acylation of **13a** and **13b** and also report iso-



5 **6**

a, $R_1 = OC_2H_5$; $R_2 = CH_3$
b, $R_1 = OCH_3$; $R_2 = CH_3$
c, $R_1 = CH_3$; $R_2 = OC_2H_5$
d, $R_1 = OCH_3$; $R_2 = OCH_3$
e, $R_1 = OCH_3$; $R_2 = OC_2H_5$
f, $R_1 = OC_2H_5$; $R_2 = OC_2H_5$
g, $R_1 = OCH_3$; $R_2 = N(CH_3)_2$
h, $R_1 = OCH_3$; $R_2 = N(CH_3)(C_2H_5)$
i, $R_1 = OCH_3$; $R_2 = N(C_2H_5)_2$

Table I. Substituted Pyrrolinones and 5-Hydroxypyrroles[a]

Compd	Registry no.	Mp or bp, °C (mm)	Yield, %	^{1}H chemical shifts ($CDCl_3$) 2-CH_3	4-CH_3	Ring H	λ_{max} (EtOH) (ϵ)	IR ($CHCl_3$), cm^{-1}
				Δ^2-Pyrrolinones[b]				
6a	62264-77-1	81–84	26[c]	2.48	1.55	9.35	282 (10 250)	1740, 1690, 1625
6b	62264-78-2	100–102	10[d]					
6c	62264-79-3	93.5–96.5	32[e]	2.47	1.60	9.25	224 (2650), 295 (12 400)	1740, 1710, 1610
6d	62319-73-7	146–147	13	2.45	1.61	9.00		
6e	62264-80-6	104–107	42					
6f	62264-81-7	126–128	45	2.43	1.61	9.10	283 (12 400)	1755, 1720, 1700, 1650
6g	62264-82-8	203–206	44	2.31[f]	1.38[f]	10.8[f]	281 (10 000)	1735, 1695, 1645
6h	62264-83-9	154–157	42	2.47	1.63	9.55	282 (10 450)	1725, 1690, 1635
6i	62264-84-0	184–188	80					
8	62264-85-1	162 (0.1)	32	2.90[g]	1.57	9.30		
13a	23657-69-4	115 (0.2)	74	2.42[h]	1.38[i]	3.0[j]	220 (4750), 289 (10 000)	1700, 1680, 1625
13b	4030-28-8	120–125	59	2.38[h]	1.40[i]	3.27,[j] 9.40	218 (4150), 281 (11 850)	1720, 1685, 1640
15a	62264-86-2	115 (0.1)	29[k]	2.47	1.30		284 (11 400)[l]	1710, 1680, 1625
15b	62264-87-3	96–101	35	2.51	1.65			1730, 1695, 1635
15c	62264-88-4	46–49	48[m]	2.54	1.51			1745, 1700, 1640
15d	62264-89-5	34–37	71[n]	2.53	1.56		285 (10 200)[l]	1740, 1710, 1685, 1630
17	4027-37-6	163–165	15	2.40	1.35	9.40	272 (10 900)[l]	1715, 1680, 1630
				Δ^3-Pyrrolinones				
14a	62264-90-8	95 (0.05)	20	1.50[i]	2.19[h]	4.20[j]	228 (12 300), 271 (2350)	1700, 1680
14b	62264-91-9	94–97	6	1.44[i]	2.21[h]	4.30,[j] 8.40	228 (13 500), 288 (1000)	1700
18	62264-92-0	130 (0.1)	26	1.54[i]	2.16[h]	4.75[j]	231 (14 450)	1785, 1730
				5-Hydroxypyrroles				
16c	62264-93-1	81–83	40	2.43	2.03			1765, 1700, 1525
16d	62264-94-2	54–56	61	2.44	2.06		226 (9000), 253 (4550)[l]	1750, 1680, 1525
16e	62264-95-3	125–127	18	2.46	2.07		227 (10 200), 256 (5000)[l]	1730, 1690, 1530
19a	62264-96-4	150 (0.1)	32	2.70	2.05		215 (16 650), 232 (8300), 260 (2150)[l]	1760, 1700, 1550
19b	62264-97-5	84–86	16	2.67	1.97		226 (20 300)[l]	1780, 1730, 1700, 1550
20	62264-98-6	115–118	9[o]	2.37	2.02		217 (13 700), 256 (7400)[l]	1750, 1680, 1530

[a] Satisfactory chemical analyses (± 0.3%) were obtained for all compounds and are presented in the supplementary material for this article. [b] The pyrrole intermediates used in the preparation of compounds **6a–i** and **8** had the following melting points (°C): **5a,** 142–143;[20] **5b,** 161–163; **5c,** 143–144;[20] **5d,** 175–176;[22] **5e,** 130–132;[21] **5f,** 127–130;[22] **5g,** 149–151;[23] **5h,** 115–119;[23] **5i,** 135–136;[23] intermediate for **8,** mp 117–119.[7] [c] Nitropyrrole **7** (36%) was also isolated in this reaction. [d] Methyl 2,4-dimethyl-5-nitropyrrole-3-carboxylate (31%, mp 183–186 °C) was also obtained in this reaction. [e] Ethyl 3,5-dimethyl-4-nitropyrrole-2-carboxylate (18%, mp 202–204 °C) was also obtained in this reaction. [f] Me_2SO-d_6 used as solvent. [g] Multiplet for 2-CH_2. [h] Doublet, J = 2 Hz. [i] Doublet, J = 7 Hz. [j] Multiplet. [k] Isolated yield from the methylation of **13b;** also obtained in 85% yield by methylation of **13a.** [l] UV spectra taken in hexane. [m] Prepared from **6a;** also obtained in 23% yield by acetylation of **13a.** [n] Prepared from **6e;** also obtained in 6% yield by reaction of **13a** with ethyl chloroformate. [o] Yield from **13b;** also obtained in 43% yield by heating **13b** with acetic anhydride.

lation of the hitherto unreported pyrrolinones **14a** and **14b,** the double bond isomers of **13a** and **13b.**

Fischer and Zerweck[5] have reported that nitropyrrole **7** was formed when **5a** was dissolved in concentrated nitric acid. In repeating this work we found that two products were formed in the reaction. Compound **7** precipitated when the reaction mixture was diluted with ice/water, while extraction of the diluted reaction solution with chloroform afforded the pyrrolinone **6a.**

Pyrrole ketones **5b** and **5c** also reacted rapidly with concentrated nitric acid to give mixtures of nitropyrrole and pyrrolinone, while pyrrole esters (**5d–f**) and amides (**5g–i**) gave pyrrolinones as the only isolated products (Table I).[6] Diethyl 3-methyl-5-propylpyrrole-2,4-dicarboxylate[7] was oxidized to **8** by concentrated nitric acid.

Pyrrolinone **6f** has already been prepared in low yield (19%) by chromium trioxide/acetic acid oxidation of Knorr's pyrrole (**5f**), but the product has been incorrectly formulated as **9** by

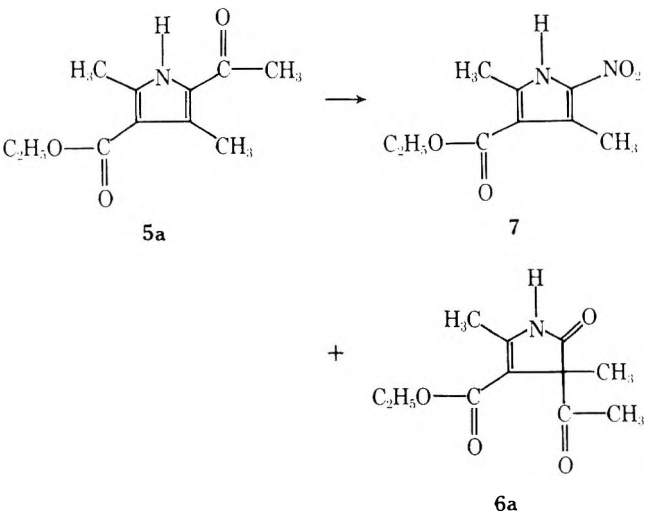
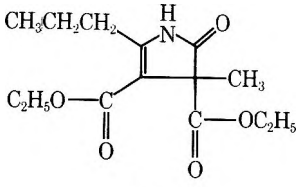


Table II. ^{13}C Chemical Shifts for Ring Carbon Atoms in Substituted Pyrrolinones

Compd	C-2	C-3	C-4	C-5
		Δ^2-Pyrrolinones		
6a	153.7	111.7	64.5	163.4
6c	152.7	122.5	57.6	168.9
6f	153.4	111.6	57.5	163.5
6g	153.0	110.1	56.4	163.2
6h	151.8	112.2	57.3	163.7
8	157.8	111.8	57.6	163.3
13a	153.6	109.3	41.8[a]	164.3
13b	151.7	110.2	43.1[a]	164.4
15a	152.5	113.8	45.9	164.3
15b	154.4	112.6	59.8	163.1
15c	155.5	110.8	63.3	163.3
15d	154.9	111.0	56.3	163.3
17	150.1	114.6	47.3	164.3
		Δ^3-Pyrrolinones		
14a	58.3[a]	141.6[b]	143.6[b]	163.2
14b	53.8[a]	143.4[b]	143.9[b]	163.4
18	56.6[a]	141.2[b]	144.3[b]	162.8

[a] Doublet in the off-resonance decoupled spectrum. [b] Assignments for C-3 and C-4 may have been inverted.

Fischer and Triebs,[8] and as **10** by Triebs and Grimm.[9] That compounds **6a–i** and **8** are pyrrolinones is supported by spectral and chemical data. All of the compounds show a signal



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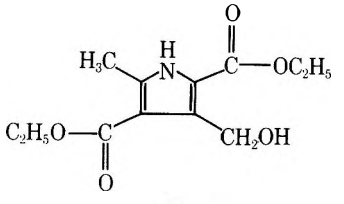

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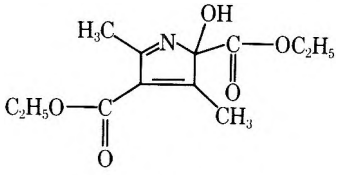

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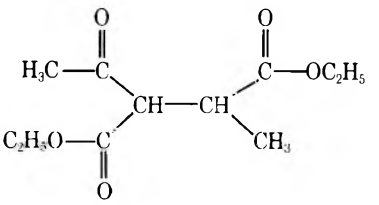
for the C-4 methyl group near δ 1.6 in the NMR spectrum (Table I); in the intermediate pyrroles the signal for this group is displaced downfield by about 0.9 ppm. Similar chemical shifts were found for the ring carbon atoms in these pyrrolinones (Table II).

The structure of **6a** was further indicated by its conversion, through N-methylation and hydrolytic removal of the acetyl group, to an isomeric mixture of **13a** and **14a.** This mixture of isomers was also prepared by allowing diethyl 2-acetyl-3-methylsuccinate (**11**) to react with methylamine to give **12a,**[10] which was then cyclized by heating at 190 °C. Only **13a,** the major isomer (75%) in this reaction, has been previously reported.[11–13] Two groups have described the related synthesis of **13b** from **11** and ammonia;[14,15] again, the isomeric pyrrolinone **14b** and intermediate **12b** were not isolated. We have found that cyclization of **12b** also gives a mixture of double bond isomers **13b** (85%) and **14b** (15%). Both isomer mixtures were readily separated into their components by chromatography on silica gel, and the isomers could be further purified by distillation (**13a** and **13b**) or by crystallization (**14a** and **14b**). While the compounds were stable to chromatography



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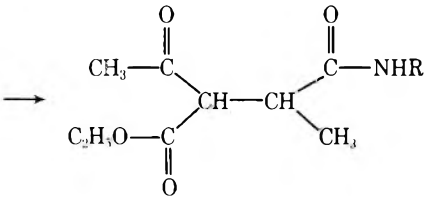

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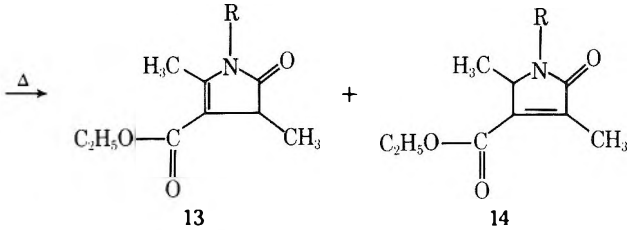


13 **14**

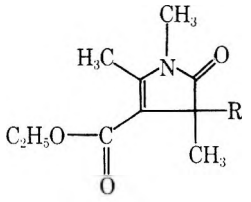
a, R = CH_3
b, R = H

and distillation, brief treatment of **13a** or **14a** with base regenerated the isomer mixture in which **13a** predominated. The greater stability of the Δ^2 isomer (**13a**) is consistent with the findings of Atkinson et al.[15] The structures for the isomers have been assigned from spectral information. Compounds **13a** and **13b** have ultraviolet maxima near 285 nm and show a signal for the C-4 ring hydrogen near δ 3.3 in the NMR spectrum.[13,15] The pyrrolinone ring ^{13}C resonances for these compounds (Table II) are similar to those found for **6a–i.** The signal for C-4 is shifted upfield (ca. 15 ppm) as expected, for this position no longer bears an exocyclic carbonyl function. The isomeric pyrrolinones **14a** and **14b** show a lower wavelength UV maximum (λ_{max} 228 nm) and an NMR signal for the C-2 ring hydrogen near δ 4.2.[13] The ^{13}C chemical shifts for the ring carbon atoms (Table II) are consistent with the proposed structures and readily allow the compounds to be distinguished from their Δ^2 isomers.

We have investigated the alkylation and acylation of **13a** and **13b** in an attempt to find alternate procedures for the synthesis of pyrrolinones of structure type **6.** Various structures, a result of C-, O-, or N- (**13b** only) acylation, can be proposed for the products formed in these reactions. Products of all the possible structure types have been isolated (Table I) and their structures have been assigned from spectral considerations. The acylation reactions occasionally gave a single product, but more often mixtures containing two major products were formed. To ensure that all products formed in significant amount in these reactions were identified, the crude product was analyzed by TLC and VPC, and the major components were identified after purification on silica gel.

The anion of **13a,** formed from **13a** and lithium diisopropylamide, reacted with methyl iodide and benzoyl chloride to give **15a** and **16a,** respectively. C- and O-acylation products were formed in the reaction of **13a** with acetyl chloride (**15c** and **16c,** 1:2 mixture) and ethyl chloroformate (**15d** and **16d,** 1:9 mixture); compounds **15c** and **15d** have also been prepared in high yield by reaction of pyrrolinones **6a** and **6f** with methyl iodide. Dimethylcarbamoyl chloride reacted with **13a** to give a low yield of the O-acylated product **16e.**

Mixtures of mono- and diacylated products were formed



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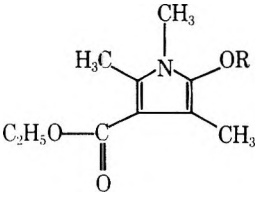
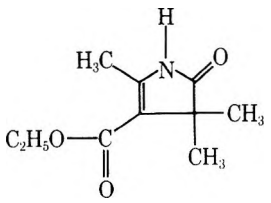


16

a, R = CH_3
b, R = COC_6H_5
c, R = $COCH_3$
d, R = $COOC_2H_5$
e, R = $CON(CH_3)_2$

when the anion of **13b**, formed from **13b** and sodium hydride, was treated with various reagents. In the reaction with methyl iodide **13a**, **17**, and **15a** were the major products, while with ethyl chloroformate **18** and **19a** were obtained. Acetyl chloride reacted with **13b** to give a mixture of **19b** and **20**; compound



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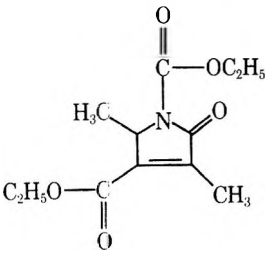

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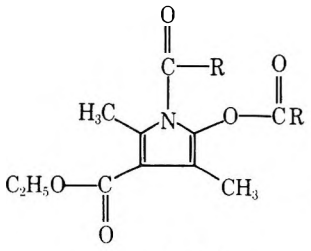
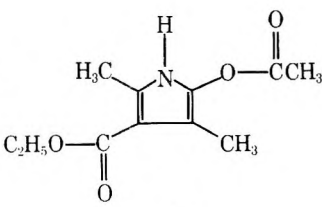


19a, R = OC_2H_5
b, R = CH_3



20

20 has also been prepared by refluxing **13b** in acetic anhydride.[16,17]

The ^{13}C NMR spectra for compounds **20**, **16c–e**, **19a**, and **19b** resemble those of other pyrroles,[18] and show four resonances between δ 105 and 135 for the ring carbon atoms. An IR band near 1550 cm^{-1} also is characteristic of the pyrrole structure and is not found for any of the pyrrolinones (Table I). The structures assigned to pyrrolinones **15a–d**, **17**, and **18** are in agreement with their spectral properties (Tables I and II).

Thus, 4,4-disubstituted pyrrolinones may be prepared by alkylation of **13a** and **13b** or by acylation of **13a**. The value of the acylation approach, however, is limited owing to formation of O-acylated products in several of the reactions. Acylation of **13b** did not afford 4,4-disubstituted pyrrolinones, but gave 5-acyloxypyrroles as the major reaction products.

Experimental Section[19]

General Procedure for Pyrrole Oxidation.[6] The pyrrole (**5**) was added with stirring to concentrated nitric acid (10 mL/g of pyrrole) at 10 °C. The reaction was kept at 10–20 °C until TLC (4:1 benzene/ethyl acetate) showed complete conversion of the pyrrole to the slower moving pyrrolinone; once the pyrrole had completely dissolved in the acid, reaction was usually complete in 5–15 min. The reaction mixture was diluted to four times its volume with ice/water, and any precipitate was removed by filtration and washed with water. The filtrate was extracted three or four times with chloroform, the combined chloroform layer was washed with water, and the chloroform was evaporated to give the pyrrolinone (**6**). This was purified by crystallization or by chromatography on silica gel followed by crystallization to constant melting point.

Oxidation of diethyl 3,5-dimethylpyrrole-2,4-dicarboxylate (5f)[21] gave diethyl 4,5-dihydro-2,4-dimethyl-5-oxo-1*H*-pyrrole-3,4-dicarboxylate (**6f**, 45%): mp 126–128 °C from ethyl acetate; NMR δ 1.22 (t, 3, CH_3), 1.28 (t, 3, CH_3), 1.61 (s, 3, CH_3), 2.43 (s, 3, CH_3), 4.17 (q, 2, OCH_2), 4.20 (q, 2, OCH_2) and 9.10 (s, 1, NH); ^{13}C NMR δ 13.4 (q), 14.1 (q), 14.3 (q), 19.2 (q), 57.5 (s), 60.0 (s), 61.8 (t), 111.6 (s), 153.4 (s), 163.5 (s), 168.6 (s), and 177.9 (s); IR 1755, 1720, 1700, and 1650 cm^{-1}; λ_{max} (EtOH) 283 nm (ϵ 12 400).

Anal. Calcd for $C_{12}H_{17}NO_5$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.14; H, 6.79; N, 5.60.

Ethyl 2-Acetyl-3-[(methylamino)carbonyl]butyrate (12a). Aqueous methylamine (10 mL of 40% solution) was added to a stirred solution of diethyl 2-acetyl-3-methylsuccinate (20 g, 0.088 mol) in ethanol (20 mL). After 20 h the solution was partitioned between chloroform and water, the chloroform was evaporated, and the residual oil was recrystallized from ethyl acetate/Skellysolve B to give 8.1 g (43%) of **12a**, mp 101–104 °C. The analytical sample was recrystallized from ethyl acetate: mp 104–107 °C; NMR δ 1.20 (d, 3, CH_3), 1.32 (t, 3, CH_3), 1.69 (s, 3, CH_3), 2.67 (d, 1, J = 10 Hz, CH), 3.08 (m, 1, CH), 4.26 (q, 2, OCH_2), and 4.59 (s, 1, NH); IR 1690 cm^{-1}.

Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 56.04; H, 8.27; N, 6.63.

The reaction was repeated using **11** (69 g), anhydrous methylamine (30 mL, liquid), and ether (50 mL) as solvent to give 40.8 g (63%) of **12a**.

Cyclization of 12a. Compound **12a** (40.0 g, 0.185 mol) was heated at 190 °C for 15 min and then cooled. The oil obtained was dissolved in benzene and chromatographed on silica gel. Elution of the column with benzene/ethyl acetate (4:1) gave 27.5 g (74%) of ethyl 4,5-dihydro-1,2,4-trimethyl-5-oxo-1*H*-pyrrole-3-carboxylate (**13a**). The analytical sample was distilled: bp 115–120 °C (0.2 mm); NMR δ 1.28 (t, 3, CH_3), 1.38 (d, 3, CH_3), 2.42 (d, 3, J = 2 Hz, CH_3), 3.0 (s, 3, CH_3), 3.0 (m, 1, CH), and 4.20 (q, 2, OCH_2); ^{13}C NMR δ 12.4 (q), 14.5 (q), 15.4 (q), 26.2 (q), 41.8 (d), 59.5 (t), 109.3 (s), 153.6 (s), 164.3 (s), and 179.8 (s); IR 1700, 1680, and 1625 cm^{-1}; λ_{max} (EtOH) 220 nm (ϵ 4750) and 289 (10 000).

Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67; N, 7.10. Found: C, 61.00; H, 7.79; N, 7.11.

Continued elution of the column gave 7.6 g (20%) of ethyl-2,5-dihydro-1,2,4-trimethyl-5-oxo-1*H*-pyrrole-3 carboxylate (**14a**). The analytical sample was distilled: bp 95 °C (0.05 mm); NMR δ 1.37 (t, 3, CH_3), 1.50 (d, 3, CH_3), 2.19 (d, 3, J = 2 Hz, CH_3), 3.02 (s, 3, CH_3), 4.20 (m, 1, CH), and 4.32 (q, 2, OCH_2); ^{13}C NMR δ 11.1 (q), 14.3 (q), 16.7 (q), 26.9 (q), 58.3 (d), 60.8 (t), 141.6 (s), 143.6 (s), 163.2 (s), and 169.5 (s); IR 1700 and 1680 cm^{-1}; λ_{max} (EtOH) 228 nm (ϵ 12 300) and 271 (2350).

Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67; N, 7.10. Found: C, 61.02; H, 7.94; N, 7.27.

Ethyl 2-Acetyl-3-(aminocarbonyl)butyrate (12b). Liquid ammonia (30 mL) was added to a stirred solution of diethyl 2-acetyl-3-methylsuccinate (69 g, 0.3 mol) in ether (200 mL). After 6 h the precipitate of **12b** (39.5 g, mp 92–98 °C) was filtered off and washed with ether. The analytical sample was recrystallized from ethyl acetate: mp 99–106 °C; NMR δ 1.18 (d, 3, CH_3), 1.32 (t, 3, CH_3), 1.68 (s, 3, CH_3), 2.75 (d, 2, J = 10 Hz, CH), 3.06 (m, 1, CH), 4.22 (q, 2, OCH_2), 4.92 (s, 1, NH), and 7.62 (s, 1, NH); IR 1715 cm^{-1}.

Anal. Calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 54.01; H, 7.74; N, 6.93.

Cyclization of 12b. Compound **12b** (128 g, 0.64 mol) was heated at 190 °C for 15 min. The solid obtained on cooling was recrystallized from ethanol (100 mL) to give 75 g (59%) of ethyl 4,5-dihydro-2,4-dimethyl-5-oxo-1*H*-pyrrole-3-carboxylate (**13b**), mp 120–125 °C. A sample was recrystallized twice from ethyl acetate for analysis: mp 125–128 °C; NMR δ 1.30 (t, 3, CH_3), 1.40 (d, 3, CH_3), 2.38 (d, 3, J = 2 Hz, CH_3), 3.27 (m, 1, CH), 4.22 (q, 2, OCH_2), and 9.4 (s, 1, NH); ^{13}C NMR δ 13.6 (q), 14.5 (q), 15.2 (q), 43.1 (d), 59.7 (t), 110.2 (s), 151.7 (s), 164.4 (s), and 182.8 (s); IR 1725, 1685, and 1640 cm^{-1}; λ_{max} (EtOH) 218 nm (ϵ 4150) and 281 (11 850).

Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.13; H, 7.16; N, 7.50.

Evaporation of the ethanol mother liquors gave 35 g of a mixture of **13b** and **14b**. This was dissolved in ethyl acetate and chromatographed on silica gel. Elution of the column with ethyl acetate gave additional **13b** (12.2 g) followed by ethyl 2,5-dihydro-2,4-dimethyl-5-oxo-1*H*-pyrrole-3-carboxylate (7.2 g, 6%). The product was recrystallized from ethyl acetate/Skellysolve B to give 5.1 g of **14b**, mp 90–94 °C. The analytical sample was recrystallized twice from ethyl

acetate: mp 94–97 °C; NMR δ 1.37 (t, 3, CH_3), 1.44 (d, 3, CH_3), 2.21 (d, 3, J = 2 Hz, CH_3), 4.37 (q, 2, OCH_2), 4.3 (m, 1, CH), and 8.40 (s, 1, NH); ^{13}C NMR 10.8 (q), 14.3 (q), 18.8 (q), 53.8 (d), 60.9 (t), 143.4 (s), 143.9 (s), 163.4 (s), and 172.9 (s); IR 1700 cm^{-1}; λ_{max} (EtOH) 228 nm (ε 13 500) and 288 (1000).

Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.28; H, 7.24; N, 8.07.

Equilibration of 13a and 14a. The purified compound (**13a** or **14a**, 1.0 g) was dissolved in ethanol (10 mL) containing sodium methoxide (10 mg). After 5 min the product was partitioned between benzene (200 mL) and water (50 mL). Evaporation of the benzene layer gave 0.95 g of product, which by TLC and NMR analysis was a mixture of **13a** (75%) and **14a** (25%).

General Procedure for Acylation of Pyrrolinones Using Sodium Hydride. Sodium hydride (1.3 g, 0.027 mol, 50% in oil) was added to a stirred solution of the pyrrolinone (0.025 mol) in tetrahydrofuran (50 mL) at 25 °C. After 5 min the acylating reagent (0.03 mol) was added and the reaction mixture was stirred for 30 min. The product was partitioned between benzene and water. Evaporation of the benzene gave an oil which was analyzed by TLC and VPC,[19] and purified by column chromatography on silica gel (initial eluent 9:1 benzene/ethyl acetate). The purified compound was then distilled or recrystallized to constant melting point.

Ethyl 4-acetyl-4,5-dihydro-1,2,4-trimethyl-5-oxo-1*H*-pyrrole-3-carboxylate (15c) was prepared from **6a** and methyl iodide; VPC of the crude product showed 88% conversion to **15c**, retention time 7.1 min.[19] Recrystallization from Skellysolve B gave 48% of **15c**: mp 46–49 °C; NMR δ 1.25 (t, 3, CH_3), 1.51 (s, 3, CH_3), 2.00 (s, 3, CH_3), 2.54 (s, 3, CH_3), 3.14 (s, 3, NCH_3), and 4.18 (q, 2, OCH_2); IR 1745, 1700, and 1640 cm^{-1}.

Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.52; N, 7.40; N, 5.73.

Hydrolysis of 15c. Compound **15c** (250 mg) and sodium methoxide (10 mg) were dissolved in ethanol (5 mL). After 5 min acetic acid (15 mg) in ethanol (1 mL) was added and the product was partitioned between benzene and water. Evaporation of the benzene gave an oil (190 mg), identified as a mixture of **13a** and **14a** by TLC, NMR, VPC, and IR analysis.

General Procedure for Acylation of 13a Using Lithium Diisopropylamide. Compound **13a** (0.025 mol) in tetrahydrofuran (25 mL) was added to a stirred solution of lithium diisopropylamide (0.03 mol) in hexane/tetrahydrofuran (1:4, 100 mL) at −40 °C. The resulting slurry was allowed to warm to room temperature, the acylating reagent (0.05 mol) was added, and the solution was stirred for a further 30 min. Workup, analysis, and purification were carried out as described above for acylation reactions using sodium hydride as base.

Registry No.—**5a,** 6314-22-3; **5b,** 62264-99-7; **5c,** 2386-26-7; **5d,** 5448-17-9; **5e,** 21898-57-7; **5f,** 2436-79-5; **5g,** 40593-29-1; **5h,** 40593-32-6; **5i,** 40593-54-2; **7,** 23314-05-8; **11,** 1113-77-5; **12a,** 62265-00-3; **12b,** 62265-01-4; ethyl 3,5-dimethyl-4-nitropyrrole-2-carboxylate, 5463-44-5; diethyl 3-methyl-5-propylpyrrole-2,4-dicarboxylate, 27093-52-3; 4,5-dihydro-2,4-dimethyl-5-oxo-1*H*-pyrrole-1,3,4-tricarboxylate triethyl ester, 62265-02-5; methyl iodide, 74-88-4; ethyl chloroformate, 541-41-3; acetic anhydride, 108-24-7; benzoyl chloride, 98-88-4; acetyl chloride, 75-36-5; dimethylcarbamoyl chloride, 79-44-7; methyl 2,4-dimethyl-5-nitropyrrole-3-carboxylate, 62265-03-6.

Supplementary Material Available. Information on the preparation and purification of the remainder of the compounds described in the paper and their elemental analyses and full spectral information (8 pages). Ordering information is given on any current masthead page.

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Photochemical Conversion of β,β,β-Trichloroethyl 6-Diazopenicillanate into 6β-Thiolpenicillin Derivatives

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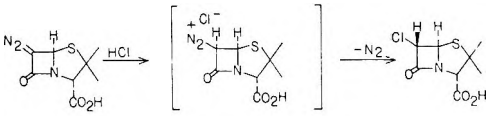
Irradiation of a mixture of β,β,β-trichloroethyl 6-diazopenicillanate (**3**) with either thiol acids or mercaptans leads predominantly to β-thiolpenicillanates in which the side chain nitrogen in the natural penicillins has been replaced with a sulfur atom. Evidence is presented for the formation of an azo intermediate which photochemically looses nitrogen giving rise to the aforementioned thiol derivatives. Sulfoxidation and thermal rearrangement afford deacetoxythiolcephalosporanates in good yield. In the case of the phenoxyacetyl or chloroacetyl derivatives **10** and **16** or **31** and **32**, the side chain can be cleaved under basic conditions giving the mercaptans **21** and **33** which were acylated by standard procedures.

The use of esters of 6-diazopenicillanic acid as a source of new antibacterial agents has recently been described;[1] however, the potential for these readily available, highly reactive intermediates has not been fully realized. As part of a general program to further investigate the properties of these esters, the irradiation of a mixture of β,β,β-trichloroethyl 6-diazopenicillanate (**3**) and either mercaptans or thiol acids was undertaken. We wish to report here the stereoselective conversion of **3** to analogues of penicillins and cephalosporins in which the side chain nitrogen has been replaced by a sulfur atom. We would also like to demonstrate their use as potential antibiotics.

Results and Discussion

The effect of the thiazolidine ring in penicillins in directing attack to the α face of the β-lactam ring is illustrated by the reaction of the diazo acid **1** with HCl.[2] Protonation takes place

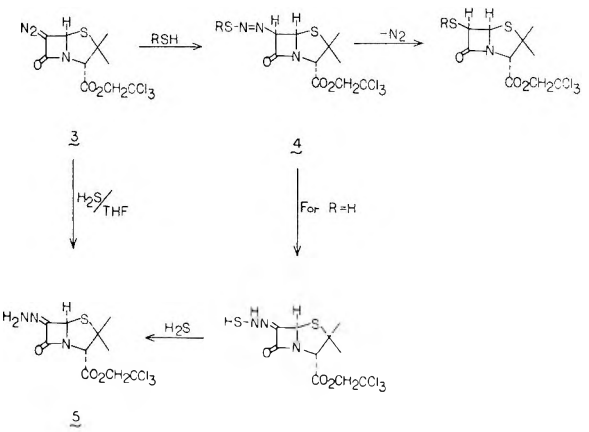


predominantly from the α face to give an intermediate in which the hydrogens at C-5 and C-6 of the β-lactam ring are cis (for numbering see figure **19**, Scheme II). Nucleophilic attack by the chloride ion, again from the α face, gives the product in which the hydrogens at C-5 and C-6 are now trans.

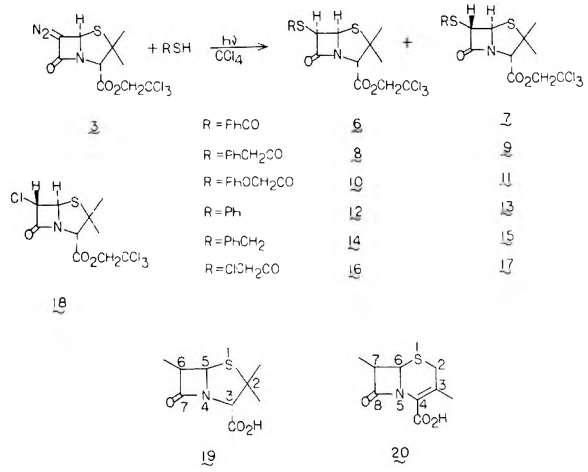
This directive effect can be an advantage. In the reaction of a mercaptan or thiol acid with a diazo ester such as **3**, if the sulfur attacks the nitrogen of the diazo moiety,[3] an azo intermediate will be formed in which the β-lactam hydrogens are cis. Loss of nitrogen with retention of configuration at C-6 will lead to a product with the desired cis stereochemistry[4] (Scheme I). Evidence suggesting that the sulfur will react at the nitrogen was observed in the reduction of **3** with hydrogen sulfide. Treatment of a THF solution of the diazo ester **3** with H_2S gave 66% yield of the hydrazone **5**. A possible mechanism is outlined in Scheme I.

A mixture of β,β,β-trichloroethyl 6-diazopenicillanate (**3**) and an excess of either thiobenzoic acid, phenylthiolacetic acid, or phenoxythiolacetic acid was irradiated in carbon tetrachloride with a medium-pressure Hanovia light source (Pyrex filter). Removal of the excess thiol acid with aqueous sodium bicarbonate and chromatography of the crude mixture on silicic acid gave the cis thiol esters **6**, **8**, and **10**, in 45–51% yield. In addition small quantities of the corresponding trans isomers **7**, **9**, and **11** were also isolated (Scheme II).

Scheme I



Scheme II



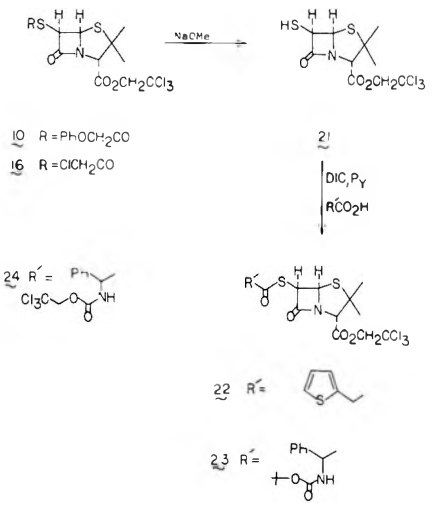
Irradiations were carried out below 20 °C. Above this temperature, there was significant to complete destruction of the acid-sensitive β-lactam ring. This lower temperature also diminishes the thermal reaction between **3** and the thiol acids leading to the undesired trans thiol esters (vide infra).

Structural assignments of the thiol esters are in complete agreement with the spectroscopic data (see Experimental Section). The stereochemistry at C-6 was assigned on the basis of the coupling between the C-5 and C-6 protons of the β-lactam ring.[5] The cis thiol esters had coupling constants of 4 Hz whereas the trans isomers had coupling constants of 2 Hz.

A mixture of **3** and thiophenol was irradiated. Chromatography on silicic acid gave the sulfides **12** and **13** as a mixture from which the cis sulfide **12** crystallized. Continuous crystallization of the mother liquors gave **12** in 56% yield. NMR analysis of the residual oil showed it to be the pure trans sulfide **13** (23%). In the same manner irradiation of a mixture of **3** and benzyl mercaptan gave, after extensive chromatography on silicic acid, the cis and trans sulfides **14** and **15** in 28 and 7% yields, respectively (Scheme II).

Attempts to prepare either **22** or **24** (Scheme III) by the

Scheme III



method just described were unsuccessful. Apparently irradiation of a mixture of **3** and a thiol acid which contains an additional functional group (and is therefore competitive in its nucleophilic character with the sulfur of the thiol acid) interferes with the reaction. A number of effective β-lactam antibiotics in the natural series (nitrogen analogues) contain such side chains so it was necessary to find a general route to these compounds.

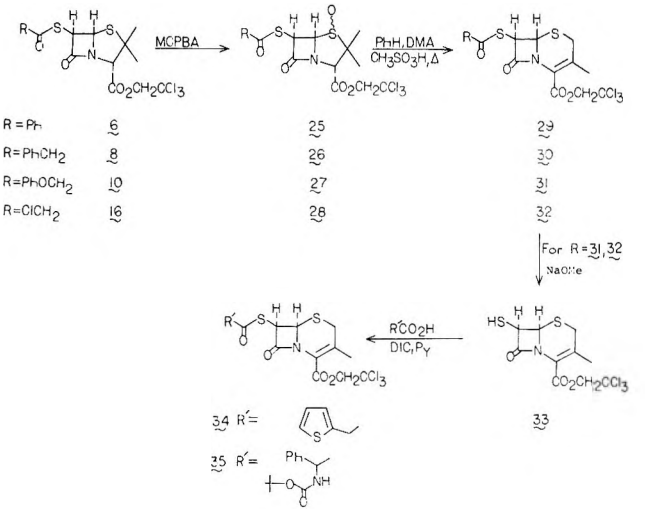
The most obvious method of preparing either **22** or **24** is by acylation of the mercaptan **21.** In general, the hydrolysis of a thiol ester under basic conditions would be expected to proceed smoothly. However, owing to the sensitivity of the β-lactam ring toward nucleophilic cleavage, it was anticipated that a thiol ester activated in the α position with an electron-withdrawing group might be required. An attempt to remove the phenylacetyl side chain from **8** by methanolysis at low temperature showed this to be the case. An NMR of the crude reaction mixture showed a complex mixture of components. However, with the phenoxy derivative **10,** which is activated relative to **8,** the reaction proceeded smoothly to give a mixture of the mercaptan **21** and methyl phenoxyacetate; the latter by-product had to be removed by chromatography (Scheme III). An activated thiol ester whose methyl ester could be removed under standard workup procedures was thus desired. For this reason, the chloroacetyl derivative **16** was prepared (Scheme II).

Irradiation of a mixture of **3** and chlorothiolacetic acid gave the thiol esters **16** and **17** in 49 and 4% yields, respectively. In addition, the trans chloride **18** was isolated in 9% yield as a crystalline material (Scheme II). This product arises from the reaction of **3** with HCl, a contaminant in chlorothiolacetic acid.[6]

Methanolysis of **16** gave the mercaptan **21** as a clear oil in 80% yield.[7] Acylation with D-α-*tert*-butoxycarboxamidophenylacetic acid[8] and thiophene-2-acetic acid in methylene chloride containing 1 equiv of *N,N'*-diisopropylcarbodiimide and pyridine gave, after column chromatography, the thiol esters **22** and **23** in 82 and 89% yields, respectively (Scheme III).

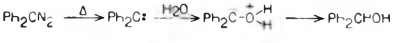
Oxidation of the cis thiol esters with *m*-chloroperbenzoic acid gave a mixture of sulfoxides[9] in high yield (Scheme IV).

Scheme IV



In the case of **25** and **26** the less polar sulfoxide (by TLC) crystallized from the crude mixture. Rearrangement of either the pure sulfoxide or the crude reaction mixture by the method originally described by Morin and co-workers[10] gave the deacetoxythiolcephalosporanates **29–32** in 40–90% yields. Methanolysis of either **31** or **32** gave the mercaptan **33** in 80% yield. Acylation as previously described for **22** and **23** gave the thiol esters **34** and **35** in 82% yield (Scheme IV).

The photochemical and thermal decomposition of diazo compounds has been studied extensively.[11] Bethell and coworkers[12] have shown that in the thermal decomposition of diphenyldiazomethane in aqueous acetonitrile an intermediate carbene reacts with the oxygen of water, giving an ylide which subsequently rearranges to diphenylmethanol. Inser-



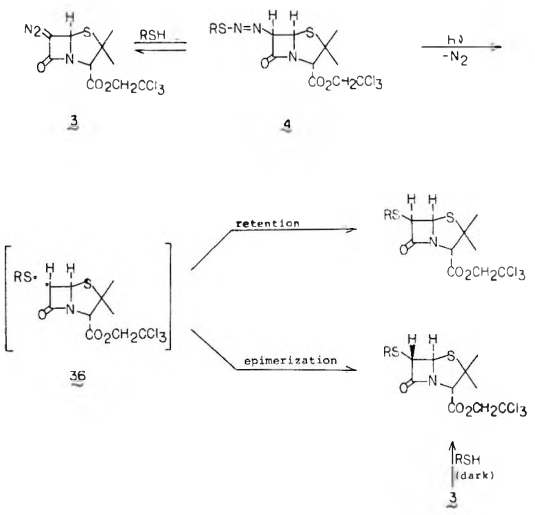
tion into an S–H bond has been reported[13] in the photolysis of bis(phenylsulfonyl)diazomethane in the presence of *n*-butyl mercaptan. Such a carbene "insertion" reaction, although possible, was considered unlikely in the case of **3.**

Light-induced formation of a carbene in **3** in the presence of either a mercaptan or thiol acid would lead to the corresponding sulfides and thiol esters. However, if a sulfonium ylide was formed it was believed that an intramolecular proton transfer,[14] giving rise to the thermodynamically more stable trans isomer, would be favored over an intermolecular proton transfer from the α face of the β-lactam ring which would give the cis isomer.

Further evidence against the formation of a carbene was observed in the irradiation of a carbon tetrachloride solution of **3** under an atmosphere of helium in the absence of any nucleophile. If a carbene were formed, such conditions should give rise to products which no longer contain the diazo group. After irradiation, NMR analysis of the crude reaction showed **3** as the only identifiable material.

There is evidence supporting the mechanism outlined in Scheme V. The cis stereochemistry of the β-lactam hydrogens is consistent with attack of the sulfur on the nitrogen with protonation at C-6 occurring from the α face of the β-lactam to give the cis azo ester **4.** Photochemical elimination of nitrogen with retention of configuration at C-6 will give the cis isomer.[15] The trans isomer can result from epimerization prior to combination of the diradical **36** or related species, (Scheme

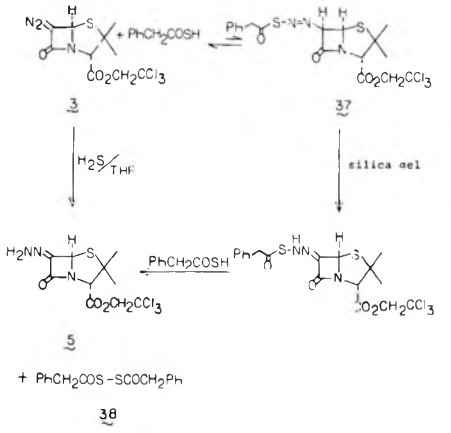
Scheme V



V) or from a thermal reaction between 3 and the thiol acid or mercaptan. In control experiments (no light) small amounts of the trans isomers were detected in an NMR of the crude reaction mixture.

Although isolation of an azo ester was not possible, its existence has been demonstrated. A TLC taken immediately after mixing **3** and phenylthiolacetic acid[16] in carbon tetrachloride showed two new components in addition to **3** and the thiol acid. One component, which is less polar than **3**, was identical with diphenylacetyl disulfide **38** (Scheme VI) isolated as a crystalline material in a large-scale photolysis. The other component, more polar than **3**, was identical with the hydrazone **5**, previously prepared by the reduction of **3** with hydrogen sulfide (vide supra). After removal of the thiol acid from the aforementioned solution of **3** and phenylthiolacetic acid with aqueous sodium bicarbonate, conditions which were shown not to destroy either the disulfide or the hydrazone, a TLC showed only one spot corresponding to the diazo ester **3** and no detectable amounts of either the disulfide or the hydrazone.

Scheme VI



An explanation for the above observation is outlined in Scheme VI. An equilibrium exists between the diazo and azo esters which react on the surface of the silica gel (TLC sheets) giving the hydrazone **5** and the disulfide **38**. Removal of the thiol acid with base destroys the equilibrium leaving only the diazo ester **3**. It was not possible to observe **37** by either NMR or UV, showing that the equilibrium is largely in favor of **3**.

Benzoyl disulfide, diphenylacetyl disulfide, and diphenoxyacetyl disulfide were isolated in large-scale photolyses of **3** and the corresponding thiol acids. The formation of these disulfides is not entirely clear.[17] Reduction of **3** is catalyzed by silica gel (vide supra). During the photolyses (10–20 h) reduction may still occur but at a slower rate, giving the disulfides and the hydrazone **5**, the latter of which has been shown to be very sensitive to the conditions of the reaction and is presumably destroyed.

After removal of the protective group(s) (see Experimental Section) the free acids were tested in vitro for bioactivity. Minimum inhibitory concentrations (MIC) values in μg/mL for **6**, **8**, and **10** against *Bacillus subtilis* ATCC 6051 were 50, <0.4 and <0.4, respectively; **31** against *Staphylococcus aerus* A 100, *Staphylococcus pyogenes* Pen R, and *Aerobacter aerogenes* (50); **29** against *Staphylococcus aerus* A 100, *Staphylococcus pyogenes* Pen R, *Streptococcus fecalis*, and *Proteus mirabilis* (50) and against *Bacillus subtilis* ATCC 6051 (25).

Experimental Section

Melting points and boiling points are uncorrected; melting points were determined on a Fisher-Johns melting point apparatus. Nuclear magnetic resonance (NMR) spectra were recorded with a Varian Associates T-60 spectrophotometer and are reported in parts per million (δ) relative to tetramethylsilane as an internal standard. Infrared spectra (IR) were recorded on a Perkin-Elmer 237 spectrophotometer. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Routine thin layer chromatographies were run on Baker-flex silica gel 1B-F TLC sheets. For analytical TLC work solutions were applied with Drummond "microcaps" disposable micropipets. Preparative thick layer chromatographies were performed on EM Reagents precoated silica gel 60 F-254 (2-mm thickness). Column chromatography was performed with Mallinckrodt silicic acid (100 mesh). Irradiations were carried out in Pyrex flasks in an enclosed 28 × 38 × 87 cm wood box with the Hanovia 450-W medium-pressure lamp suspended horizontally above the flask. Solutions were flushed for 30 min with a slow stream of helium which was continued throughout the irradiations.

β,β,β-Trichloroethyl 6-diazopenicillanate (3) was prepared by the method of Sheehan and co-workers.[18]

Phenylthiolacetic acid, phenoxythiolacetic acid, and thiophene-2-thiolacetic acid were prepared by the method of Sjöberg.[19]

Chlorothiolacetic acid was prepared by the method of Arndt and Bekir.[6]

Thiophene-2-acetic acid was obtained from Research Organic/Inorganic Chemical Corp., Belleville, N.J.

Thiophene-2-acetyl chloride was prepared according to the literature.[20]

D-α-β,β,β-Trichloroethyloxycarboxamidophenylacetic acid[8] and D-α-*tert*-butoxycarboxamidophenylacetic acid[21] were prepared according to the literature.

Photolysis of β,β,β-Trichloroethyl 6-Diazopenicillanate (3) with Thiobenzoic Acid. A solution of 2.00 g (5.58 mmol) of **3** and 3.48 g (27.8 mmol) of thiobenzoic acid in 150 mL of carbon tetrachloride was irradiated with a Hanovia 450-W medium-pressure lamp (Pyrex filter) under an atmosphere of helium at 18 °C for 8 h. The solution was washed with 5% aqueous $NaHCO_3$ and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residual oil was submitted to column chromatography on silicic acid using methylene chloride as an eluent. Isolation of the fastest moving fraction gave benzoyl disulfide (163.8 mg) as a white, crystalline material. Trituration with ether gave the pure disulfide: mp 130.0–132.0 °C (lit.[22] mp 129–130 °C); NMR ($CDCl_3$) δ 7.0–8.2 (m, 10 H).

Isolation of a slower moving fraction gave the trans thiol ester **7** in 4% yield as a light brown oil. Upon standing the oil crystallized. Recrystallization from ether–petroleum ether gave an analytical sample: mp 69.0–72.0 °C; IR ($CHCl_3$) 1780 and 1675 cm^{-1}; NMR ($CDCl_3$ δ 1.65 (s, 3 H), 1.82 (s, 3 H), 4.65 (s, 1 H), 4.75 (s, 2 H), 5.02 (d, 1 H, J = 2.0 Hz), 5.20 (d, 1 H, J = 2.0 Hz), 7.0–8.0 (m, 5 H).

Anal. Calcd for $C_{17}H_{16}NO_4Cl_3S_2$: C, 43.56; H, 3.44; N, 2.99; Cl, 22.69; S, 13.68. Found: C, 43.80; H, 3.45; N, 2.93; Cl, 22.61; S, 13.40.

Isolation of the slowest moving fraction furnished a light brown oil in 51% yield which crystallized on standing. Recrystallization from ether gave the analytically pure cis thiol ester **6** as a white, crystalline material: mp 103.5–104.0 °C; IR ($CHCl_3$) 3010, 2960, 1780, and 1675 cm^{-1}; NMR ($CDCl_3$) δ 1.58 (s, 3 H), 1.73 (s, 3 H), 4.53 (s, 1 H), 4.68 (s, 2 H), 5.47 (d, 1 H, J = 4.0 Hz), 5.60 (d, 1 H, J = 4.0 Hz), 7.0–8.0 (m, 5 H).

Anal. Calcd for $C_{17}H_{16}NO_4Cl_3S_2$: C, 43.56; H, 3.44; N, 2.99; Cl, 22.69; S, 13.68. Found: C, 43.20; H, 3.81; N, 2.84; Cl, 22.46; S, 13.66.

Photolysis of β,β,β-Trichloroethyl 6-Diazopenicillanate (3) with Phenylthiolacetic Acid. In the same manner as described above diphenylacetyl disulfide (115 mg) was isolated as a crystalline material. Recrystallization from ether–petroleum ether gave the pure disulfide: mp 61.0–62.0 °C (lit.[23] mp 62 °C); IR ($CHCl_3$) 1710 cm^{-1}; NMR ($CDCl_3$) δ 3.90 (s, 4 H), 7.10 (s, 10 H).

Isolation of a slower moving fraction gave the trans thiol ester **9** in 3% yield as a light brown oil: IR ($CHCl_3$) 1780 and 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.60 (s, 3 H), 1.73 (s, 3 H), 3.83 (s, 2 H), 4.58 (s, 1 H), 4.70 (s, 2 H), 4.80 (d, 1 H, J = 2.0 Hz), 5.05 (d, 1 H, J = 2.0 Hz), 7.13 (s, 5 H).

Isolation of the slowest moving fraction furnished a light brown oil in 50% yield which crystallized on standing. Recrystallization from ether–petroleum ether gave the analytically pure cis thiol ester **8** as a white, crystalline solid: mp 83.0–84.0 °C; IR ($CHCl_3$) 3005, 2955, 1770, and 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.60 (s, 3 H), 1.70 (s, 3 H), 3.83 (s, 2 H), 4.53 (s, 1 H), 4.73 (s, 2 H), 5.33 (d, 1 H, J = 4.0 Hz), 5.55 (d, 1 H, J = 4.0 Hz), 7.18 (s, 5 H).

Anal. Calcd for $C_{18}H_{18}NO_4Cl_3S_2$: C, 44.78; H, 3.76; N, 2.90; Cl, 22.03; S, 13.28. Found: C, 44.70; H, 3.60; N, 2.86; Cl, 22.10; S, 13.59.

Photolysis of β,β,β-Trichloroethyl 6-Diazopenicillanate (3) with Phenoxythiolacetic Acid. In the same manner as described above diphenoxyacetal disulfide (58 mg) was isolated as a crystalline material. Recrystallization from methylene chloride–petroleum ether gave the analytically pure disulfide: mp 105.5–107.0 °C; IR ($CHCl_3$) 3010 and 1725 cm^{-1}; NMR ($CDCl_3$) δ 4.83 (s, 4 H), 6.7–7.7 (m, 10 H).

Anal. Calcd for $C_{16}H_{14}O_4S_2$: C, 57.47; H, 4.22; S, 19.18. Found: C, 57.36; H, 4.22; S, 19.23.

Isolation of a slower moving fraction furnished a light brown oil in 5% yield which crystallized on standing. Recrystallization from methylene chloride–ether–petroleum ether gave the analytically pure trans thiol ester **11**: mp 90.0–91.0 °C; IR ($CHCl_3$) 1775 and 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.63 (s, 3 H), 1.77 (s, 3 H), 4.63 (s, 1 H), 4.70 (s, 2 H), 4.73 (s, 2 H), 4.87 (d, 1 H, J = 2.0 Hz), 5.12 (d, 1 H, J = 2.0 Hz), 6.7–7.7 (m, 5 H).

Anal. Calcd for $C_{18}H_{18}NO_5Cl_3S_2$: C, 43.34; H, 3.64; N, 2.81; Cl, 21.32; S, 12.86. Found: C, 43.31; H, 3.70; N, 2.83; Cl, 21.47; S, 12.83.

Isolation of the slowest moving fraction furnished the cis thiol ester **10** in 45% yield as a light brown oil: IR ($CHCl_3$) 1775 and 1695 cm^{-1}; NMR ($CDCl_3$) δ 1.60 (s, 3 H), 1.67 (s, 3 H), 4.60 (s, 1 H), 4.73 (s, 2 H), 4.80 (s, 2 H), 5.43 (d, 1 H, J = 4.0 Hz), 5.70 (d, 1 H, J = 4.0 Hz), 6.8–7.6 (m, 5 H).

Anal. Calcd for $C_{18}H_{18}NO_5Cl_3S_2$: C, 43.34; H, 3.64; N, 2.81; Cl, 21.32; S, 12.86. Found: C, 43.04; H, 3.68; N, 2.90; Cl, 21.60; S, 13.12.

Photolysis of β,β,β-Trichloroethyl 6-Diazopenicillanate (3) with Thiophenol. A solution of 1.00 g (2.79 mmol) of **3** in 65 mL of CCl_4 was cooled to 8–10 °C before 1.4 mL (13.7 mmol) of thiophenol in 10 mL of CCl_4 was added dropwise over 5 min. The solution was irradiated with a Hanovia 450-W medium-pressure lamp (Pyrex filter) under an atmosphere of helium at ~10 °C for 20 h. The solvent was removed under reduced pressure and the residue chromatographed on silicic acid using mixtures of methylene chloride–carbon tetrachloride as an eluent. After removal of the excess thiophenol the cis and trans sulfides **12** and **13** were isolated as a mixture from which the cis sulfide crystallized. Continuous crystallization of the mother liquors from methylene chloride–ether gave 56% yield of the cis sulfide **12** and 23% yield of an oil which was shown by NMR analysis to be the pure trans sulfide **13**.

Recrystallization of **12** from methylene chloride–ether gave an analytically pure sample: mp 122.0–123.0 °C; IR ($CHCl_3$) 1780 cm^{-1}; NMR ($CDCl_3$) δ 1.63 (s, 3 H), 1.73 (s, 3 H), 4.60 (s, 1 H), 4.73 (s, 2 H), 4.77 (d, 1 H, J = 4.0 Hz), 5.57 (d, 1 H, J = 4.0 Hz), 7.0–7.7 (m, 5 H).

Anal. Calcd for $C_{16}H_{16}NO_3Cl_3S_2$: C, 43.60; H, 3.66; N, 3.18; Cl, 24.13; S, 14.55. Found: C, 43.53; H, 3.88; N, 3.20; Cl, 24.30; S, 14.46.

Trans Sulfide 13: IR ($CHCl_3$) 1775 and 1765 cm^{-1}; NMR ($CDCl_3$) δ 1.63 (s, 3 H), 1.78 (s, 3 H), 4.53 (d, 1 H, J = 2.0 Hz), 4.70 (s, 1 H), 4.80 (s, 2 H), 5.28 (d, 1 H, J = 2.0 Hz), 7.2–7.7 (m, 5 H).

Photolysis of β,β,β-Trichloroethyl 6-Diazopenicillanate (3) with Benzyl Mercaptan. A solution of 2.00 g (5.58 mmol) of **3** and 3.25 mL (27.6 mmol) of benzyl mercaptan in 150 mL of carbon tetrachloride was irradiated with a Hanovia 450-W medium-pressure lamp (Pyrex filter) under an atmosphere of helium at 38–40 °C for 22 h. The solvent was removed under reduced pressure and the residue chromatographed on silicic acid using mixtures of methylene chloride–carbon tetrachloride as an eluent. Isolation of the faster moving fraction furnished the trans sulfide **15** as a light brown oil: IR ($CHCl_3$) 1770 cm^{-1}; NMR ($CDCl_3$) δ 1.57 (s, 3 H), 1.70 (s, 3 H), 3.83 (s, 2 H), 4.12 (d, 1 H, J = 2.0 Hz), 4.63 (s, 1 H), 4.73 (s, 2 H), 4.92 (d, 1 H, J = 2.0 Hz), 7.22 (s, 5 H).

Isolation of the slower moving fraction furnished an oil which crystallized on standing. Recrystallization from methylene chloride–petroleum ether gave the analytically pure cis sulfide **14**: mp 82.0–83.0 °C; IR ($CHCl_3$) 1770 cm^{-1}; NMR ($CDCl_3$) δ 1.60 (s, 3 H), 1.80 (s, 3 H), 3.87 (s, 2 H), 4.30 (d, 1 H, J = 4.0 Hz), 4.53 (s, 1 H), 4.73 (s, 2 H), 5.33 (d, 1 H, J = 4.0 Hz), 7.22 (s, 5 H).

Some of the fractions collected between pure **14** and **15** were mixtures. The total yield of the trans sulfide **15** (weight in mixtures determined from NMR integration) was 7%. The yield of the cis sulfide **14** was 28%.

Photolysis of β,β,β-Trichloroethyl 6-Diazopenicillanate (3) with Chlorothiolacetic Acid. A solution of 2.0 g (5.58 mmol) of **3** in 180 mL of carbon tetrachloride was cooled to ~3 °C before chlorothiolacetic acid (3.08 g, 27.9 mmol) in 20 mL of carbon tetrachloride was added dropwise over 30 min. The solution was irradiated with a Hanovia 450-W medium-pressure lamp (Pyrex filter) under a helium atmosphere at 3–5 °C for 15 h. The solution was washed with 5% aqueous $NaHCO_3$ and dried ($MgSO_4$) and the solvent removed under reduced pressure. The residual oil was submitted to column chromatography on silicic acid using methylene chloride as an eluent. Isolation of the fastest moving fraction gave the trans chloride **18** (84.2 mg, 8%) as a crystalline material. Recrystallization from methylene chloride–petroleum ether gave an analytically pure sample: mp 110.0–111.0 °C; IR ($CHCl_3$) 1775 cm^{-1}; NMR ($CDCl_3$) δ 1.67 (s, 3 H), 1.73 (s, 3 H), 4.67 (s, 1 H), 4.81 (s, 3 H, $-CH_2CCl_3$ + 1 β-lactam H), 5.53 (d, 1 H, J = 2.0 Hz).

Anal. Calcd for $C_{10}H_{11}NO_3Cl_4S$: C, 32.72; H, 3.02; N, 3.82; Cl, 38.63; S, 8.74; Found: C, 32.77; H, 3.01; N, 3.81; Cl, 38.45; S, 8.66.

Isolation of a slower moving fraction gave the trans thiol ester **17** (106 mg, 4%) as an oil: IR ($CHCl_3$) 1775 cm^{-1}; NMR ($CDCl_3$) δ 1.60 (s, 3 H), 1.75 (s, 3 H), 4.18 (s, 2 H), 4.62 (s, 1 H), 4.73 (s, 2 H), 4.82 (d, 1 H, J = 2.0 Hz), 5.13 (d, 1 H, J = 2.0 Hz).

Isolation of the slowest moving fraction gave 1.20 g (49%) of the cis thiol ester **16** as an oil: IR ($CHCl_3$) 1780 cm^{-1}; NMR ($CDCl_3$) δ 1.63 (s, 3 H), 1.73 (s, 3 H), 4.22 (s, 2 H), 4.53 (s, 1 H), 4.73 (s, 2 H), 5.30 (d, 1 H, J = 4.0 Hz), 5.58 (d, 1 H, J = 4.0 Hz).

Synthesis of D-α-β,β,β-Trichloroethyloxycarboxamidophenylthiolacetic Acid. A mixture of 547 mg (1.67 mmol) of D-α-β,β,β-trichloroethyloxycarboxamidophenylacetic acid, 250 μL (3.44 mmol) of thionyl chloride, and 10 mL of dry benzene was refluxed overnight. Removal of the solvent and excess thionyl chloride under reduced pressure gave D-α-β,β,β-trichloroethyloxycarboxamidophenylacetyl chloride as a light brown oil: IR ($CHCl_3$) 1790 and 1735 cm^{-1}; NMR ($CDCl_3$) δ 4.70 (s, 2 H), 5.50 (d, 1 H, J = 7.0 Hz), 5.6–6.1 (m, 1 H), 7.23 (s, 5 H).

The acid chloride in 10 mL of methylene chloride was added dropwise to a hydrogen sulfide saturated solution of pyridine at 0 °C. The solution was stirred at 0 °C for 1.5 h and at room temperature for 2 h. The solution was partitioned between methylene chloride and ice water. The aqueous layer was acidified with concentrated HCl. The organic layer was separated and extracted with aqueous $NaHCO_3$. Separation of the organic layer, partitioning the aqueous layer with methylene chloride, acidification with concentrated HCl, separation of the organic layer, drying ($MgSO_4$) and removal of the solvent under reduced pressure gave D-α-β,β,β-trichloroethyloxycarboxamidophenythiolacetic acid as a clear oil: NMR ($CDCl_3$) δ 4.67 (s, 2 H), 5.2–5.5 (m, 2 H, –SH and PhH–), 5.8–6.5 (m, 1 H), 7.17 (s, 5 H).

Synthesis of β,β,β-Trichloroethyl 6β-Mercaptopenicillanate (21). Sodium methoxide (43 mg, 0.80 mmol) in 20 mL of anhydrous methanol was added dropwise over 2 h to a stirred solution at −78 °C (CO_2–acetone) of 349 mg (0.79 mmol) of β,β,β-trichloroethyl 6β-(chloroacetylthio)penicillanate (**16**) in 30 mL of anhydrous methanol. After the addition the stirring was continued at −78 °C for 5.5 h. The CO_2–acetone bath was replaced with a CO_2–acetonitrile bath and the stirring continued at −50 to −65 °C for 3.5 h. Methylene chloride was added and the solution washed with ice-cold 10% HCl and 5% $NaHCO_3$. The organic solution was dried ($MgSO_4$) and the solvent removed under reduced pressure. The residual oil was submitted to column chromatography on silicic acid using a 1:1 mixture (v/v) of methylene chloride–carbon tetrachloride as an eluent. The mercaptan **21** (229 mg, 80%) was isolated as an oil: IR (neat) 2955, 2550, and 1775 cm^{-1}; NMR ($CDCl_3$) δ 1.67 (s, 3 H), 1.80 (s, 3 H), 2.48 (d, 1 H, J = 21 Hz), 4.40–7.73 (m, 2 H, H-3 and H-6), 4.79 (s, 2 H), 5.60 (d, 1 H, J = 4.0 Hz).

Synthesis of β,β,β-Trichloroethyl 6β-(Thiophene-2-acetylthio)penicillanate (22). A solution of 120 μL (0.76 mmol) of *N,N*-

diisopropylcarbodiimide in 10 mL of methylene chloride was added dropwise over 30 min to an ice-cold solution of 108 mg (0.76 mmol) of thiophene-2-acetic acid, 61 μL (0.76 mmol) of pyridine, and 273 mg (0.75 mmol) of the mercaptan **21** in 50 mL of methylene chloride. After the addition the solution was stirred overnight at room temperature. Extraction of the solution with ice-cold 10% HCl and aqueous $NaHCO_3$, drying ($MgSO_4$) of the organic solution, and removal of the solvent under reduced pressure gave an oily solid (solid due to urea formed as by-product) which was chromatographed on silicic acid using methylene chloride as an eluent. Isolation of the major fraction gave the thiol ester **22** as an oil (325 mg, 89%) which crystallized on standing. Recrystallization from ether–petroleum ether gave an analytically pure sample: mp 86.0–87.0 °C; IR ($CHCl_3$) 1775 and 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.63 (s, 3 H), 1.73 (s, 3 H), 4.07 (s, 2 H), 4.55 (s, 1 H), 4.75 (s, 2 H), 5.32 (d, 1 H, J = 4.0 Hz), 5.67 (d, 1 H, J = 4.0 Hz), 6.7–7.3 (m, 3 H).

Anal. Calcd for $C_{16}H_{16}NO_4Cl_3S_3$: C, 39.31; H, 3.30; N, 2.86; Cl, 21.76; S, 19.68. Found: C, 39.49; H, 3.36; N, 2.78; Cl, 21.72; S, 19.58.

Synthesis of β,β,β-Trichloroethyl 6β-(D-α-*tert*-Butoxycarboxamidophenylacetylthio)penicillanate (23). In the same manner as described for **22** the thiol ester **23** was isolated as an oil (839 mg, 88%) after purification by column chromatography on silicic acid using 1% ether–methylene chloride (v/v) as an eluent: IR (neat) 3350, 2975, 1775, 1720, and 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.57 (s, 9 H), 1.60 (s, 3 H), 1.70 (s, 3 H), 4.50 (s, 1 H), 4.72 (s, 2 H), 5.2–5.6 (m, 4 H), 7.17 (s, 5 H).

Synthesis of β,β,β-Trichloroethyl 6β-(Phenylcarbothio)penicillanate 1-Oxide (25). A solution of *m*-chloroperbenzoic acid (454 mg, 2.63 mmol) in 20 mL of chloroform was added dropwise over 30 min to an ice-cold solution of the sulfide **6** (1.24 g, 2.64 mmol) in 50 ml of chloroform. After the addition the solution was stirred at 0 °C for 2 h, washed with aqueous $NaHCO_3$ and dried ($MgSO_4$) and the solvent removed under reduced pressure. Trituration of the residual oil with ether gave the sulfoxide **25** (1.04 g, 81%) as a crystalline material which was shown by NMR analysis to be predominantly one isomer (less polar isomer by TLC on silica gel–CH_2Cl_2). Recrystallization from methylene chloride–petroleum ether gave the analytically pure sulfoxide **25** (less polar) as white needles: mp 178.0–179.0 °C; IR ($CHCl_3$) 3005, 1805, 1760, and 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.37 (s, 3 H), 1.80 (s, 3 H), 4.63 (d, 1 H, J = 12.0 Hz), 4.77 (s, 1 H), 5.03 (d, 1 H, J = 12.0 Hz), 5.30 (d, 1 H, J = 4.0 Hz), 6.03 (d, 1 H, J = 4.0 Hz), 7.2–8.2 (m, 5 H).

Anal. Calcd for $C_{17}H_{16}NO_5Cl_3S_2$: C, 42.12; H, 3.33; N, 2.89; Cl, 21.94; S, 13.23. Found: C, 42.12; H, 3.26; N, 2.87; Cl, 21.97; S, 13.21.

Synthesis of β,β,β-Trichloroethyl 6β-(Phenylacetylthio)penicillanate 1-Oxide (26). A solution of *m*-chloroperbenzoic acid (180 mg, 1.04 mmol) in 25 mL of chloroform was added dropwise over 2 h to an ice-cold solution of the sulfide **8** (483 mg, 1.04 mmol) in 50 mL of chloroform. After the addition, the solution was stirred at 0 °C for 2 h, washed with aqueous $NaHCO_3$, and dried ($MgSO_4$) and the solvent removed under reduced pressure. Crystallization of the residual oil from methylene chloride–petroleum ether gave the sulfoxide **26** (139 mg, 27%, less polar isomer by TLC, (CH_2Cl_2) as white needles: mp 164.0–166.0 °C; IR ($CHCl_3$) 1805, 1760, and 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (s, 3 H), 1.77 (s, 3 H), 3.87 (s, 2 H), 4.61 (d, 1 H, J = 12.0 Hz), 4.70 (s, 1 H), 5.00 (d, 1 H, J = 12.0 Hz), 5.15 (d, 1 H, J = 4.0 Hz), 5.70 (d, 1 H, J = 4.0 Hz), 7.30 (s, 1 H).

Anal. Calcd for $C_{18}H_{18}NO_5Cl_3S_2$: C, 43.34; H, 3.64; N, 2.81; Cl, 21.32; S, 12.86. Found: C, 43.42; H, 3.50; N, 2.74; Cl, 21.49; S, 12.83.

The mother liquor from the aforementioned crystallization was chromatographed on silicic acid using methylene chloride as an eluent. Isolation of the faster moving fraction gave an additional 189 mg of the sulfoxide **26** (total yield of **26** was 63%). Isolation of the slower moving fraction gave the isomeric sulfoxide **26** (144 mg, 28%) as a crystalline material. Recrystallization from CH_2Cl_2–petroleum ether gave the analytically pure sample as white needles: mp 125.0–126.5 °C; IR ($CHCl_3$) 1800, 1775, 1710, and 1705 cm^{-1}; NMR ($CDCl_3$) δ 1.40 (s, 3 H), 1.67 (s, 3 H), 3.90 (s, 2 H), 4.52 (s, 1 H), 4.63 (d, 1 H, J = 12.0 Hz), 4.80 (d, 1 H, J = 4.0 Hz), 4.97 (d, 1 H, J = 12.0 Hz), 5.30 (d, 1 H, J = 4.0 Hz), 7.32 (s, 5 H).

Anal. Calcd for $C_{18}H_{18}NO_5Cl_3S_2$: C, 43.34; H, 3.64; N, 2.81; Cl, 21.32; S, 12.86. Found: C, 43.27; H, 3.55; N, 2.83; Cl, 21.38; S, 12.75.

Synthesis of β,β,β-Trichloroethyl 7β-(Phenylcarbothio)deacetoxycephalosporanate (29). A solution of 963 mg (1.98 mmol) of the sulfoxide **25** (mixture of α and β isomers), 32 mL of dry benzene, 24 mL of *N,N*-dimethylacetamide, and 3 drops of methanesulfonic acid were refluxed under a Dean-Stark trap, protected from moisture with a drying tube, for 19 h (temperature of external heating bath was maintained between 110 and 120 °C). Removal of the solvent by distillation under reduced pressure (temperature of bath ~50 °C, 2–3 mm) and chromatography of the dark brown residue on silicic acid using methylene chloride as an eluent gave the thiol ester **29** (659 mg, 71%) as a white solid. Recrystallization from methylene chloride–petroleum ether gave the analytically pure sample as thin, white needles: mp 175.5–176.0 °C; IR ($CHCl_3$) 3005, 1780, 1740, and 1670 cm^{-1}; NMR ($CDCl_3$) δ 2.23 (s, 3 H), 3.13 (d, 1 H, J = 18.0 Hz), 3.53 (d, 1 H, J = 18.0 Hz), 4.70 (d, 1 H, J = 13.0 Hz), 5.03 (d, 1 H, J = 13.0 Hz), 5.10 (d, 1 H, J = 4.0 Hz), 5.64 (d, 1 H, J = 4.0 Hz), 7.1–8.2 (m, 5 H).

Anal. Calcd for $C_{17}H_{14}NO_4Cl_3S_2$: C, 43.74; H, 3.02; N, 3.00; Cl, 22.78; S, 13.74. Found: C, 43.66; H, 3.04; N, 3.01; Cl, 22.73; S, 13.64.

Synthesis of β,β,β-Trichloroethyl 7β-(Phenylacetylthio)deacetoxycephalosporanate (30). In the same manner as described for **29** (pure less polar sulfoxide **26** used) the thiol ester **30** (232 mg, 91%) was isolated as an oil which crystallized on standing. Recrystallization from methylene chloride–petroleum ether gave the analytically pure sample: mp 103.0–104.5 °C; IR ($CHCl_3$) 3005, 1780, and 1730 cm^{-1}; NMR ($CDCl_3$) δ 2.20 (s, 3 H), 3.10 (d, 1 H, J = 18.0 Hz), 3.43 (d, 1 H, J = 18.0 Hz), 3.83 (s, 2 H), 4.77 (d, 1 H, J = 12.0 Hz), 4.95 (d, 1 H, J = 12.0 Hz), 4.95 (d, 1 H, J = 4.0 Hz), 5.33 (d, 1 H, J = 4.0 Hz), 7.10 (s, 5 H).

Anal. Calcd for $C_{18}H_{16}NO_4Cl_3S_2$: C, 44.96; H, 3.35; N, 2.91; Cl, 22.12; S, 13.34. Found: C, 44.97; H, 3.38; N, 2.84; Cl, 22.10; S, 13.16.

Synthesis of β,β,β-Trichloroethyl 7β-(Phenoxyacetylthio)deacetoxycephalosporanate (31). A solution of *m*-chloroperbenzoic acid (357 mg, 2.06 mmol) in 20 mL of chloroform was added dropwise over 30 min to an ice-cold solution of the sulfide **10** (1.025 g, 2.05 mmol) in 50 mL of chloroform. After the addition, the solution was stirred at 0 °C for 3.5 h, washed with aqueous $NaHCO_3$, and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residual oil (1.05 g) was dissolved in 32 mL of dry benzene. *N,N*-Dimethylacetamide (24 mL) and 3 drops of methanesulfonic acid were added and the mixture refluxed under a Dean-Stark trap, protected from moisture with a drying tube, for 19 h (temperature of external heating bath maintained at 110–120 °C). Removal of the solvent by distillation (temperature of heating bath 50–60 °C, 2–3 mm) and chromatography of the dark brown residue on silicic acid using methylene chloride as an eluent gave the thiol ester **31** (716 mg, 70%) as a crystalline material. Recrystallization from CH_2Cl_2–petroleum ether gave the analytically pure sample: mp 148.5–149.5 °C; IR ($CHCl_3$) 3005, 1780, and 1735 cm^{-1}; NMR ($CDCl_3$) δ 2.23 (s, 3 H), 3.17 (d, 1 H, J = 18.0 Hz), 3.53 (d, 1 H, J = 18.0 Hz), 4.70 (s, 2 H), 4.70 (d, 1 H, J = 12.0 Hz), 5.00 (d, 1 H, J = 12.0 Hz), 5.05 (d, 1 H, J = 4.0 Hz), 5.45 (d, 1 H, J = 4.0 Hz), 6.7–7.4 (m, 5 H).

Anal. Calcd for $C_{18}H_{16}NO_5Cl_3S_2$: C, 43.52; H, 3.25; N, 2.82; Cl, 21.41; S, 12.91. Found: C, 43.57; H, 3.58; N, 2.77; Cl, 21.40, S, 12.66.

Synthesis of β,β,β-Trichloroethyl 7β-(Chloroacetylthio)deacetoxycephalosporanate (32). In the same manner as described for **31**, the thiol ester **32** (396 mg, 39%) was isolated as a crystalline material. The product was recrystallized from ether–petroleum ether: mp 134–137 °C; IR ($CHCl_3$) 1780 and 1735 cm^{-1}; NMR ($CDCl_3$) δ 2.28 (s, 3 H), 3.20 (d, 1 H, J = 17.0 Hz), 3.57 (d, 1 H, J = 17.0 Hz), 4.27 (s, 2 H), 4.77 (d, 1 H, J = 12.0 Hz), 5.00 (d, 1 H, J = 12.0 Hz), 5.10 (d, 1 H, J = 4.0 Hz), 5.46 (d, 1 H, J = 4.0 Hz).

Synthesis of β,β,β-Trichloroethyl 7β-Mercaptodeacetoxycephalosporanate (33). The same manner as described for **21** (starting from either the phenoxyacetyl or chloroacetyl derivatives **31** or **32**) the mercaptan **33** was isolated in 75–80% yield as an oil (in the case of **31** methyl phenoxyacetate had to be removed by chromatography: silicic acid–methylene chloride): IR (neat) 2550, 1770, and 1735 cm^{-1}; NMR ($CDCl_3$) δ 2.32 (d, 4 H, J = 4.0 Hz, $-CH_2$ and $-SH$), 3.20 (d, 1 H, J = 18.0 Hz), 3.57 (d, 1 H, J = 18.0 Hz), 4.4–5.2 (m, 3 H, $-CH_2CCl_3$ and H-6), 5.01 (d, 1 H, J = 4.0 Hz).

Synthesis of β,β,β-Trichloroethyl 7β-(Thiophene-2-acetylthio)deacetoxycephalosporanate (34). In the same manner as described for **22**, the thiol ester **34** was isolated as an oil (352 mg, 82%) after chromatography on silicic acid using methylene chloride as an eluent: IR ($CHCl_3$) 1780, 1735, and 1700 cm^{-1}; NMR ($CDCl_3$) δ 2.30 (s, 3 H), 3.20 (d, 1 H, J = 18.0 Hz), 3.60 (d, 1 H, J = 18.0 Hz), 4.17 (s, 2 H), 4.83 (d, 1 H, J = 12.0 Hz), 5.07 (d, 1 H, J = 12.0 Hz), 5.13 (d, 1 H, J = 4.0 Hz), 5.57 (d, 1 H, J = 4.0 Hz), 6.8–7.4 (m, 3 H).

Synthesis of β,β,β-Trichloroethyl 7β-(D-α-*tert*-Butoxycarboxamidophenylacetylthio)deacetoxycephalosporanate (35). In the same manner as described for **22**, the thiol ester **35** was isolated as an oil (316 mg, 82%) after chromatography on silicic acid using 1% ether–methylene chloride (v/v) as an eluent: IR (neat) 3350, 1780, and 1705 cm^{-1}; NMR ($CDCl_3$) δ 1.55 (s, 9 H), 2.23 (s, 3 H), 3.15 (d, 1 H, J = 18.0 Hz), 3.43 (d, 1 H, J = 18.0 Hz), 4.73 (d, 1 H, J = 12.0 Hz), 5.00 (d, 1 H, J = 12.0 Hz), 5.03 (d, 1 H, J = 4.0 Hz), 5.2–5.5 (m, 3 H), 7.25 (s, 5 H).

Synthesis of β,β,β-Trichloroethyl 7-Hydrazonopenicillanate (5). A solution of 3.04 g (8.5 mmol) of the diazo ester **3** in 250 mL of THF was saturated with H_2S and then stirred (stoppered) at room temperature overnight. After removal of the solvent (no heat) under reduced pressure, a yellowish-white solid remained. Trituration with ether gave the hydrazone **5** (2.02 g, 66%) as a white solid: mp 167–168 °C dec; IR ($CHCl_3$) 1775 cm^{-1}; NMR ($CDCl_3$) δ 1.60 (s, 3 H), 1.67 (s, 3 H), 4.53 (s, 1 H), 4.67 (s, 2 H), 5.60 (s, 1 H), 5.7–6.2 (m, 2 H).

Anal. Calcd for $C_{10}H_{12}N_3O_3Cl_3S$: C, 33.30; H, 3.35; N, 11.65; Cl, 29.49; S, 8.98. Found: C, 33.34; H, 3.52; N, 11.61; Cl, 29.60; S, 8.72.

General Procedure for the Removal of the Protective Group. The ester (100–200 mg) was dissolved in 90% HOAc (1–2 mL of DMF was added if ester did not dissolve) and the solution cooled to 0 °C before 1–1.5 g of zinc dust was added. The mixture was stirred at 0 °C for 3–5 h. Removal of the zinc by filtration through Celite into a flask containing 100 mL of ice water and washing of the zinc with methylene chloride (50 mL) yielded a two-phase system. Separation of the organic layer, extraction of the aqueous layer with several methylene chloride–zinc washings, drying ($MgSO_4$), and removal of the solvent under reduced pressure (no heat) afforded the free acid. For purification (if required) the acid was dissolved in methylene chloride and extracted with aqueous $NaHCO_3$. The aqueous layer, after being extracted several times with methylene chloride, was cooled with ice and acidified with dilute HCl. Extraction with methylene chloride, drying ($MgSO_4$), and removal of the solvent under reduced pressure (no heat) gave the pure acid.

For **23** and **35** after removal of the trichloroethyl group as described above, the acid was dissolved in 1 mL of anisole and the solution cooled to 0 °C before 7 mL of trifluoroacetic acid (previously cooled to 0 °C) was added. After stirring at 0 °C for 1 h, the solvent was removed under reduced pressure (2–3 mm keeping the solution at 0 °C during the process). Freeze drying of the residual oil from benzene afforded the acids as solid compounds which were bioassayed without purification.

Acknowledgment. This work was supported by a grant from the Sloan Basic Research Fund. We are grateful to Miss Nadine Hunt and Professor A. L. Demain of the Department of Nutrition and Food Science for bioassays.

Registry No.—**3,** 51056-24-7; **5,** 62166-72-7; **6,** 62166-73-8; **7,** 62166-74-9; **8,** 62166-75-0; **9,** 62166-76-1; **10,** 62166-77-2; **11,** 62166-78-3; **12,** 62166-79-4; **13,** 62166-80-7; **14,** 62166-81-8; **15,** 62166-82-9; **16,** 62166-83-0; **17,** 63039-69-0; **18,** 62166-84-1; **21,** 62166-85-2; **22,** 62166-86-3; **23,** 62166-87-4; α-**25,** 62166-88-5; β-**25,** 62166-89-6; α-**26,** 62166-90-9; β-**26,** 62166-91-0; **29,** 62166-92-1; **30,** 62166-93-2; **31,** 62166-94-3; **32,** 62197-68-6; **33,** 62166-95-4; **34,** 62166-96-5; **35,** 62166-97-6; thiobenzoic acid, 98-91-9; benzoyl disulfide, 644-32-6; diphenylacetyl disulfide, 15088-78-5; diphenoxyacetyl disulfide, 62166-98-7; thiophenol, 108-98-5; benzyl mercaptan, 100-53-8; D-α-β,β,β-trichloroethyloxycarboxamidophenylacetic acid, 26553-34-4; thionyl chloride, 7719-09-7; D-α-β,β,β-trichloroethyloxycarboxamidophenylacetyl chloride, 49597-72-0; D-α-β,β,β-trichloroethyloxycarboxamidophenylthiolacetic acid, 62166-99-8; thiophene-2-acetic acid, 1918-77-0; phenylthiolacetic acid, 62167-00-4; phenoxythiolacetic acid, 62167-01-5; chlorothiolacetic acid, 867-49-2.

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(8) Protection of the nitrogen in **23** with the *t*-Boc instead of the trichloroethyl group (see figure **24**) allows selective removal of the protective groups. See experimental Section and R. R. Chauvette, P. A. Pennington, C. W. Ryan, R. D. G. Cooper, F. L. José, I. G. Wright, E. M. Van Heyningen, and G. W. Huffman, *J. Org. Chem.*, **36,** 1259 (1971).
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On the Electronic Effects of the Heteroatom in Five-Membered Heterocycles. Photoelectron Spectra of Selenolo and Pyrrolo Analogues of Thieno[2,3-*b*]thiophene and Thieno[3,2-*b*]thiophene[1]

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In order to study the effects of the heteroatoms, the photoelectron spectra of thieno[2,3-*b*]selenophene (**3**), selenolo[2,3-*b*]selenophene (**4**), thieno[3,2-*b*]selenophene (**5**), selenolo[3,2-*b*]selenophene (**6**), thieno[2,3-*b*]pyrrole (**7**), selenolo[2,3-*b*]pyrrole (**8**), pyrrolo[2,3-*b*]pyrrole (**9**), thieno[3,2-*b*]pyrrole (**10**), and selenolo[3,2-*b*]pyrrole (**11**) have been measured and analyzed. Replacement of sulfur by selenium can be considered as a minor perturbation, i.e., simple perturbation theory is valid. The effect on the π electronic system of a replacement of sulfur or selenium by an NH group is governed by a balance between the influence of the increase of the resonance integral for the bonds involving the heteroatom and a strongly destabilizing inductive effect due to the polarity of the N–H bond. The effective electronegativity of the NH group is found to be not too different from that of a sulfur atom.

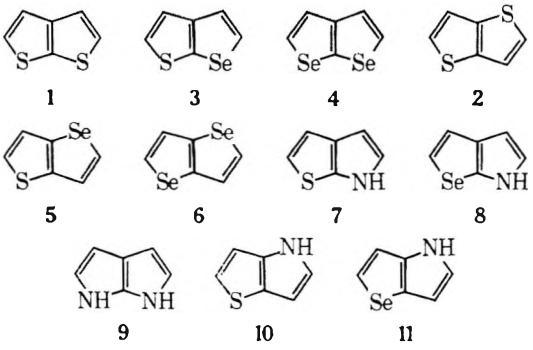
A description of the electronic effects associated with the heteroatom in a heterocyclic compound is of fundamental importance in chemistry and biology. Heterocyclic chemistry is a rich field for the application of perturbation theoretical arguments, and qualitative descriptions of the influence of the heteroatom are in most cases based directly or indirectly on simple perturbation theory.[5] A prominent example of a series of heterocycles is the compounds C_4H_4X, where X may be O, S, Se, NH, etc. In Figure 1 we have indicated the positions of the first two ionization potentials[6,7] of the compounds furan, pyrrole, thiophene, and selenophene, arranged in the order of decreasing electronegativity of the heteroatom. Within the validity of Koopmans' theorem (see later), the first and the second ionization potential correspond to removal of an electron from the highest and the second highest molecular orbital, $a_2(\pi)$ and $b_1(\pi)$, respectively. The general shape of these orbitals is indicated below. According to simple per-

$a_2(\pi)$ $b_1(\pi)$

turbation theory, the energy of the $a_2(\pi)$ level should be much less affected by a change of heteroatom than the energy of the $b_1(\pi)$ level. Inspection of Figure 1 shows that this expectation holds excellently for the series furan, thiophene, and selenophene, but pyrrole is a striking exception. Consider for instance the passing from thiophene to pyrrole: the shift of the $a_2(\pi)$ level is much larger than the shift of the $b_1(\pi)$ level, and both shifts are toward lower binding energies, which is apparently inconsistent with an increase of electronegativity of the heteroatom.

In order to obtain a better understanding of the effects operating in these systems, we have studied the PE spectra of thieno[2,3-*b*]selenophene (**3**),[8] selenolo[2,3-*b*]selenophene (**4**),[9] thieno[3,2-*b*]selenophene (**5**),[10] selenolo[3,2-*b*]selenophene (**6**),[11] thieno[2,3-*b*]pyrrole (**7**),[12] selenolo[2,3-*b*]pyrrole (**8**),[13] pyrrolo[2,3-*b*]pyrrole (**9**),[13] thieno[3,2-*b*]pyrrole (**10**),[13] and selenolo[3,2-*b*]pyrrole (**11**).[13] The PE spectra of thieno[2,3-*b*]thiophene (**1**) and thieno[3,2-*b*]thiophene (**2**) have been measured previously.[14]

In the first section of the paper we discuss the compounds **1–6**, where simple perturbation theoretical arguments appear to be valid. In the second and largest part of the paper we discuss the compounds **7–11** in order to describe the effects leading to the breakdown of simple perturbation theory when



sulfur or selenium is replaced by NH. We use the results of current semiempirical methods and refer to recent ab initio results, but the emphasis has been put on a conceptual analysis in terms familiar to most organic chemists.

I. PE Spectra of 1–6

The PE spectra of **3–6** are shown in Figure 2 and the vertical ionization potentials of the first four bands are listed in Table I. The PE spectra of **1** and **2** have been published previously,[14] and the vertical ionization potentials are included in Table I. The PE spectra of the series **1–3–4** all look very similar, as do the PE spectra of the series **2–5–6**. This is not surprising, since sulfur and selenium have very similar electronegativities,[15] and substitution of sulfur by selenium can be expected to be a minor perturbation of the valence electronic system. In the following section is given a more detailed discussion of this matter in connection with a description of the effects due to the NH group.

In our interpretation of these spectra we assume the validity of Koopmans' theorem.[16] In this approximation, the negative value of the orbital energy, ϵ_J, is set equal to the vertical ionization potential, $I_{V,J}$:

$$-\epsilon_J = I_{V,J} \quad (1)$$

As in the case of **1** and **2**[14] we take the steep onset of the first few PE bands as an indication that the bands correspond to ionizations from π orbitals. From the similarity of the PE spectra mentioned above, the correlation diagram given in Figure 3 can be drawn. To check this diagram we have carried out semiempirical calculations using a parametrized Hückel (HMO) procedure,[5] and the EWMO,[17,18] CNDO/2,[19] and MINDO/3[20] methods. The results of the HMO and MINDO/3 calculations are summarized in Table I, and a correlation diagram based on the HMO results is presented in Figure 4.

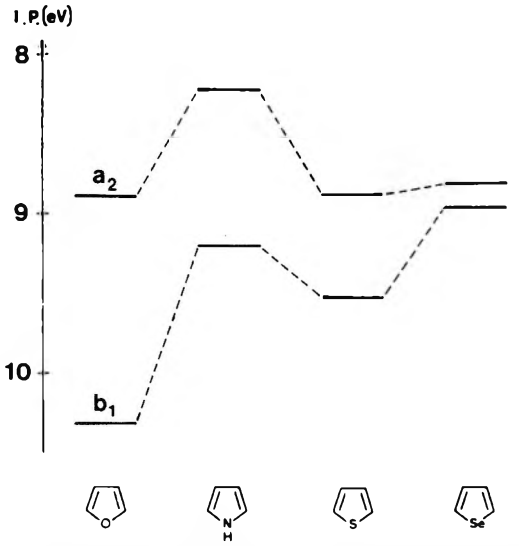


Figure 1. Correlation of the observed first and second ionization potentials of the compounds furan, pyrrole, thiophene, and selenophene.

HMO Model. The parameters for the HMO calculations were chosen in a straightforward way. α_X and β_{CX} values for X = S and Se were taken as those used previously: $\alpha_S = -9.4$, $\alpha_{Se} = 8.5$, $\beta_{CS} = -1.8$, and $\beta_{CSe} = -1.5$ eV.[21] The β_{CC} value was also kept in accordance with the previous work: $\beta_{CC} = -3.0$ eV.[21] The α_C value was then adjusted to reproduce the observed first ionization potential of thiophene (8.87 eV[6]) and selenophene (8.80 eV[7]). The HOMOs of these compounds have a node through the position of the heteroatom X, and are thus independent of the choice of α_X and β_{CX} parameters in the HMO model. A good agreement is found for $\alpha_C = -7.0$ eV, which yields a common value of −8.85 eV for the energies of these levels. The results for thiophene and selenophene are then (eV)

	Thiophene	Selenophene
$a_2(\pi)$	−8.85	−8.85
$b_1(\pi)$	−9.64	−8.93
$b_1(\pi)$	−12.56	−12.23

The agreement with the observed energies[6,7] is satisfactory; in particular, the consistency with the recent analysis of the PE spectrum of thiophene by Niessen et al.[22] is gratifying.

Results and Discussion. The results of the HMO calculations on the compounds **1–6** agree reasonably well with the experimental energies; see Table I. The results support the assignments suggested previously[14] for **1** and **2**; this assignment is furthermore supported by the MINDO/3 results for **1** and **2** given in Table I. Comparison of the correlation diagrams in Figures 3 and 4 shows that the HMO calculations reproduce the significant trends in the PE spectra for this series of compounds. Most of the observed shifts of the bands can be understood in terms of simple first-order perturbation theory applied to the HMOs of **1** and **2** (see Figure 4). The HOMO of **1** has a small amplitude on the sulfur atoms, while the next MO has a large amplitude in these positions. These orbitals are thus destabilized to different extents by replacement of sulfur by selenium, and a reversal of the ordering of these two closely spaced levels is predicted in the series **1–3–4**. Similar shifts are shown by the two highest occupied orbitals in **2**, which have the same symmetry (a_u in C_{2h}). At first glance it may appear strange that the energy of the second highest MO approaches the energy of the HOMO in the series

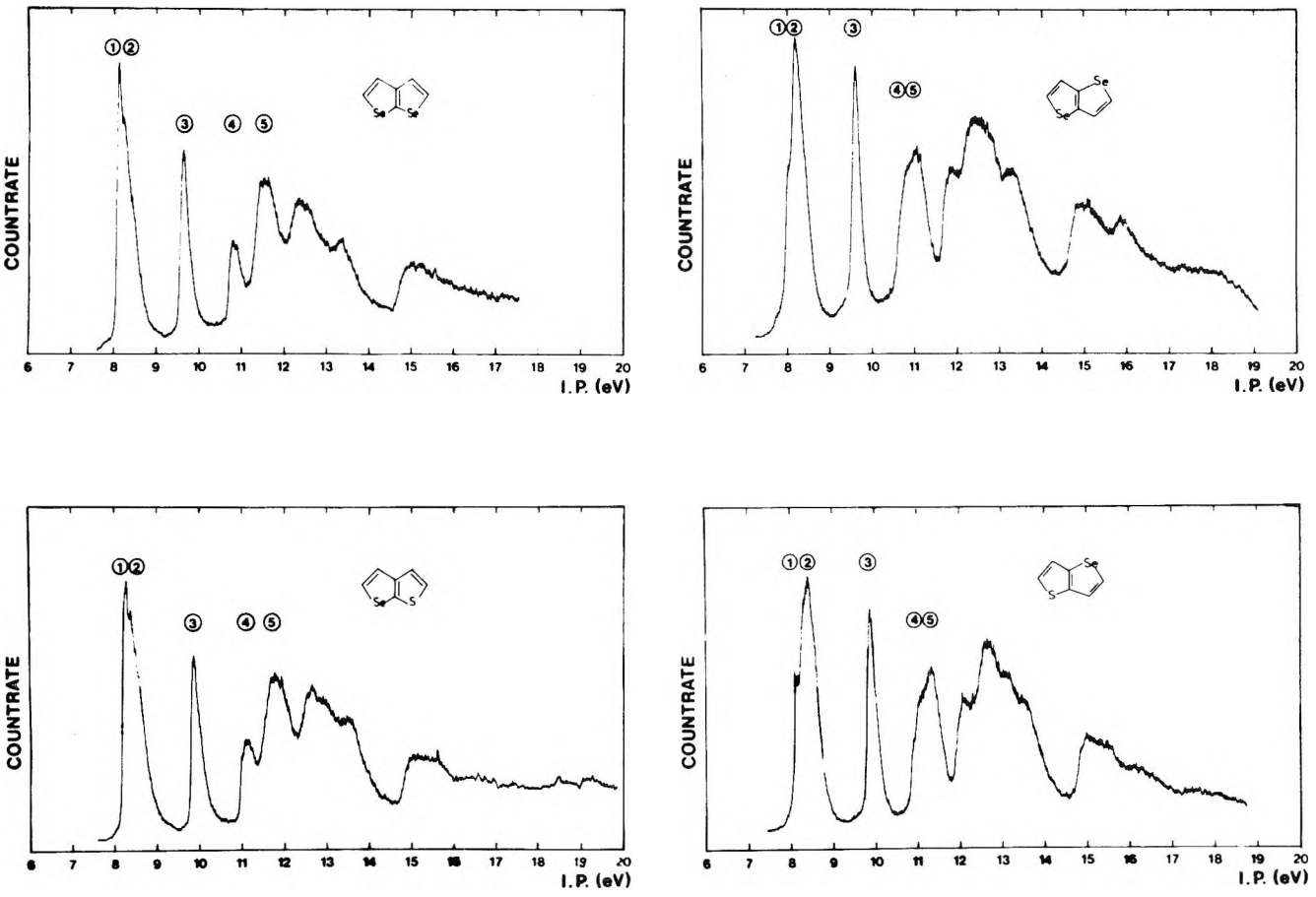


Figure 2. PE spectra of the compounds **3–6**.

Table I. Measured Vertical Ionization Potentials, $I_{V,J}$, and Orbital Energies, ϵ_J, for 1–6. All Values in eV

Registry no.	Compd	Band	$I_{V,J}$[a]	Assignment[a]	ϵ_J (HMO)	ϵ_J (MINDO/3)[b]
250-84-0	1 (C_{2v})	①	8.32	$4b_1$ (π)	−8.48	−8.27
		②	8.41	$3a_2$ (π)	−8.60	−8.47
		③	10.08	$3b_1$ (π)	−10.28	−9.76
		④	11.27	$2a_2$ (π)	−11.10	−11.50
23787-71-5	3 (C_s)	①	8.28	8a″ (π)	−8.32	
		②		7a″ (π)	−8.49	
		③	9.88	6a″ (π)	−9.87	
		④	11.12	5a″ (π)	−10.91	
250-85-1	4 (C_{2v})	①	8.16	$4a_2$ (π)	−8.16	
		②		$5b_1$ (π)	−8.45	
		③	9.66	$4b_1$ (π)	−9.51	
		④	10.82	$3a_2$ (π)	−10.59	
251-41-2	2 (C_{2h})	①	8.10	$4a_u$ (π)	−8.25	−8.15
		②	8.61	$3a_u$ (π)	−8.94	−8.57
		③	10.04	$3b_g$ (π)	−10.25	−9.67
		④	11.5	$2b_g$ (π)	−11.11	−11.53
		⑤		$15a_g$ (σ)		−9.33
20503-37-1	5 (C_s)	①	8.08	8a″ (π)	−8.19	
		②	8.39	7a″ (π)	−8.61	
		③	9.86	6a″ (π)	−9.97	
		④	11.3	5a″ (π)	−10.93	
		⑤		32a′ (σ)		
251-49-0	6 (C_{2h})	①	8.05	$5a_u$(π)	−8.09	
		②	8.20	$4a_u$ (π)	−8.50	
		③	9.63	$4b_g$ (π)	−9.47	
		④	11.1	$3b_g$ (π)	−10.84	
		⑤		$18a_g$ (σ)		

[a] The ionization potentials and assignments reported for 1 and 2 are taken from ref 14. [b] Some σ orbitals between the π orbitals have been omitted. The calculations were based on geometries derived from the experimental structure of thiophene; see ref 25.

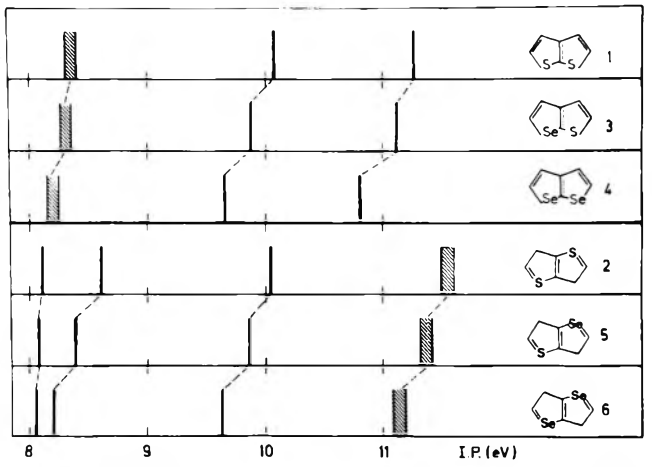


Figure 3. Correlation of the observed first four ionization potentials in the series 1–3–4 and 2–5–6; see Table I.

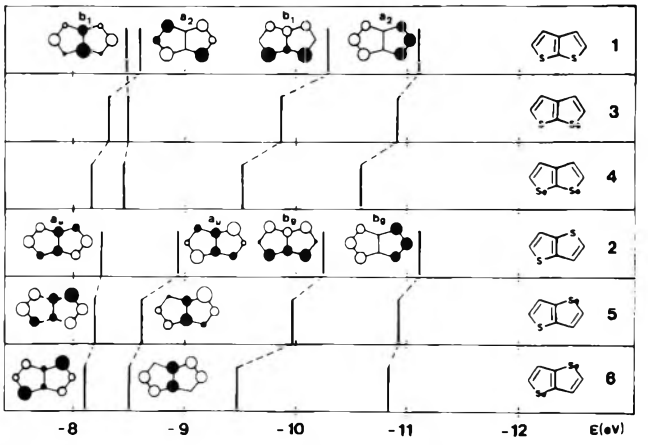
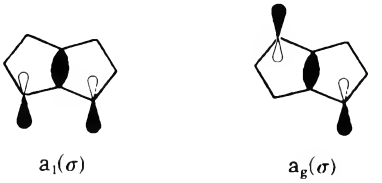


Figure 4. Correlation of the calculated energies of the four highest occupied HMO levels for the series 1–3–4 and 2–5–6; see Table I. The shape of the most important orbitals is indicated schematically.

2–5–6 without shifting the latter much. The shapes of the orbitals shown in Figure 4, however, indicate that the interaction is considerable, corresponding to the initial stages of an avoided crossing.

We finally briefly mention a few results regarding the highest occupied σ level in these compounds. According to the results of an extended Hückel calculation reported previously,[14] the highest occupied σ orbital in 1 and 2 transforms according to A_1 and A_g, respectively. The corresponding amplitudes are indicated schematically below.



These results are confirmed by the CNDO/2 and MINDO/3 methods, and by the results of EWMO calculations for 1–6. The calculations predict a destabilization of the $a_g(\sigma)$ orbital relative to the $a_1(\sigma)$ orbital due to a very strong antibonding interaction between the n_+ "lone pair" combination and the central C–C σ bond in the series 2–5–6. Our assignment of the overlapping bands ④ and ⑤ in the spectra of this series of compounds to ionization out of a π and a σ level is consistent with this result.

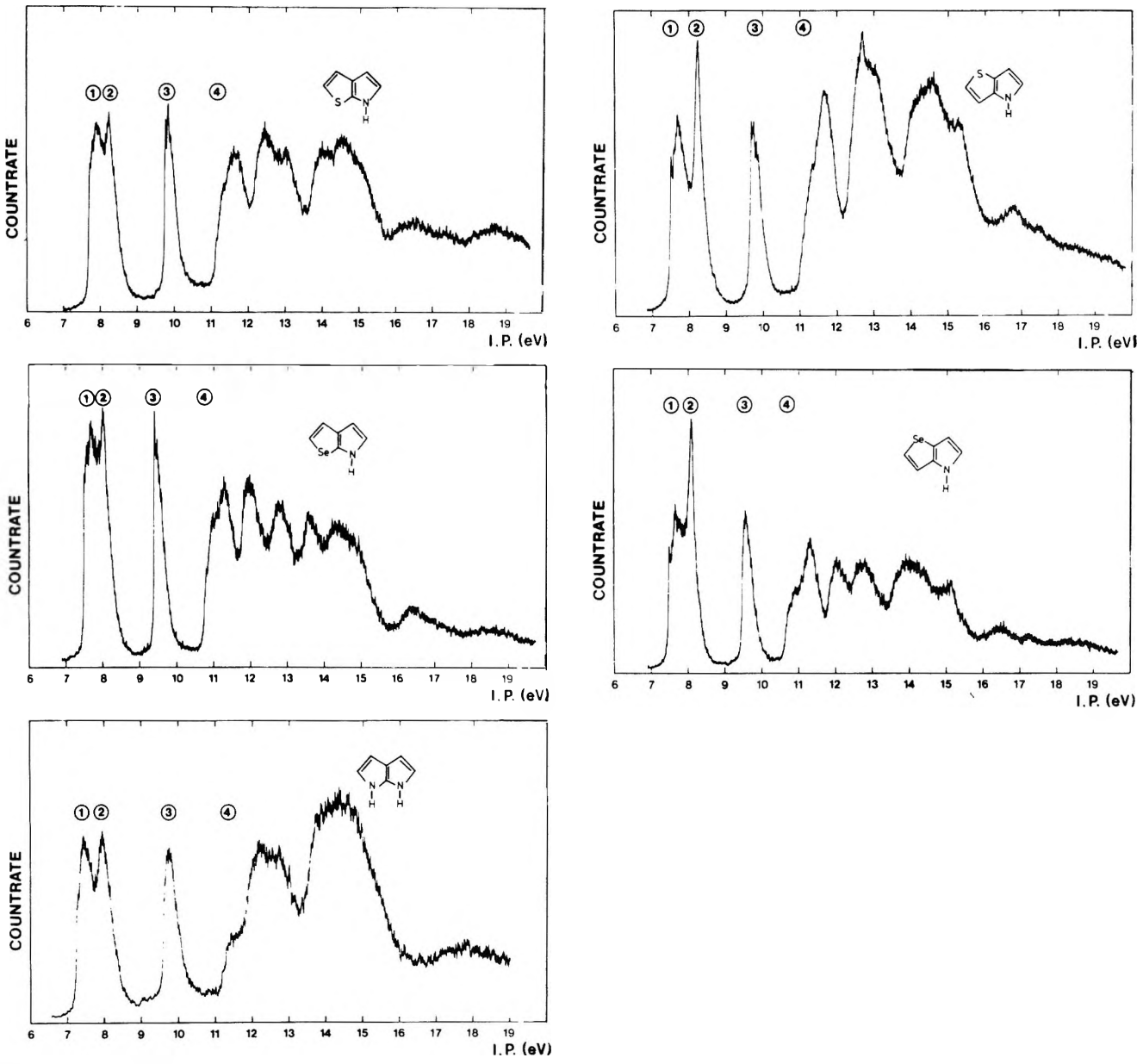


Figure 5. PE spectra of the compounds 7–11.

II. PE Spectra of 7–11

Replacement of sulfur or selenium in the compounds 1–6 by an NH group yields the compounds 7–11. The PE spectra of these compounds are shown in Figure 5, and the vertical ionization potentials are given in Table II. The assignment of the first broad peak in the spectra of the compounds 1–6 to two overlapping transitions (band ① and ②) is immediately supported by the comparison with the spectra of 7–11: the peak is clearly split into two components.

Electronic Effects of the NH Group. The discussion of the PE spectra of 1–6, was simplified by the circumstance that replacement of sulfur by selenium can be considered as a minor perturbation. Replacement of sulfur or selenium by an NH group, however, is not a small perturbation, and simple perturbation theory is no longer valid. As indicated in the introduction, this is easily seen by a comparison of the PE spectrum of pyrrole with the PE spectra of thiophene and selenophene (see Figure 1). Usual π electron theory will fail to describe this phenomenon properly, since the dominant interactions in pyrrole take place through the σ system; while the pyrrole nitrogen is a π electron donor, it is a much stronger σ electron acceptor.[23] An all-valence electron model with inclusion of electron interaction terms is appropriate for an understanding of these effects. In closed-shell SCF theory the orbital energy ϵ_J can be considered as a sum of two terms,[24]

$$\epsilon_J = H_{JJ} + \sum_K (2J_{JK} - K_{JK}) = H_{JJ} + G_{JJ} \qquad (2)$$

where the summation is over the occupied orbitals. The first term, H_{JJ}, represents the kinetic energy of an electron in the orbital J plus its potential energy due to the attraction by the nuclei. The second term, G_{JJ}, represents an average value of the repulsion between the electron in the orbital J and all other electrons in the molecule. The orbital energy ϵ_J is thus the sum of two large contributions with opposite sign.

Consider now the HOMO of furan, $a_2(\pi)$. This orbital is localized in the butadiene fragment with zero amplitude on the heteroatom, as mentioned before (see Figure 6). Replacing the oxygen atom by a sulfur atom or an NH group leads to an increase of H_{JJ} and a decrease of G_{JJ} for this orbital, as illustrated in the top of Figure 6 where the results of a CNDO/2 calculation are shown. This can be explained by the change of geometry taking place;[25] part of the attracting core, as well as part of the repulsing electron density, is moved away from the region of the $a_2(\pi)$ orbital. The shifts are particularly large

Table II. Measured Vertical Ionization Potentials, $I_{V,J}$, and Orbital Energies, ϵ_J, for 7–11. All Values in eV

Registry no.	Compd	Band	$I_{V,J}$	Assignment	ϵ_J (HMO)	ϵ_J (MINDO/3)[a]
		①	7.97	6a″ (π)	−7.99	
250-79-3	7	②	8.31	5a″ (π)	−8.11	
	(C_s)	③	9.89	4a″ (π)	−10.09	
		④	11.45	3a″ (π)	−11.30	
		①	7.74	7a″ (π)	−7.89	
42425-03-6	8	②	8.09	6a″ (π)	−8.04	
	(C_s)	③	9.48	5a″ (π)	−9.53	
		④	11.13	4a″ (π)	−11.16	
		①	7.46	$2a_2$ (π)	−7.60	−7.53
58326-34-4	9	②	7.91	$3b_1$ (π)	−7.97	−7.51
	(C_{2v})	③	9.73	$2b_1$ (π)	−9.96	−9.61
		④	11.47	$1a_2$ (π)	−11.33	−11.89
				$16a_1$ (σ)		−10.11
		①	7.70	6a″ (π)	−7.81	
250-94-2	10	②	8.24	5a″ (π)	−8.41	
	(C_s)	③	9.66	4a″ (π)	−9.97	
		④	11.3	3a″ (π)	−11.24	
		①	7.67	7a″ (π)	−7.77	
58326-29-7	11	②	8.10	6a″ (π)	−8.22	
	(C_s)	③	9.60	5a″ (π)	−9.66	
		④	10.95	4a″ (π)	−10.88	

[a] Some σ orbitals between the π orbitals have been omitted. The geometry of **9** was derived from the experimental geometry of pyrrole; see ref 25.

in going from furan to thiophene; the decrease of G_{JJ}, however, is found to practically compensate the increase of H_{JJ}, so that the orbital energy ϵ_J stays constant; see the bottom of Figure 6. This can be observed throughout the series furan, thiophene, selenophene, and tellurophene.[6,7,26] In the case of going from furan to pyrrole the increase of H_{JJ} is found to be larger than the decrease of G_{JJ}, leading to a net destabilization of the $a_2(\pi)$ level; see Figure 6. This is a direct consequence of the high polarity of the N–H bond, which tends to increase the G_{JJ} value by increasing the electron density in the ring: ab initio Hartree–Fock calculations[22,27] show that the total excess charge on the five ring atoms is ca. 25% larger in pyrrole than in furan or thiophene. Substitution of the NH hydrogen atom by an electron-donating methyl group leads to further destabilization of the $a_2(\pi)$ level.[28,29] We may thus summarize that although the individual shifts of H_{JJ} and G_{JJ} are much larger in the case of going from furan to thiophene than in the case of going from furan to pyrrole,[30] the destabilizing and stabilizing effects tend to cancel in the first case, but not in the second case.

We then turn briefly to the second highest occupied orbital in these compounds, $b_1(\pi)$. This orbital has a high amplitude on the heteroatom and it would appear reasonable to expect that the shifts of this level can be predicted by simple perturbation theory. One would thus predict a stabilization of this level when the heteroatom is replaced by a more electronegative atom. Calculated[22,27] and observed (Figure 1) energies support this prediction in the case of going from thiophene to furan, but not in the case of going from thiophene to pyrrole. The calculations by Niessen et al.[22,27] predict essentially the same energy of this orbital in thiophene and pyrrole, and the measured binding energies show a destabilization of 0.3 eV of the level in pyrrole relative to the level in thiophene (see Figure 1); the increase in electronegativity of the heteroatom is thus not able to outweigh the destabilizing inductive effect discussed in the preceding paragraph. This is largely due to the circumstance that although nitrogen is clearly more electronegative than sulfur,[15] the effective electronegativity of the NH *group* is probably not too different from that of a sulfur atom. The nitrogen atom in pyrrole gains approximately 0.4 electron, but ca. three-quarters of that is withdrawn from the hydrogen atom bonded to it;[27] the capacity to withdraw electrons from the neighboring carbon atoms is thus strongly deactivated, and the effective electronegativity of the NH group is much less than that of the nitrogen atom.

Contrary to the two highest occupied orbitals discussed above, $a_2(\pi)$ and $b_1(\pi)$, the third and most bonding π orbital in these compounds has large C–X bond contributions, and is thus quite sensitive to the strength of this π bond as measured by the value of the resonance integral β_{CX}. In the case of going from thiophene to furan, the large stabilizing effect due to the large magnitude of β_{CO} relative to β_{CS} cooperates with the increase of electronegativity of the heteroatom to yield a very large stabilization of the third π level, ca. 3 eV.[22] When passing from thiophene to pyrrole, it turns out that the stabilizing effect due to the bond contributions dominates over the destabilizing inductive effect of the NH group, and the level is stabilized by ca. 1 eV.[22,27] In this paper, however, we deal primarily with levels related to the two first π orbitals, $a_2(\pi)$ and $b_1(\pi)$.

So far we have not considered the effects due to a possible deviation from Koopmans' approximation (1). Niessen et al.[22,27] have recently calculated "Koopmans' defects" for furan, pyrrole, thiophene, and others, by means of highly sophisticated many-body perturbation theory. They obtained very small corrections for the $a_2(\pi)$ levels, in agreement with the close correspondence between calculated ab initio orbital energies and measured ionization potentials shown in Figure 6. This means that the analysis based on (2) is valid. The corrections obtained for the inner π levels were not negligible, but the shifts of the calculated ionization potentials were in all cases well predicted by the shifts of the corresponding orbital energies. This indicates that a description of the trends in the PE spectra of these compounds in terms of MO theory is reasonable.

HMO Model. The discussion given in the preceding paragraph of this section attempts to explain why the effects of replacement of sulfur or selenium atoms in compounds like **1–6** by NH groups cannot be described by simple perturbation theory. Any reasonable model must include the large inductive

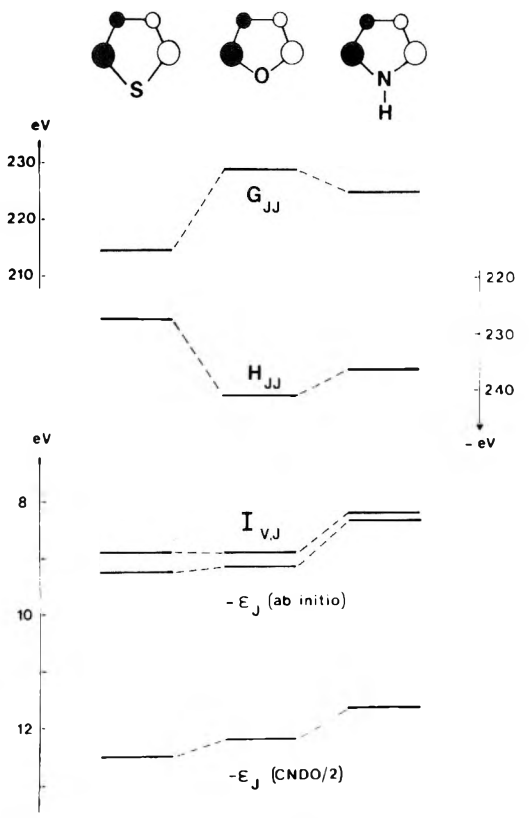


Figure 6. Top: Correlation of the calculated values of H_{JJ} and G_{JJ} (see the text) for the $a_2(\pi)$ orbitals in thiophene, furan, and pyrrole. The results were obtained by the CNDO/2 method and are based on the experimental geometries given in ref 25. Note that the values for H_{JJ} are negative. Bottom: Correlation of the measured ionization potentials $I_{V,J}$ and of the calculated orbital energies $\epsilon_J = H_{JJ} + G_{JJ}$ for the $a_2(\pi)$ levels in thiophene, furan, and pyrrole. The ab initio results are taken from ref 22 and 27; the CNDO/2 results correspond to the results mentioned above.

effect of the NH group on the carbon frame. Eland[6] has proposed a parametrization of the HMO model which leads to good agreement with the first few PE bands of pyrrole, indole, and aniline. This parametrization employs α_C values of smaller magnitude than the value −7.0 eV derived for thiophene and selenophene in the preceding section: $\alpha_C = -6.37$ eV and $\alpha_C^{adj} = \alpha_C - 0.27$ eV.[31] This is consistent with the destabilizing tendency described above (Elands's choice was not based on this argument, however; he was unable to obtain a good agreement for thiophene). The remaining parameters proposed by Eland are $\beta_{CC} = \beta_{CN} = -2.70$ eV and $\alpha_N = \alpha_C + \beta_{CC} = -9.07$ eV. It is interesting to note that this α_N value is not very different from the value −9.4 eV obtained for α_S,[21] indicating that the effective electronegativities are in fact quite similar (see also ref 5c, p 127).

We have performed a calculation using Eland's parameters on pyrrolo[2,3-*b*]pyrrole (**9**), and the results are in good agreement with experiment; see Table II.[32] We take this as an indication that the parametrization may be adequate for the series **7–11.** We apply Eland's parameters in the following way: for all atoms and bonds in a pyrrole fragment in **7–11** we use Eland's values, and in the remaining portions we keep the parameters derived in the previous section. It should be noted that the parameters lead to an underestimation of the binding energy of the third π level in the PE spectrum of pyrrole (~13.7 eV[27]); accordingly, we limit our attention primarily to the first three levels in **7–11** which are related to the first two levels in pyrrole.

Results and Discussion. The results of the calculations are listed in Table II, where also the results of a MINDO/3 calculation on **9** are included. The comparison of the observed and calculated energies shows that the HMO model, being pushed that far, is able to yield a very reasonable agreement with experiment. A correlation diagram of the first three PE bands in the series of [2,3-*b*]-fused compounds **1, 7, 9, 8,** and **4** is presented in Figure 7, and the corresponding diagram based on the HMO results is given in Figure 8. It is apparent that a number of significant trends are reproduced by the calculation, as discussed in the following. Successive replacement of sulfur atoms in **1** by NH groups to yield **7** and **9** is predicted to lead to a destabilization of the three highest occupied π levels, consistent with the destabilization of the two highest occupied π levels of pyrrole relative to the corresponding levels in thiophene. This is due primarily to the general shift toward lower binding energies introduced by the use of smaller α_C magnitudes for the pyrrole fragments. The two highest occupied near-degenerate π levels of **1** are predicted to experience very different shifts, leading to a considerable split of the levels as observed in the PE spectra (Figures 5 and 7). The a_2 level is destabilized more than the b_1 level, which means that the order is being reversed in the series **1–7–9.** A similar crossing was predicted in the series **1–3–4** (see Figure 4), although mainly for a different reason. The different shifts of the two levels are in the present case largely due to the difference in C–X bonding characteristics; the C–X bond contributions of the b_1 orbital are small and tend to cancel, while the a_2 orbital is significantly C–X antibonding. The large increase (0.90 eV) of the magnitude of β_{CN} relative to β_{CS} does thus produce a destabilization in the case of the a_2 level. Another factor contributing to the predicted splitting is the circumstance that the magnitude of the α_N value employed is actually somewhat less (0.34 eV) than the magnitude of α_S; this destabilizes the a_2 level relative to the b_1 level due to the large difference in amplitude on the heteroatoms; see Figures 4 and 8. The results of the MINDO/3 calculations listed in the tables also correspond to a larger destabilization of the a_2 level than of the b_1 level, although the difference is small. We thus tend to assign the ordering of these levels as indicated in Figures 7 and 8 and in Table II.

The fourth and fifth π levels are significantly C–X bonding, and a stabilization of these levels due to the increase of the magnitude of β_{CN} relative to β_{CS} is predicted to dominate over the destabilizing effects. As mentioned above, the predicted stabilization of these levels is expected to be underestimated as in the case of the third π level of pyrrole. The shifts of band ④ in the PE spectra are nevertheless quite accurately predicted by the shifts of the calculated fourth π level; see the tables. We consider it likely that this π level is involved in the ionization process corresponding to band ④, probably overlapping the onset of the σ levels.

The results for the series **4–8–9** can be understood in similar terms as the results for the series **1–7–9.** The increase of the magnitude of β_{CN} relative to β_{CSe} is very large (1.30 eV) and the increase of the magnitude of α_N relative to α_{Se} is also considerable (0.57 eV). This means that a domination of the stabilizing contributions is predicted already for the third π level; see Figure 8. The observed shifts of this level are not monotonic, however; see Figure 7. Successive replacement of the selenium atoms in **4** by NH groups to yield **8** and **9** shifts band ③ in the PE spectrum first toward lower, then toward higher binding energies, yielding a small overall shift toward higher binding energies. Such a behavior is hinted by the calculated results, and can be explained by a large distortion of the third π orbital in **8** which introduces a C–N antibonding contribution; see Figure 8.

Concluding Remarks

The results of the simple model not only describe a number of qualitative trends, but are also in satisfactory numerical

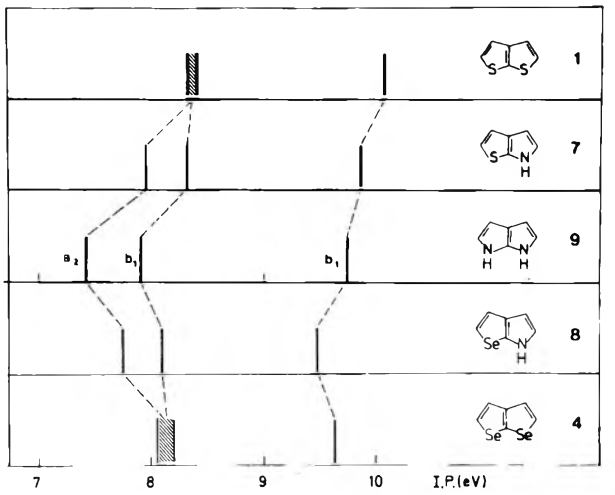


Figure 7. Correlation of the observed first three ionization potentials in the series **1–7–9–8–4**; see the tables.

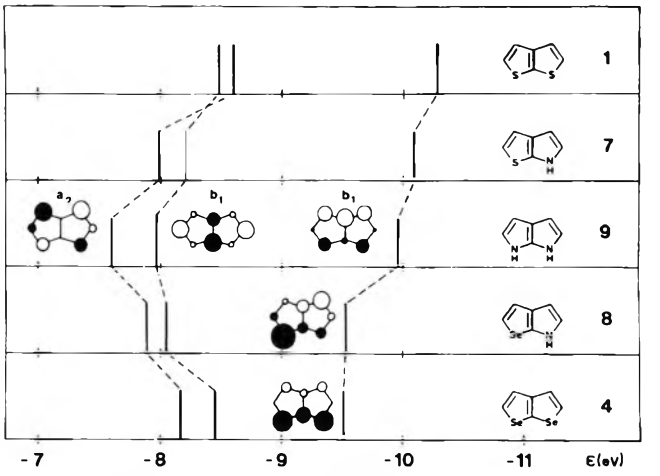


Figure 8. Correlation of the calculated energies of the three highest occupied HMO levels for the series **1–7–9–8–4**; see the tables. The shape of the important orbitals is indicated schematically.

agreement with the PE data. This is illustrated by the linear regression of the measured ionization potentials on the calculated orbital energies for all the compounds **1–11**; see Figure 9 (the linear regression coefficient is 0.993 and the standard deviation is 0.158 eV). The overall satisfactory performance of the model invites further confidence in the basic concepts behind it.

We may thus conclude that a description of the effects of the heterogroup NH relative to heteroatoms from group VI requires specific attention to the interactions taking place in the σ electron system. In particular, the large polarity of the N–H bond tends to increase the electron density on the ring atoms, implying a large destabilizing inductive effect on the carbon atom frame and a large reduction of the effective electronegativity of the NH group compared with the nitrogen atom. These effects can be described in terms of simple MO theory, which yields a good agreement with the PE data for the series **1–11**. It appears that little evidence for these effects can be found from a study of electronic absorption spectra, since the influence on the excited states is similar to the influence on the ground state; this is indicated by the result that calculations with no representation of the effects described above give reasonable excitation energies.[33] We wish furthermore to point out that no direct conclusions regarding the "aromaticity" or "reactivity" of these compounds should be drawn from the present results, since these questions are probably much too complex to be meaningfully discussed in terms of one-electron properties.[34]

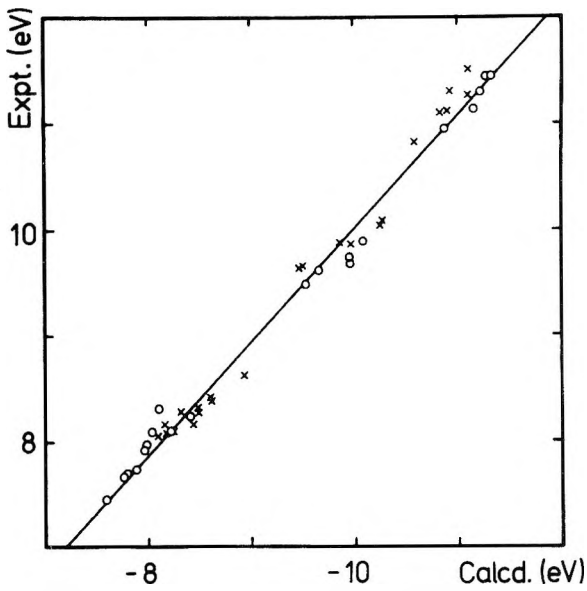


Figure 9. Linear regression of the experimental ionization potentials on the calculated HMO orbital energies for the compounds **1–11**; see the tables. The crosses correspond to the compounds **1–6**, and circles correspond to the NH containing species **7–11**.

III. Experimental Section

The compounds **3–11** were prepared according to the prescriptions in the literature.[8–13]

The PE spectra were recorded on a PS 18 photoelectron spectrometer (Perkin-Elmer Ltd., Beaconsfield) equipped with a heated probe. In the case of **9** the sample was heated to 105 °C; in the remaining cases the temperature was close to 30 °C. The spectra were calibrated with argon, and a resolution of about 20 meV on the argon line was obtained. Each spectrum was recorded several times to ensure the reproducibility of the results.

Calculations. The HMO[5] calculations were carried out on a Hewlett-Packard 9800-30 computer. The parameters applied are discussed in detail in the paper. The EWMO,[17,18] CNDO/2,[19] and MINDO/3[20] calculations were performed on the IBM 370/168 computer at the computing center of the TH Darmstadt, using double precision versions of computer programs published by QCPE, Indiana University. The standard parameters inherent in the programs were employed.[18–20]

For the calculations on furan, pyrrole, and thiophene the geometries determined by microwave spectroscopy[25] were employed. In case of the compounds **1–11** the geometries were estimated from the experimental geometries of thiophene,[25] selenophene,[35] and pyrrole[25] by simple fusion of the constituent rings. For the "mixed" compounds **3, 5, 7, 8, 10,** and **11** the length of the central C–C bond was taken as 1.37 Å.

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Registry No.—Furan, 110-00-9; pyrrole, 109-97-7; thiophene, 110-02-1; selenophene, 288-05-1.

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Novel Aromatic Systems. 9.[1a] Proton and Carbon-13 Nuclear Magnetic Resonance Spectroscopic Study of the Heteroaromatic 6π 1,3-Dioxolium (Dithiolium) and 10π Benzo-1,3-dioxolium (Dithiolium) Ions

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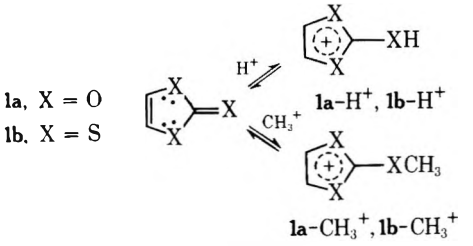
The 6π heteroaromatic character of protonated (HSO_3F–SbF_5–SO_2) and methylated (CH_3F–SbF_5–SO_2) vinylene carbonate (**1a**) and its trithio analogue (**1b**) is investigated by ^1H and ^{13}C NMR spectroscopy. The 10π heteroaromatic character of the benzo derivative of **1a** in addition to the parent 1,3-benzodioxolium ion (**4**) and 1,3-benzodithiolium ion (**5**) has also been studied.

Aromatic character has been frequently attributed to molecules in which lone pair electrons on heteroatoms enter into conjugation with unsaturated bonds forming stable Hückel-type aromatic systems.[2] Heterocyclic compounds containing oxygen and sulfur represented by the 1,3-dioxolium and 1,3-dithiolium ions (as well as parent compounds) should, as 6π-electron systems, be quite stable. Few examples of substituted 1,3-dioxolium cations[3] have been reported in contrast to extensive reports concerning the 1,3-dithiolium salts.[4] The reactivity and electronic spectra of "pseudoaromatic" sulfur compounds have been studied using simple MO–LCAO methods.[5] We therefore thought it of interest to examine the ionic systems resulting from protonation and methylation of vinylene carbonate (**1a**) and 1,3-dithia-2-thione (**1b**). In addition, we have extended our studies to include 10π electron systems, 2-hydroxy-1,3-benzodioxolium ion (**2**-H^+), the parent 1,3-benzodioxolium ion (**4**), and 1,3-benzodithiolium ion (**5**).



Results and Discussion

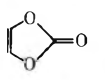
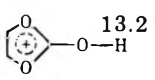
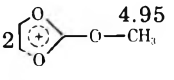
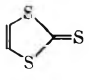
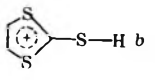
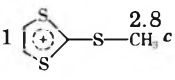
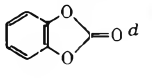
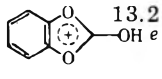
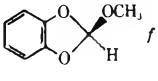
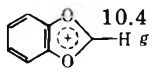
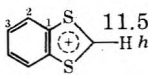
Protonated and methylated ions, respectively, were prepared from their corresponding precursors with the general methods developed previously.[6a,b] ^1H and ^{13}C NMR data, for the precursors and the ions studied, are summarized in Tables I and II, respectively.

6π Heteroaromatic Ions. Stable ions result from protonation (**1a**-H^+, **1b**-H^+) using FSO_3H–SbF_5–SO_2 solution and, methylation (**1a**-CH_3^+) using CH_3F–SbF_5 "complex" in SO_2 solution at −60 °C. Methylated ion (**1b**-CH_3^+) was studied as the stable iodide salt[7] in SO_2 solution. Methylation of **1b** with CH_3F–SbF_5 "complex" in SO_2 solution resulted in, as yet, unidentifiable species in the ^1H NMR spectrum.

We consider the carbon-13 chemical shifts of ring carbons to be quite informative concerning trends of charge delocalization since extensive evidence has resulted indicating the sensitivity of charge and ^{13}C NMR shifts.[8] The assignment of resonances was made by the now familiar procedure of Grant and co-workers.[9,10] When needed, "off-resonance" proton decoupled spectra were obtained to assure correct peak assignments.

Vinylene carbonate (**1a**) in 1:1 M/M FSO_3H–SbF_5 in SO_2 solution was found to be protonated on the carbonyl oxygen. The ^1H NMR spectrum at −60 °C consisted of two peaks, one at δ 8.2 ppm of relative area 2, and one at δ 13.2 ppm of area 1. In addition, the olefinic protons are deshielded by 1.3 ppm

Table I. ^{1}H NMR Parameters of Heteroaromatic Ions[a]

Precursor	Heteroaromatic ion
7.2 	8.2  13.2
	8.2  4.95
7.5 	8.5  [b]
	8.1  2.8 [c]
7.2–7.25 (m)  [d]	8.0  13.2 [e]
7.1 3.62  [f]	8.1–8.2  10.4 [g]
	7.95–8.9  11.5 [h]

[a] In parts per million (δ) from external Me_4Si (capillary). Protonated in FSO_3H–SbF_5–SO_2 at −60 °C. Methylated with CH_3F–SbF_5 "complex"–SO_2 at −40 °C. [b] Not observable. [c] Methylated species studied as stable iodide salt in SO_2 solution at −40 °C. [d] In SO_2ClF at −10 °C. [e] Protonated in FSO_3H–SbF_5–SO_2ClF at −80 °C. [f] In CCl_4, ambient probe temperature. [g] Ion prepared in FSO_3H–SO_2 at −70 °C. [h] In CD_3CN, ambient probe temperature.

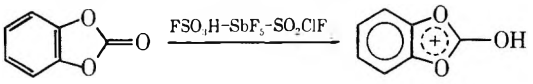
when compared to the neutral molecule in SO_2 solution. This additional deshielding suggests the presence of a significant ring current, the resulting ion being a 6π-electron heteroaromatic system. Methylation of **1a** resulted only by using CH_3F–SbF_5 "complex" in SO_2 solution while other methylating agents [$HC(OCH_3)_2^+PF_6^-$–SO_2, $(CH_3)_3O^+BF_4^-$–SO_2, CH_3OSO_2F–SO_2] proved unsuccessful. The ^{1}H NMR spectrum of **1a**-CH_3^+ at −60 °C consisted of two signals, one at δ 8.2 ppm with relative area 2, and one at δ 4.95 ppm of area 3. Again one observes the same downfield absorption of the olefinic protons due to significant charge delocalization into the ring.

^{13}C NMR parameters for vinylene carbonate (**1a**) show significant shielding of the carbonyl carbon (δ^{13}C 154.8) due most probably to the proximity of lone pair electrons on the adjacent heteroatoms. The carbonyl shift is very similar in ethylene carbonate, the saturated analogue of **1a**.[11] The olefinic carbons appear at δ^{13}C 132.2, a resonance value typical of sp^2 carbons of substituted alkenes and aromatics.[11] Upon protonation, the carbon-13 chemical shifts for the 1,3-dioxolium ion formed are deshielded by 6.1 ppm for the olefinic carbons and 9.5 ppm for the carbonyl carbon. Carbon-13 chemical shifts for methylated vinylene carbonate (**1a**-CH_3^+) show striking shift differences for the carbonyl carbon when compared to **1a** and **1a**-H^+, while the olefinic carbon shift is the same as that of **1a**-H^+. Carbon-13 chemical shifts for the 1,3-dioxolium ion formed are deshielded by 3.1 ppm for the olefinic carbons and 27.0 ppm for the carbonyl carbon.

Protonation of 1,3-dithia-2-thione (**1b**) in 1:1 M/M FSO_3H–SbF_5 in SO_2 solution occurred on the thiocarbonyl sulfur. The ^{1}H NMR spectrum at −60 °C consisted of only one peak at δ 8.5 ppm assigned to the olefinic protons, while the protonated sulfur resonance could not be observed even at the lowest accessible temperatures. Methylation of **1b** with iodomethane yielded a stable iodide salt soluble in an SO_2 solution. Methylated species (**1b**-CH_3^+) at −40 °C showed two NMR signals, one at δ 8.1 ppm with relative area 2, and one at δ 2.8 ppm of area 3.

^{13}C NMR parameters for 1,3-dithia-2-thione (**1b**) show significant shielding of the thiocarbonyl group appearing 14.1 ppm upfield of the carbonyl carbon contained in the oxygen analogue. Protonated species (**1b**-H^+) resulted in downfield shifts of 6.3 ppm for olefinic carbons and 4.5 ppm for the thiocarbonyl carbon. The downfield shifts observed for olefinic carbons (4.0 ppm) and the thiocarbonyl carbon (8.8 ppm), along with protonation parameters, indicate greater ability of sulfur to accept a positive charge when compared to oxygen in this aromatic series.[12]

10π Heteroaromatic Ions. When catechol carbonate (**2**) in SO_2ClF is added to a SO_2ClF–FSO_3H–SbF_5 solution at −78 °C an amber-colored solution results which gave a ^{1}H NMR spectrum consisting of two singlets, one at δ 8.0 of relative area 4 corresponding to aromatic ring protons and δ 13.2 of area 1 assigned to the protonated carbonyl (C=$^+$OH). The aromatic

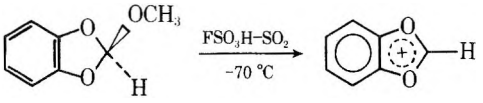


2 **2**-H^+

protons of **2**-H^+ are deshielded approximately 0.8 ppm from precursor **2**. The protonated carbonyl was observed only at low temperatures (≤−80 °C), presumably a result of rapid exchange with the superacid solvent system. To verify the structure of **2**-H^+, the ^{13}C NMR spectrum was obtained. The aromatic carbons C-1 (δ^{13}C 113.6) and C-2 (δ^{13}C 130.3) are deshielded by $\Delta\delta C_1$ 2.0 and $\Delta\delta C_2$ 4.2, respectively. The protonated carbonyl δ^{13}C 165.1 ppm is deshielded by 12.6 ppm from the precursor.

The ^{13}C NMR data obtained for **2**-H^+ (a 10π system) are useful for comparison to the ^{13}C NMR data obtained for 2-hydroxy-1,3-dioxolium ion (**1**-H^+) (a 6π system). The protonated carbonyl of **2**-H^+ is only slightly deshielded from that of **1**-H^+, $\Delta\delta$C 0.8 ppm.

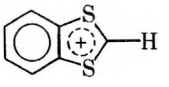
The parent 1,3-benzodioxolium ion (**4**) was prepared in FSO_3H–SO_2 from 2-methoxy-1,3-benzodioxole (**3**).[13,14]



3 **4**

The ^{1}H NMR spectrum of **4** consists of two singlets at δ 8.1 and 8.2 deshielded approximately 1.0 ppm from the precursor (**3**) and a sharp singlet for the methine H, δ 10.4. The ^{13}C NMR spectrum of **4** confirms the assigned structure since only four ^{13}C NMR peaks are observed for this symmetrical ion. Aromatic ring carbons C-2 (δ^{13}C 114.8) and C-3 (δ^{13}C 132.3) are deshielded 6.8 and 10.6 ppm from corresponding carbons of precursor **3**. The δ^{13}C 170.4 for C^+ is deshielded by 51.9 ppm from the precursor ^{13}C NMR value.

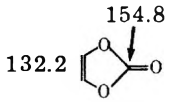
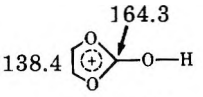
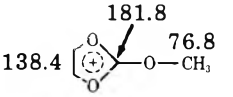
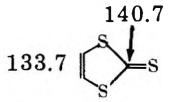
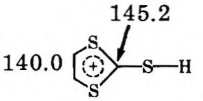
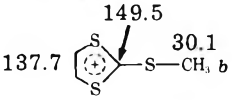
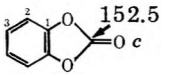
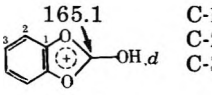
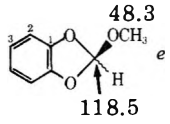
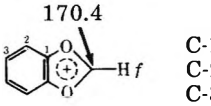
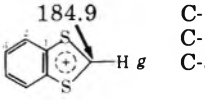
We also studied the sulfur analogue of **4**, the parent 1,3-benzodithiolium ion (**5**). Ion **5** was studied as the stable perchlorate salt[15] which proved to be readily soluble in CD_3CN.



5

The ^{1}H NMR spectrum of **5** consists of a series of multiplets δ 7.95–8.9 of relative area 4 and a sharp singlet at δ 11.5 of area 1 assigned to the methine proton. The ^{13}C NMR data for **5** may be compared to those of the all-oxygen analogue (**4**) as an indication of the extent of relative charge delocalization into the aromatic ring. Ring carbon C-2 (δ^{13}C 127.7) is deshielded by 12.9 ppm from the C-2 ^{13}C NMR value for **4** whereas ring carbon C-3 (δ^{13}C 131.8) is slightly shielded, $\Delta\delta$C 0.5. The C^+ ^{13}C NMR value (δ^{13}C 184.9) for **5** is deshielded by 14.5 ppm compared to the C^+ value for ion **4**, indicating rela-

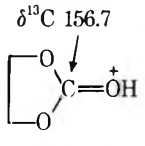
Table II. ^{13}C NMR Parameters of Heteroaromatic Ions[a]

Precursor	Heteroaromatic ion
	 
	 
 C-1 144.4 C-2 111.6 C-3 126.1	 C-1 143.7 C-2 113.6 C-3 130.3
 C-1 146.0 C-2 108.0 C-3 121.7	 C-1 144.4 C-2 114.8 C-3 132.3
	 C-1 145.5 C-2 127.7 C-3 131.8

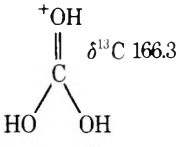
[a] In parts per million from external Me_4Si (capillary). Protonated in FSO_3H–SbF_5–SO_2 at −60 °C. Methylated with CH_3F–SbF_5 "complex"–SO_2 at −40 °C. [b] Methylated species studied as stable iodide salt in SO_2 solution at −40 °C. [c] In $CDCl_3$, ambient probe temperature. [d] Protonated in FSO_3H–SbF_5–SO_2ClF at −80 °C. [e] In SO_2ClF at −70 °C. [f] Ion prepared in FSO_3H–SO_2 at −70 °C. [g] In CD_3CN, ambient probe temperature.

tively more charge localized on the carbenium center in the all-sulfur analogue **5**.

The protonated carbonyl of ethylene carbonate (**6**) and of carbonic acid (**7**) is analogous to that of protonated vinylene



6



7

carbonate (**1a**-H^+) and protonated catechol carbonate (**2**-H^+). In fact, the ^{13}C NMR shifts $\delta^{13}C$ 156.7 and $\delta^{13}C$ (Me_4Si) 166.3 of **6** and **7** are similar to that of **1a**-H^+ and **2**-H^+[19] which at first would seem to indicate that **1a**-H^+ and **2**-H^+ are only simple protonated carbonates. However, in this case, it is not expected that there would be any charge delocalization into the π bond or the aromatic ring of **1a**-H and **2**-H^+H respectively. Such deshielding, however, evident from the ^{13}C NMR spectra of **1a**-H^+ and **2**-H^+ clearly indicate that **1a**-H^+ and **2**-H^+ are, indeed, 6π and 10π aromatic systems.

Conclusions

Stable oxygen and sulfur heteroorganic ions such as the 1,3-dioxolium ion (6π), 1,3-dithiolium ion (6π), and the 1,3-benzodioxolium ion (10π) result from the protonation in superacid [FSO_3H–SbF_5–SO_2 (SO_2ClF)] of their carbonyl precursors. Vinylene carbonate is methylated with CH_3F–SbF_5 complex in SO_2 solution, whereas 1,3-dithia-2-thione forms a stable iodide salt upon methylation with methyl iodide.

The parent 1,3-benzodioxolium and 1,3-benzodithiolium ions were also prepared and studied by ^1H and ^{13}C NMR spectroscopy. The NMR data indicate significant delocalization of charge over the 6- and 10π systems, respectively. However, at this stage of our understanding of chemical shifts vs. charge distribution relationships, no conclusion can be reached as to the exact nature of the ring currents involved and relative contribution of resonance forms.

Experimental Section

Materials. Starting materials used were commercially available of the highest purity (Aldrich and Strem Chemical Co.).

2-Methylthio-1,3-dithiolium Iodide (1b-CH_3^+). The stable iodide salt was prepared according to the procedure of Klingsberg.[6]

Catechol Carbonate (2). The carbonate was prepared according to the procedure of Huismann.[16]

Preparation of Ions. The protonated ions were prepared by adding the precursor (0.5 mL) to a stirred solution of 1:1 M/M FSO_3H–SbF_5 (1.5 mL) in an equal volume of SO_2 or SO_2ClF at −78 °C. Samples prepared in this manner gave spectra which showed no appreciable chemical shift differences with temperature or small concentration variations. The acid was always in excess as indicated by an acid peak at about δ 10.9 in the ^1H NMR spectrum. The ^{13}C NMR spectra of heteroorganic ions were recorded only if the ^1H NMR data matched the reported values in the literature. For ions not yet reported, the structure of the protonated forms could be established from the ^1H NMR spectral data (chemical shifts, multiplicity patterns, and peak area integration). After obtaining the ^{13}C NMR spectrum, the sample was checked again by ^1H NMR spectroscopy to determine if any decomposition had occurred. Samples studied in FSO_3H–SO_2 solution were prepared by dissolving the precursor (0.5 mL) in SO_2 (0.5 mL). This solution was added dropwise to a rapidly stirred solution of FSO_3H (2 mL)–SO_2 (1 mL) at −78 °C. The acid was always in excess as indicated by an acid peak at about δ 10.8 in the ^1H NMR spectrum.

The methylated ions were prepared by reacting the precursors with the "methyl fluoride–antimony pentafluoride complex" in SO_2 solution, under conditions previously described.[6b]

NMR Spectroscopy. ^1H NMR spectra were obtained on a Varian Associates Model A56/60-A spectrometer equipped with a variable temperature probe. ^{13}C NMR spectra were obtained in part on a modified Varian Associates Model HA-100 spectrometer equipped with a FT-100 Fourier transform accessory (V-4357 pulsing and control unit); a broad-band proton decoupler of 25.14 MHz was derived from a gated power amplifier capable of putting out approximately 80 W into the transmitter coils. The pulse width used was 35 μs, and the pulse interval, 1.5 s. The available computer memory (4000 input channels) and the need to provide multichannel excitation over the region of interest (sweep width 6800 Hz) limited the data acquisition time to 0.2 s.

The free induction signal derived after each pulse is signitized and accumulated in a Varian 620/i computer (8K). Approximately 5000–7000 accumulations were made to obtain each spectrum. Field/frequency regulation was maintained by a homonuclear internal lock system. The lock used was the proton decoupled carbon-13 resonance of a 60% carbon-13 labeled methyl iodide sample contained in a precision coaxially spaced capillary (o.d. ca. 0.2 and 0.4 mm) inserted in the sample NMR tube (5 mm o.d.).

Fourier transformation of the accumulated free induction signal gave the frequency spectrum[17,18] from which was measured the

chemical shift of each signal, relative to the reference methyl iodide signal. All the chemical shifts reported here have been corrected to a Me_4Si reference by the relationship

$$\text{ppm } (Me_4Si) = \frac{H_2 \text{ (obsd)} - 977 - T(°C) \times 0.70}{25.2}$$

The ^{13}C NMR spectra for the remaining heteroorganic ions and precursors were obtained on a Varian Associates Model XL-100 spectrometer equipped with a broad decoupler and variable temperature probe. The instrument operates at 25.2 MHz for carbon-13, and is interfaced with a Varian 620L computer. The combined system was operated in the pulse Fourier transform mode, employing a Varian Fourier transform accessory. Typically 3000–5000 pulses, each of width 20–30 μs, needed to be accumulated in order to give a satisfactory signal to noise ratio for all signals of interest. Field frequency stabilization was maintained by locking on the fluorine-19 external sample of fluorobenzene. Chemical shifts were measured from the carbon-13 signal of 5% carbon-13 enriched tetramethylsilane in a 1.75-mm capillary held concentrically inside the standard 12-mm sample tube.

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

Registry No.—**1a**, 288-53-9; **1a**-H^+, 62139-47-3; **1a**-CH_3^+, 62139-48-4; **1b**, 930-35-8; **1b**-H^+, 62139-49-5; **1b**-CH_3^+, 56125-66-7; **2**, 2171-74-6; **2**-H^+, 62139-50-8; **3**, 6823-42-3; **4**, 39525-29-6; **5**, 274-31-7.

References and Notes

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(14) The ^1H NMR spectrum resulting from the treatment of **3**-SO_2 with FSO_3H–SO_2 deviates from that reported by Volz and Zimmerman.[13] Two singlets, δ 4.8 and 4.5, are observed for dimethoxycarbenium ion (see similar spectral and multiplicity assignments according to Borch[15]) and a singlet δ 4.3 corresponding to the methyl protons of methyl fluorosulfonate.[16]
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Carbon-13 Nuclear Magnetic Resonance Spectra of Bridgehead Substituted Bicyclo[3.3.1]nonanes

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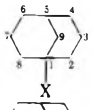
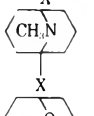
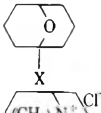
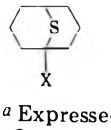
The ^{13}C NMR spectra of several bicyclo[3.3.1]nonanes, 9-methyl-9-azabicyclo[3.3.1]nonanes, 9-oxabicyclo[3.3.1]-nonanes, and 9-thiabicyclononanes with bridgehead substituents are interpreted. Heteroatom bridgehead substituents cause downfield shifts of the resonances for γ-anti carbons 3, 5, and 7 in agreement with previous results for bridgehead substituents and in contrast to the upfield γ-anti shifts induced by heteroatoms in monocycles. Equatorial tertiary hydroxyl groups in cyclohexanols cause downfield shifts of the γ-anti carbons.

Within the last several years, ^{13}C NMR spectroscopy has emerged as a very powerful tool for structural analysis in organic chemistry.[1] The power of this technique derives in large measure from several empirically determined, rather well-ordered types of effects exerted by substituents on the chemical shifts of the various carbon atoms in a particular molecule. For example, it has been demonstrated on numerous occasions that a carbon atom disposed γ-gauche to a methyl group resonates at a relatively higher magnetic field than when it is located γ-gauche to a hydrogen or γ-anti to a methyl group.[2] Steric interactions are usually cited as being responsible for such *upfield* shifts. Interestingly, it has also been found that downfield shifts are observed when the encumbered carbon is separated from its steric antagonist by four bonds.[3] While the experimentally obtained γ and δ "steric" shifts are opposite in direction (thus indicating that the shielding mechanisms include significant contributions from terms of other than a steric nature), their individual consistencies render them very valuable in stereochemical assignments.

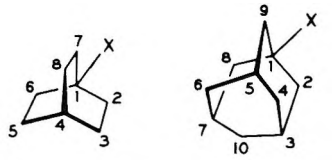
Recently, Eliel and co-workers have disclosed their intriguing findings related to the upfield chemical shifts observed for carbon nuclei γ to a heteroatom.[4] Briefly, their data have confirmed that a *gauche heteroatom* (N, O, F, S, Cl) produces an upfield (steric) shift of a ^{13}C NMR signal *greater* than the upfield shift caused by a gauche carbon group

Table I. Carbon-13 Chemical Shifts for 1-Substituted Bicyclo[3.3.1]nonanes[a,b]

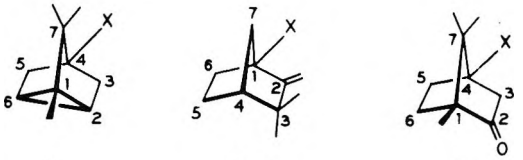
Nucleus	Substituent	C-1	C-2(8)	C-3(7)	C-4(6)	C-5	C-9
	8a, X = H	28.2	31.9	22.8	31.9	28.2	35.2
	8b, X = OH	69.2	39.7	23.1	30.3	32.3	43.6
	8c, X = Cl	71.8	42.1	24.5	29.8	32.9	46.0
	8d, X = CO_2H[c]	41.0	33.2	22.0	30.4	28.0	36.0
	9a, X = H	52.3	26.4	20.4	26.4	52.3	40.9[d]
	9b, X = OH	82.5	33.8	22.0	25.6	57.6	34.2[d]
	9c, X = Cl	90.6	37.6	23.1	25.3	58.9	37.6[d]
	10a, X = H	66.5	29.3	18.8	29.3	66.5	
	10b, X = OH	94.0	36.3	20.6	28.4	72.4	
	10c, X = Cl	99.9	40.2	21.7	27.8	74.2	
	11a, X = H	65.0	27.2	18.4	27.2	65.0	53.0[d]
	11b, X = Cl	93.8	38.8	22.0	26.6	73.3	50.2[d]
	12a, X = H	33.2	32.1	21.6	32.1	33.2	
	12b, X = OH	76.9	41.1	23.4	30.8	40.8	

[a] Expressed in parts per million. [b] Compounds 8–10 measured in $CDCl_3$ with internal Me_4Si; compound 11 measured in D_2O with external $NaO_3S(CH_2)_3Si(CH_3)_3$. [c] Signal for CO_2H, 185.9. [d] Chemical shift for NCH_3.

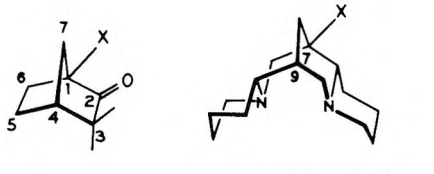
(methyl or methylene); moreover, their investigation has demonstrated that a carbon atom situated γ-anti to a *second row heteroatom* (N, O, F) generally resonates at a significantly higher field than a carbon nucleus located γ-anti to a methyl or methylene group or to a third row heteroatom (S, Cl). As pointed out by Eliel et al., the only exceptions at that time[5] to the shielding γ-anti effects occurred in systems having the heteroatom attached to a bridgehead carbon as reported by Maciel and co-workers for the bicyclo[2.2.2]octane (**1**) and adamantane (**2**) frameworks.[8] Subsequent to Eliel's survey,[4]



1 **2** **3**



4 **5a** **5b**



5c **6a**: X = H **6b**: X = OH

the ^{13}C NMR spectra of some bridgehead functionalized derivatives in the bicyclo[2.2.1]heptane nucleus [i.e., norbornanes (**3**),[9a] tricyclenes (**4**),[9b] camphenes (**5a**),[9c] camphors (**5b**),[9d] and camphenilones (**5c**)[9e]] have been studied; both downfield and upfield γ-anti shifts were observed with these substrates. Also, the conversion of α-isospartein (**6a**) to 7-hydroxy-α-isospartein (**6b**) results in a 1.3-ppm upfield shift of the bridgehead carbon (9).[10,11]

Significantly, all the compounds in Eliel's survey[4] have the heteroatom attached to primary or secondary carbon atoms. By necessity, all bridgehead substituents are attached to tertiary carbons. The following data indicate that changing from primary or secondary substrates to tertiary compounds reverses the direction of the γ-anti effect for monocyclic systems also.

In order to gain additional information pertaining to the directions and magnitudes of the γ-anti effect of bridgehead substituents we have measured the magnetic resonances of the carbon atoms of a few 1-substituted bicyclo[3.3.1]nonanes. In addition, we have studied the ^{13}C NMR of several substrates with a heteroatom (N, O, S) incorporated into the molecular framework at the 9 position of the bicyclo[3.3.1]-nonane system.[6,12] The heterobicyclic materials were chosen for study in order to ascertain whether or not the ring heteroatom (which is part of the antiperiplanar arrangement; see formula **7a**) would alter significantly the γ-anti effects found

7a **7b**

for the parent carbobicyclic counterparts. Furthermore, the bicyclo[3.3.1]nonane geometry contains a second γ-anti arrangement (see structure **7b**) which, because of differences in bond angles and lengths,[13] could give rise to γ-anti effects different from those exhibited by **7a**.

Results and Discussion

Table I collects the chemical shift data for the various 1-substituted bicyclo[3.3.1]nonanes we have examined. The assignments of the chemical shifts are based on the relative intensities of certain signals, splitting patterns observed with fully coupled spectra, and general, well-documented substituent effect trends.[1] Table II lists the specific effects of bridgehead substituents on the chemical shifts of the carbon atoms.

Carbobicyclic Compounds. The conversion of hydrocarbon **8a** to bridgehead alcohol **8b** results in carbon 5 being deshielded by 4.1 ppm while carbon 3(7) is shifted downfield by only 0.3 ppm. Likewise, the transformation of **8a** to chloride

Table II. Bridgehead Substituent Effects for Bicyclo[3.3.1]nonanes[a,b]

Compd	Function	C-1	C-2(8)	C-3(7)	C-4(6)	C-5	C-9
8b	OH	41.0	7.8	0.3	−1.6	4.1	8.4
8c	Cl	43.6	10.2	1.7	−2.1	4.7	10.8
8d	CO_2H	12.8	1.3	−0.8	−1.5	−0.2	0.8
9b	OH	30.2	7.4	1.6	−0.8	5.3	−6.7[c]
9c	Cl	38.3	11.2	2.7	−1.1	6.6	−3.3[c]
10b	OH	27.5	7.0	1.8	−0.9	5.9	
10c	Cl	33.4	10.9	2.9	−1.5	7.7	
11b	Cl	28.8	11.6	3.6	−0.6	8.3	−2.8[c]
12b	OH	43.7	9.0	1.8	−1.3	7.6	

[a] Chemical shifts for substituted compound minus chemical shifts for parent, expressed in parts per million. [b] Negative values indicate upfield shifts. [c] For NCH_3.

Table III. Survey of γ-Anti Effects of Bridgehead Substituents[a,b]

	Type I[c]				Type II[c]				
Compd	Carbon	X = OH	X = Cl	X = CO_2H	Carbon	X = OH	X = Cl	X = CO_2H	Ref
1					3(5,8)	0.4	2.2	−1.5	8
2	3(5,7)	4.1	4.7	−0.2					8
3	4	−1.6	−1.6	1.4	3(5)	0.5	1.1	0.2	9a
4	1	3.5	1.2	1.7					**9b**
4	2(6)	−1.4	−1.3	−1.0					
5a	4	−2.9	−2.1	0.4	3	0.3	1.0	1.2	9c
5a					5	1.1	1.9	0.7	
5b	1	1.1	0.5	−0.9	2	−2.7	−5.6	−2.7	9d
5b					6	−2.0	−1.3	−0.8	
5c	4	−4.1	−2.6	−0.9	3	−0.6	0.4	1.2	9e
5c					5	5.2	8.7	3.7	
8	5	4.1	4.7	−0.2	3(7)	0.3	1.7	−0.8	

[a] Expressed in parts per million. [b] Negative values indicate upfield shifts. [c] See text for explanations of types.

8c produces downfield shifts of 4.7 and 1.7 ppm for carbons 5 and 3(7), respectively. Thus, it appears that the type of γ-anti arrangement (i.e., **7a** or **7b**) can be important. For convenience the γ-anti effect produced by the arrangement depicted in **7a** is classified as *type I* (the γ-anti carbon is a bridgehead carbon) while the γ-anti effect corresponding to **7b** is defined as *type II* (the γ-anti carbon is not a bridgehead carbon). To help visualize how the two types of γ-anti effects found for alcohol **8b** and chloride **8c** relate to the results of previous reports dealing with bridgehead substituted carbobicyclic systems, Table II has been assembled. First of all, it is interesting to note that the type I γ-anti effects for the very similar frameworks adamantane (**2**) and bicyclo[3.3.1]nonane (**8**) are *identical* (as are the corresponding α and β substituent effects[8b]). Perhaps this fact indicates that the small differences in the pertinent corresponding bond angles or bond distances are inconsequential in the transmission of the γ-anti substituent effect. The other type I effects shown in Table III are mostly shielding. Perhaps the change in direction of the γ-anti effects of the bicyclo[2.2.1]heptane substances (**3–5**) compared to the bicyclo[3.3.1]nonane substrates (**2** and **8**) reflects the substantial difference in CCC angle at the carbon joining the bridgehead carbons: 93.1° in the case of **3** (X = H) and 111.3° for **8a**.[13] However, the tricyclene system (**4**) remains anomalous even though it is geometrically similar to the norbornane skeleton.[13b] Clearly, more data are needed before a general explanation of the type I γ-anti effect can be advanced reliably. On the other hand, there does seem to be a unifying trend for the type II γ-anti effects: for the hydroxy and chloro substituents the shifts are generally deshielding, with a chlorine producing a shift about 1 ppm greater in magnitude than a hydroxyl group.

Heterobicyclic Materials. Previous reports on 9-heterobicyclo[3.3.1]nonanes have not considered the effects of bridgehead functionality on the chemical shifts of the carbons comprising the bicyclic systems.[6,12a–c,e] Examination of the data contained in Tables I and II reveals some interesting trends. Again, the type I γ-anti effects are substantially greater in magnitude than the type II γ-anti effects. For the bridgehead hydroxy derivatives the differences between the type I and type II γ-anti effects are 3.7 ppm for the 9-aza skeleton (**9**), 4.1 ppm for the 9-oxa skeleton (**10**), and 4.8 ppm for the 9-thia skeleton (**12**). These values compare favorably with the related difference of 3.9 ppm found for the carbobicyclic system (**8**). For the bridgehead chloro substrates the differences between the type I and type II γ-anti effects are slightly larger than those found for the hydroxy derivatives (3.9 ppm for **9c** and 4.8 ppm for **10c**) and are somewhat greater than that found for the carbobicyclic system (3.0 ppm for **8c**). An attractive rationalization of the observed differences in the magnitudes of the type I and type II γ-anti effects is based upon the geometrical freedom of the bicyclo[3.3.1]nonane framework: the type I arrangement (**7a**) allows only for bond angle and/or bond length changes, but no changes in the dihedral angle formed by the two planes X–C(1)–C(9) and C(1)–C(9)–C(5) which must remain near 180°. However, for the type II arrangement (**7b**), the dihedral angle formed by the planes X–C(1)–C(2) and C(1)–C(2)–C(3) can vary. In fact, for most of the compounds we report this angle is probably less than 180° due to flattening of the six-membered rings to relieve the C(3)–C(7) steric interactions.[13a] Interestingly, the cationic nature of the *N,N*-dimethylazonia derivative **11b** appears to have little effect on the difference between the type I and type II effects relative to the parent *N*-methylamine derivative **9c** (4.7 vs. 3.9 ppm, respectively).

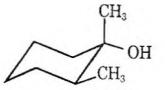
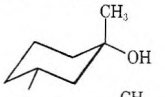
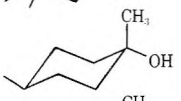
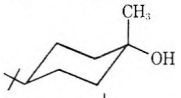
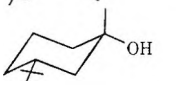
Analysis of the data on the type I and type II γ-anti effects

Table IV. Differences in Bridgehead Substituent Effects between Corresponding 9-Heterobicyclo[3.3.1]nonanes and Bicyclo[3.3.1]nonanes[a]

Entry	Comparison	C-1 (α)	C-2(8) (β)	C-3(7) (γ-II)	C-4(6) (δ)	C-5 (γ-I)
1	**9b–8b**	−10.8	−0.4	1.3	0.8	1.2
2	**9c–8c**	−5.3	1.0	1.0	0.5	1.9
3	**10b–8b**	−13.5	−0.8	1.5	0.7	1.8
4	**10c–8c**	−10.2	0.7	1.2	0.6	3.0
5	**11b–8c**	−14.8	1.4	1.9	1.5	3.6
6	**12b–8b**	2.7	1.2	1.5	0.3	3.5

[a] Substituent effects for the 9-heterobicyclo[3.3.1]nonanes minus the substituent effects for the bicyclo[3.3.1]nonanes expressed in parts per million.

Table V. γ-Anti Effects for Tertiary Hydroxyl Groups

Compd	δ[a]	Reference δ(CH_3 ref)[b]	Reference δ(H ref)[c]	γ effect CH_3 ref[d]	γ effect H ref[e]	Item
	C-3 32.2[f]	31.9[g]	32.1[g]	0.3	0.1	1
	C-5 24.3[f]	23.4[g]	24.3[g]	0.9	0.0	2
	C-3 30.6[f]	28.9[g]	27.6[g]	1.7	3.0	3
	C-5 23.8[f]	23.2[g]	21.3[g]	0.6	2.5	4
	C-3,5 32.4[f]	*i*	31.5[h]	*i*	0.9	5
	C-3,5 25.1[f]	*i*	22.6[h]	*i*	2.5	6
	C-3 45.8[f]	*i*	43.4[h]	*i*	2.4	7
	C-5 24.0[f]	*i*	22.3[h]	*i*	1.7	8

[a] Chemical shift, parts per million from Me_4Si, of designated carbon. [b] Chemical shift, parts per million from Me_4Si, of designated carbon in reference compound wherein the OH group is replaced by CH_3. [c] Chemical shift, parts per million from Me_4Si, of designated carbon in reference compound wherein the OH group is replaced by H. [d] γ-Anti effect, parts per million, relative to CH_3 reference compound. [e] γ-Anti effect, parts per million, relative to H reference compound. [f] Reference 15. [g] From Table 3.5, p 65, ref 1, based on primary data reported in ref 2b. [h] Calculated values for standard compounds obtained as described in ref 4, footnote 24. [i] The γ-anti effects relative to CH_3 are not entered in the table for items 5–8. The calculated resonances of the pertinent carbons in the CH_3 reference compounds would be the same as for the H reference compounds since the effect of an equatorial methyl group on the γ ring methylene is negligible. Accordingly, the calculated γ-anti effects will be the same for both reference series.

from the viewpoint of comparing directly the heterobicyclic and carbobicyclic materials indicates that the heterobicyclic compounds show consistently greater deshielding effects than the corresponding carbobicyclic substrates (Table IV). The other comparisons assembled in Table IV show that the α effects of the carbobicyclics are substantially more deshielding than the heterobicycles, except for sulfur; the β effects are slightly more deshielding in the case of a bridgehead hydroxy substituent and slightly less deshielding with a bridgehead chloride atom; the δ effects of the carbobicyclic compounds are all slightly less deshielding than those of the heterobicyclic substances.

Conclusions and Comparisons with Monocyclic Compounds. The consistency of our results for the substituent effects in these bicyclic compounds is quite good. In particular, replacement of a bridgehead hydrogen with chlorine or hydroxyl causes a downfield shift in the resonances of carbons 3, 5, and 7. In a single example a bridgehead carboxyl group causes a slight upfield shift of the resonances of these carbons.[14]

Since the shifts caused by bridgehead hetero substituents are opposite in direction to those caused by the same functions in monocyclic systems, we must inquire of the reasons for the difference. The key parameter seems to be the degree of substitution of the carbon bearing the hetero substituent. Every example in the survey of γ-anti effects in monocyclic systems[4] has the hetero substituent placed on a primary or secondary carbon. By necessity all examples of bridgehead substituted compounds have the hetero function on a tertiary carbon. Recently, Senda et al. have analyzed the ^{13}C NMR spectra of some tertiary cyclohexanols. Selected compounds from their study form the basis of Table V. The chemical shifts of carbon atoms γ-anti to an equatorial hydroxyl group are compared to the chemical shifts of the analogous carbons in hydrocarbons wherein the hydroxyl function is replaced by hydrogen or methyl.

The γ-anti effects recorded for items 1–4 are based entirely on measured literature values. Those in items 5–8 are based on literature values for the alcohols[15] but calculated values for the reference compounds, as was the practice in the earlier survey of γ-anti effects.[4] The alcohols are drawn in their predominant conformations.[15]

The γ-anti effects for the set of alcohols in Table V are uniformly downfield, except for item 2 (H reference), which is zero. Accordingly, the degree of substitution of the functionalized carbon is an important factor in determining the direction of the γ-anti effect for hydroxyl. Hydroxy groups in tertiary cyclohexanols and chloro and hydroxy groups at the

bridgeheads of bicyclic and tricyclic ring systems usually cause downfield shifts of the the resonances of γ-anti carbon atoms. Further examples will be required to determine the generality and reliability of this phenomenon.[20]

Experimental Section

^{13}C NMR spectra were measured at 25.15 MHz with a JEOL JNM PS-100 spectrometer interfaced with a Nova 1200 computer.[16] Compounds **8**–**10** were run in $CDCl_3$ solution with internal Me_4Si; compounds **11** were run in D_2O solution with external $NaO_3S(CH_2)_3Si(CH_3)_3$. With the exception of **8c**,[17,18] all of the materials employed in this study were available from previous studies or prepared according to literature procedures.[19]

Acknowledgments. This work was supported by a grant from the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Registry No.—**8a**, 280-65-9; **8b**, 15158-56-2; **8c**, 15158-55-1; **8d**, 17530-63-1; **9a**, 491-25-8; **9b**, 56258-84-5; **9c**, 51209-45-1; **10a**, 281-05-0; **10b**, 37996-41-1; **10c**, 40164-34-9; **11a**, 56258-87-8; **11b**, 62067-15-6; **12a**, 281-15-2; **12b**, 50436-34-5.

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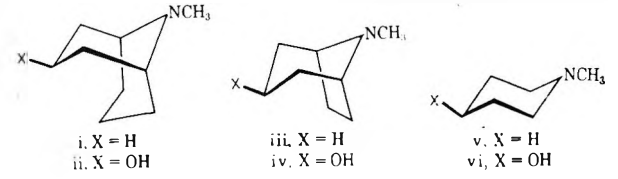

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An Unusual Magnetic Equivalence in the Proton Magnetic Resonance of Dialkylbenzamides

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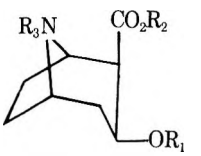
N-Benzoylnorecgonine methyl ester, *N*-benzoylpiperidine, and *N,N*-diethylbenzamide exhibit one set of ^1H NMR signals for aromatic protons whereas cocaine and seven other benzoate esters, acetophenone, α,α,α-trimethylacetophenone, α,α,α-trichloroacetophenone. benzamide, and *N*-ethylbenzamide have two sets separated by ca. δ 0.6. The observed unusual magnetic equivalence of the first three compounds is attributed to the steric interaction of the dialkylamine and the phenyl group with the resultant loss of coplanarity between the phenyl and carbonyl functional groups.

During the course of our investigations on the photochemical behavior of cocaine (I),[1] its photoproducts,[2] and related compounds,[3] the aromatic protons of cocaine were observed to occur as two groups of multiplets in the ^1H NMR spectrum at δ 7.93 (m, 2 H) and 7.36 (m, 3 H), whereas the aromatic proton resonances of *N*-benzoylnorecgonine methyl ester (II), cocaine's O → N benzoyl migration–demethylation product, appear as a sharp singlet at δ 7.45, Table I. This investigation examines the reasons for the surprising proton



I, R_1 = COPh; R_2 = CH_3; R_3 = CH_3
II, R_1 = H; R_2 = CH_3; R_3 = COPh
III, R_1 = COPh; R_2 = CH_3; R_3 = H
IV, R_1 = COPh; R_2 = H; R_3 = CH_3

Table I. ^1H NMR Chemical Shifts of Aromatic Protons of Cocaine and Related Compounds[a]

No.	Compd	Chemical shifts of aromatic protons, δ
I		7.93 (m, 2 H, *o*), 7.36 (m, 3 H, *m,p*)
II		7.45 (s, 5 H)
III		7.96 (m, 2 H, *o*), 7.30 (m, 3 H, *m,p*)
IV		7.90 (m, 2 H, o), 7.36 (m, 3 H, *m,p*)
V	Cyclohexyl benzoate	8.03 (m, 2 H, *o*), 7.40 (m, 3 H, *m,p*)
VI	*N*-Methyl-3-piperdinyl benzoate	8.03 (m, 2 H, *o*), 7.40 (m, 3 H, *m,p*)
VII	*N*-Methyl-4-piperdinyl benzoate	8.03 (m, 2 H, *o*), 7.40 (m, 3 H, *m,p*)
VIII	Methyl benzoate	8.00 (m, 2 H, *o*), 7.40 (m, 3 H, *m,p*)
IX	*N*-Benzoyl-piperidine	7.30 (s, 5 H)
X	α,α,α-Trimethylaceto-phenone	7.71 (m, 2 H, *o*), 7.33 (m, 3 H, *m,p*)
XI	α,α,α-Trichloroaceto-phenone	8.20 (m, 2 H, *o*), 7.50 (m, 3 H, *m,p*)
XII	Acetophenone	7.85 (m, 2 H, *o*), 7.40 (m, 3 H, *m,p*)
XIII	*N,N*-Diethylbenzamide	7.30 (s, 5 H)
XIV	*N*-Ethylbenzamide	7.80 (m, 2 H, *o*), 7.26 (m, 3 H, *m,p*)
XV	Benzamide	8.00 (m, 2 H, *o*), 7.50 (m, 3 H, *m,p*)
XVI	Atropine	7.20 (s, 5 H)

[a] All spectra were recorded in carbon tetrachloride, and the temperature of the A-60 NMR probe was 36 °C.

magnetic equivalence of II and complements earlier studies on the ^1H NMR signal nonequivalence of *N*-alkyl groups in relation to ortho, meta, and para substituents on the phenyl ring.[4-6] The dual set of resonances for the aromatic protons is associated with the direct linkage of the carbonyl group with the phenyl ring. In the model compound atropine (XVI) where the carbonyl group and the phenyl ring are not conjugated, all the aromatic protons appear as a singlet at δ 7.20.

Under ordinary circumstances, carbonyl substituents on aromatic rings cause the ortho protons to be shifted further downfield in the ^1H NMR spectra than the meta and para ones.[7] There is excellent deuterium labeling work which demonstrates this in an unambiguous fashion.[7] Consequently, the proton resonance of I in the downfield shift position from "normal" aromatic proton resonances is caused by the ortho aromatic protons of the phenyl ring which are in an unusual magnetic environment. The positioning of the ortho proton resonance has been attributed to the magnetic anisotropy of the carbonyl group. Logically then, the aromatic protons of II which appear at δ 7.45 are of the "normal" type with no unusual magnetic effects on the ortho aromatic protons.

For routine benzoyl ester groups, nonequivalence of the aromatic protons is expected,[8] i.e., the ortho protons are differentiated from the meta and para ones. in accord with this, all seven benzoate esters examined, I, III–VIII, exhibit two sets of ^1H NMR signals for their aromatic protons, cf. Table I.

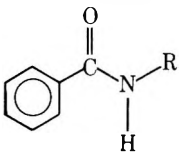
The critical changeover point occurs among the amides. Benzamide and *N*-ethylbenzamide exhibit two sets of ^1H NMR proton signals at δ 8.0 and 7.4 as do the benzoate esters, whereas *N,N*-diethylbenzamide has one set of aromatic proton signals at δ 7.30. The latter observation focuses attention on the *N*-ethylbenzamide and *N,N*-diethylbenzamide model compounds because these are the borderline set of compounds for the observed ^1H NMR phenomenon. The ^1H NMR spectrum of *N*-benzoylnorecgonine methyl ester (II), one of the two compounds responsible for causing the investigation, has one set of aromatic proton signals in agreement with that of *N,N*-diethylbenzamide and *N*-benzoylpiperidine (IX).

Though benzamides show some tendency for cluster formation at higher concentrations, the observations recorded herein are not due to this phenomenon. First, the ^1H NMR spectra of *N*-ethylbenzamide and *N,N*-diethylbenzamide were obtained at room temperature in concentrations of 1, 1×10^{-1}, 5×10^{-2}, 1×10^{-2}, 5×10^{-3}, and 2×10^{-3} M in carbon tetrachloride to study the effect of solute concentration in relation to cluster formation. *N,N*-Diethylbenzamide gives an aromatic proton singlet at δ 7.30 at all concentrations while *N*-ethylbenzamide shows two sets of signals at δ 7.80 and 7.26 in a 1 M solution whereas at lower concentrations (1×10^{-1}, 5×10^{-2}, 1×10^{-2}, 5×10^{-3} M) the signals appear at δ 7.63 and 7.33. Second, in polar solvents where cluster formation is less likely, the room temperature ^1H NMR spectra of *N*-ethylbenzamide in deuterated acetone and dimethyl sulfoxide exhibit two sets of aromatic proton signals (δ 7.70, 7.30 and 7.83, 7.40, respectively) and *N,N*-diethylbenzamide a singlet (δ 7.30 in both).

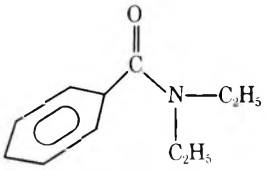
The magnetic equivalence of aromatic protons of the more bulky amides is not due to simple steric requirements alone. α,α,α-Trimethylacetophenone was synthesized and its ^1H NMR spectrum observed in order to evaluate the steric hindrance effect of a large substitution on one side of the carbonyl. Interestingly, the *tert*-butyl ketone also had two aromatic ^1H NMR proton signals centered at δ 7.71 and 7.33 similar to the *N*-ethylbenzamide and the parent compound, acetophenone. Thus the steric interaction of the bulky *tert*-butyl group did not change the nonequivalence of the aromatic protons. To demonstrate that this observation was not caused by a fortuitous canceling of factors originating in the electron-releasing property of the methyl groups, the sterically hindered α,α,α-trichloroacetophenone was synthesized; and it, too, exhibited two sets of aromatic proton signals in the ^1H NMR spectrum albeit with shifts downfield.

By using a combination of resonance and steric arguments, an explanation consistent with the data can be obtained. For optimum resonance interaction of benzamide, the phenyl ring, the carbonyl, and the disubstituted amide should be coplanar. There is a cross conjugation of the amide with the carbonyl group which is absent or minimized in benzoate esters and phenyl ketones. Whereas the barriers to rotation about normal carbon–carbon and carbon–nitrogen double bonds are in excess of 40 kcal/mol,[9] the carbon–nitrogen bond in amides possesses sufficient double bond character to provide a remarkable barrier to rotation, i.e., 10–25 kcal/mol.

The coplanarity which gives rise to the dual set of aromatic proton resonances can be achieved readily in benzamide (XV) and *N*-ethylbenzamide (XIV), but for *N,N*-diethylbenzamide (XIII), II, and IX, the nitrogen–carbonyl resonance is maintained but the phenyl ring is forced out of conjugation with the carbonyl group. The effect of the lack of the coplanarity between the phenyl ring and amide carbonyl is the equivalence of the aromatic protons as well as the differentiation of the two sets of methylene protons of the *N*-ethyl groups.[10]



XIV, R = C_2H_5
XV, R = H



XIII

If the explanation is correct, the observation that α,α,α-trimethylacetophenone and α,α,α-trichloroacetophenone exhibit two sets of aromatic protons whereas *N,N*-diethylbenzamide gives one must again be reviewed. The rationalization for the observed results is that the second alkyl group of *N,N*-diethylbenzamide more directly sterically interferes with the phenyl ring due to the partial double bond character of the C–N bond than does the non-cross-conjugated, more freely rotating alkyl group of α,α,α-trimethylacetophenone. Furthermore, the reduction in resonance between the aromatic ring and the carbonyl of *N,N*-diethylbenzamide presumably is compensated for by an increase in the double bond character of the nitrogen carbonyl linkage.[5a]

Experimental Section

The melting points were obtained on a Fisher-Johns melting point apparatus. The infrared spectra were taken on a Beckman Model IR-12 spectrophotometer. The proton magnetic resonance spectra were taken at room temperature on a Varian Associates A-60 instrument using tetramethylsilane as an internal standard. The chemical shifts of various compounds are given in δ units.

Cocaine hydrochloride was purchased from Merck and Co., Inc., St. Louis, Mo. Atropine, trimethylacetyl chloride, piperidine, 1-methyl-3-piperidinol, and 1-methyl-4-piperidinol were obtained from Aldrich Chemical Co., Inc., Milwaukee, Wis. Trichloroacetyl chloride was purchased from Eastman Kodak Co., Rochester, N.Y. All alcohols, acid chlorides, and benzoyl chloride were freshly distilled before use.

Cocaine (I). Free cocaine was obtained by neutralizing cocaine hydrochloride with 10% NH_4OH solution followed by extraction with ether and recrystallization from ethanol: mp 98 °C (lit.[11] mp 98 °C); NMR (CCl_4) δ 7.93 (m, 2 H, C_6H_5), 7.36 (m, 3 H, C_6H_5), 5.10 (m, 1 H, $-CHOCOC_6H_5$), 3.60 (s, 3 H, $-COOCH_3$), 3.50 (1 H, C_1 H), 3.20 (1 H, C_5 H), 2.90 (1 H, C_2 H), 2.20 (NCH_3), and 1.70–2.10 (m, ring CH_2 protons).

***N*-Benzoylnorecgonine Methyl Ester (II), Norcocaine (III), and *O*-Benzoylecgonine (IV).** Norcocaine was obtained by oxidation of cocaine by potassium permanganate at controlled pH 2: mp 78–80 °C (lit.[12] mp 80–82 °C); NMR (CCl_4) δ 7.96 (m, 2 H of C_6H_5), 7.30 (m, 3 H of C_6H_5), 5.00 (m, 1 H, CHOCOPh), 3.60 (s, 3 H, OCH_3), 3.10 (s, 1 H, $CHCO_2CH_3$), and 1.60–2.30 (m, 8 H, ring CH_2 and CH). *O*-Benzoylecgonine (IV) was also obtained in the above reaction:[2] mp 196–197 °C (lit.[13] mp 197–201 °C); NMR (CCl_4) δ 7.90 (m, 2 H of C_6H_5), 7.36 (m, 3 H of C_6H_5), 5.13 (m, 1 H, CHOCOPh), 3.15 (m, 1 H, $CHCO_2H$), 2.40 (s, 3 H, NCH_3), and 1.80–2.20 (m, 8 H, ring CH_2 and CH protons). *N*-Benzoylnorecgonine methyl ester (II) was obtained by $KMnO_4$ oxidation of cocaine in basic medium:[14] mp 141 °C; NMR (CCl_4) δ 7.45 (s, 5 H, aromatic), 3.6 (s, 3 H, OCH_3).

Cyclohexyl Benzoate (V). Equimolar quantities of benzoyl chloride and cyclohexanol in dry benzene were stirred vigorously for 2 h. The reaction mixture was extracted with sodium carbonate solution. The organic layer was washed with water and dried over anhydrous sodium sulfate. A yellowish liquid was obtained after removal of benzene. The cyclohexyl benzoate was collected at 192 °C (61 mm) [lit.[15] bp 192–193 °C (61 mm)]; IR (CCl_4) 1705 cm^{-1} (C=O); NMR (CCl_4) δ 8.03 (m, 2 H, C_6H_5), 7.40 (m, 3 H, C_6H_5), 5.00 (m, 1 H, $CHOCOC_6H_5$), and 1.6 (br m, 10 H, ring CH_2).

***N*-Methyl-3-piperidinyl Benzoate (VI).** This compound was prepared by stirring equimolar quantities of benzoyl chloride and *N*-methyl-3-piperidinol in dry benzene at room temperature for 2 h and worked up as usual. The pure *N*-methyl-3-piperidinyl benzoate was collected at 94–95 °C (0.05 mm) [lit.[16] 94–97 °C (0.05 mm)]: IR (CCl_4) 1710 cm^{-1} (C=O); NMR (CCl_4) δ 8.03 (m, 2 H, C_6H_5), 7.40 (m, 3 H, C_6H_5), 5.00 (m, 1 H, $-CHOCOC_6H_5$), 2.25 (s, 3 H, NCH_3), and 1.70–3.00 (m, 8 H, ring CH_2).

***N*-Methyl-4-piperidinyl Benzoate (VII).** Following the procedure of VI, *N*-methyl-4-piperidinyl benzoate was prepared and distilled at 161–163 °C (10 mm). The melting point of *N*-methyl-4-piperidinyl benzoate hydrochloride was 200 °C (lit.[17] 219–220 °C): IR (CCl_4) 1710 cm^{-1} (C=O); NMR (CCl_4) δ 8.03 (m, 2 H, C_6H_5), 7.40 (m, 3 H, C_6H_5), 5.00 (m, 1 H, $-CHOCOC_6H_5$), 2.25 (s, 3 H, NCH_3), and 1.70–2.90 (m, 8 H, ring CH_2).

***N*-Benzoylpiperidine (IX).** A mixture of piperidine and benzoyl chloride in dry benzene in a 2:1 molar ratio was stirred for 2 h. The workup of reaction mixture yielded *N*-benzoylpiperidine: bp 195 °C (25 mm) [lit.[18] 195 °C (25 mm)]; NMR (CCl_4) δ 7.30 (s, 5 H, C_6H_5), 3.40 (m, 4 H, $-CH_2NCH_2-$), and 1.60 (m, 6 H, ring CH_2).

α,α,α-Trimethylacetophenone (X). α,α,α-Trimethylacetophenone was prepared by Friedel–Crafts reaction using trimethylacetyl chloride, dry benzene, anhydrous aluminum chloride as reagents: bp 104 °C (13 mm) [lit.[19] bp 103–104 °C (13 mm)]; IR (CCl_4) 1675 cm^{-1} (C=O); NMR (CCl_4) δ 7.71 (m, 3 H, C_6H_5), 7.33 (m, 2 H, C_6H_5), and 1.30 (s, 9 H, CH_3).

α,α,α-Trichloroacetophenone (XI). This was also prepared by Friedel–Crafts reaction using trichloroacetyl chloride, dry benzene, and anhydrous aluminum chloride as reagents. α,α,α-Trichloroacetophenone was distilled as a colorless liquid: bp 145 °C (25 mm) [lit.[20] 145 °C (25 mm)]; IR (CCl_4) 1715 cm^{-1} (C=O); NMR (CCl_4) δ 8.20 (m, 2 H, C_6H_5) and 7.50 (m, 3 H, C_6H_5).

***N,N*-Diethylbenzamide (XIII).** A mixture of diethylamine and benzoyl chloride in molar ratio of 2:1 in dry benzene was stirred for 1 h and worked up to yield *N,N*-diethylbenzamide: bp 280 °C (lit.[21] bp 280–282 °C); NMR (CCl_4) δ 7.30 (s, 5 H, C_6H_5), 3.30 (q, 2 H, $-CH_2CH_3$), and 1.10 (t, 3 H, $-CH_2CH_3$).

***N*-Ethylbenzamide (XIV).** This was prepared by passing dry ethylamine into the ethereal solution of benzoyl chloride. After saturation and standing for 2.5 h, the ether layer was extracted with sodium carbonate solution, washed with water, and dried over anhydrous sodium sulfate. Removal of ether resulted in a white solid which was recrystallized from alcohol: mp 60 °C (lit.[21] mp 68–69 °C); NMR (CCl_4) δ 7.80 (m, 2 H, C_6H_5), 7.26 (m, 3 H, C_6H_5), 3.30 (q, 2 H, $-CH_2CH_3$), and 1.13 (t, 3 H, $-CH_2CH_3$).

Atropine (XVI). Atropine: NMR (CCl_4) δ 7.20 (s, 5 H, aromatic), 4.90 (t, J = 5 Hz, 1 H, C_3 H), 4.00 (m, 1 H, $COCHPhCH_2OH$), 3.63 (m, 2 H, CH_2OH), 2.80–2.90 (br, 2 H, C_5 H and C_1 H), 2.10 (s, 3 H, NCH_3), and 1.30–2.15 (br, s, 9 H, C_4, C_6, C_7 CH_2 protons, OH).

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Registry No.—I, 50-36-2; I HCl, 53-21-4; II, 17366-44-8; III, 18717-72-1; IV, 519-09-5; V, 2412-73-9; VI, 16597-31-2; VII, 16597-30-1; VII HCl, 40378-58-3; VIII, 93-58-3; IX, 776-75-0; X, 938-16-9; XI, 2902-69-4; XII, 98-86-2; XIII, 1696-17-9; XIV, 614-17-5; XV, 55-21-0; XVI, 51-55-8; benzoyl chloride, 98-88-4; cyclohexanol, 108-93-0; *N*-methyl-3-piperidinol, 3554-74-3; *N*-methyl-4-piperidinol, 106-52-5; piperidine, 110-89-4; trimethylacetyl chloride, 3282-30-2; benzene, 71-43-2; trichloroacetyl chloride, 76-02-8; diethylamine, 109-89-7; ethylamine, 75-04-7.

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Nitrogen-15 Magnetic Resonance Spectroscopy. Natural-Abundance Nitrogen-15 Spectra of Some 2-Amino-2-deoxy-D-hexose Derivatives[1]

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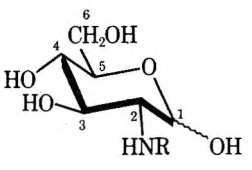
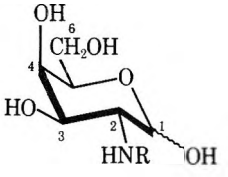
The nitrogen-15 nuclear magnetic resonance spectra of some 2-amino-2-deoxy-D-hexose hydrochlorides and 2-acetamido-2-deoxy-D-hexoses and *N*-benzoyl-D-glucosamine are reported. The differences in chemical shifts for the various hexopyranose structures are discussed in terms of steric, stereoelectronic, and hydrogen-bonding effects. These model compounds were used to study substituent effects related to amino sugar containing polysaccharides and antibiotics.

In recent years, the number of amino sugars which have been isolated from natural products has increased tremendously. In fact, the number of amino sugars characterized in living organisms is greater than that of all other sugars. This rapid development of knowledge in the field of amino sugar containing substances has inspired a rather comprehensive review[2] which surveys their chemistry and biological functions.

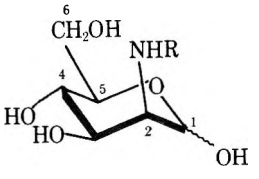
We are interested in the application of nitrogen-15 NMR spectroscopy for structural analysis of nitrogenous sugars, particularly polysaccharides and oligosaccharides such as heparin, and the neomycin-related antibiotics which contain deoxystreptamine and various other amino sugars. Recent improvements in the sensitivity of NMR instrumentation provide an opportunity to investigate these substances at their natural-abundance ^{15}N levels, and, with this end in mind, we have undertaken a study of a number of simple amino sugars. In particular, the chemical shifts and resonance-line intensities have been obtained for the pyranose anomers present at equilibrium for 25% aqueous solutions for the 2-amino-2-deoxy derivatives of D-glucose (GA·HCl), D-galactose (GalA·HCl), and D-mannose (MA·HCl), and for the respective 2-acetamido-2-deoxy derivatives (NAG, NAGal, NAM). The spectrum of *N*-benzoyl-α-D-glucosamine (NBG) in dimethyl sulfoxide (Me_2SO) has also been determined. Published data concerning the equilibrium composition of the aminohexopyranose anomers[3,4] have been correlated with the peak intensities in our spectra to corroborate the assignments.



R = H, GA·HCl
R = $COCH_3$, NAG
R = COPh, NBG



R = H, GalA·HCl
R = $COCH_3$, NAGal



R = H, MA·HCl
R = $COCH_3$, NAM

The nitrogen-15 chemical shifts of the α- and β-aminohexoses are shown in Table I. In general, the ^{15}N signal intensities allow estimates of the anomer concentrations at equilibrium, which are in qualitative agreement with ratios previously determined by proton nuclear magnetic resonance (^{1}H NMR)[3]. The ^{15}N spectra of the 2-acetamido-2-deoxy-D-hexoses have not indicated the presence of additional configurational isomers as a consequence of restricted rotation about the N–CO bond. Analogous studies by Bundle and coworkers[5] have shown that the ^{13}C chemical shifts of the methyl and carbonyl groups of the 2-acetamido function in 2-deoxy-D-hexoses are sensitive to the anomeric configuration and have established that the relative ^{13}C signal intensities allow estimation of the anomer ratios at equilibrium.

The influence of axial substituents on ^{13}C shifts in various hexopyranose systems has received considerable attention in recent years.[5-7] Much less is known concerning the effects of substituents on the ^{15}N chemical shifts in nitrogen-containing hexopyranoses.[8] Lichter and Roberts[9] have established that shifts of simple, substituted amines are subject to the same kinds of steric and electronic influences as ^{13}C shifts. They demonstrated that γ_N substituent effects are upfield shifts which increase with increasing substituent electronegativity and can be attributed to stereoelectronic perturbations of the ^{15}N shielding. Similar arguments have been used previously to account for ^{13}C shieldings in substituted norbornanes.[10] However, there are other factors which can influence ^{15}N chemical shifts. For example, shift effects arising from inter- or intramolecular hydrogen bonding are well established.[11,12] Molecular association in neat liquids or in solvents where hydrogen bonding is expected to be extensive can result in either upfield or downfield shifts, depending on the type of nitrogen and the type of interactions involved.[13] Shift effects induced via stereoelectronic perturbations and/or those emanating from hydrogen bonding may contribute to the appreciable differences between the nitrogens of the α and β forms of NAM and MA·HCl, 6.7 and 7.4 ppm, respectively. Similar observations have been made in the ^{15}N spectra of *cis*- and *trans*-1,2-diaminocyclobutane;[9] however, both the electronegativity and the spatial arrangement of the adjacent amino group attached to the cyclobutane ring differ from those of the analogous hydroxyl group in the pyranose systems. In the β anomers, the anomeric hydroxyl and axial 2-amino function are gauche, and a considerable portion of the upfield shift observed for the ammonium (or acetamido) nitrogen relative to its shielding in the corresponding α isomer can be attributed to the γ effect associated with the gauche form. Thus, although the difference between the two aminomannose anomers will reflect a composite of steric, stereoelectronic, and hydrogen-bonding effects, the simplest interpretation is a predominant steric effect in the β anomer. A similar trend is found for aminopyranoses containing equatorial 2-amino functions, but Δδ between the anomers is much less pronounced. The β anomers of aminoglucose and aminogalactose derivatives are shielded by 0.7–1.6 ppm. The 1-OH and equatorial 2-ammonium (acetamido) groups are gauche in both the α and β forms. Consequently, it does not seem likely that an increase in the steric crowding of γ sub-

Table I. ^{15}N Chemical Shifts of Aminohexopyranoses in Water[a]

Sugar	δ_α (intensity)[b,e]	δ_β (intensity)[f]	$\Delta\delta$, ppm	Anomer ratio[c] α	β
GA·HCl	340.3 (61)	341.9 (39)	1.6	63	37
NAG	252.4 (69)	253.1 (31)	0.7	68	32
GalA·HCl	341.6 (55)	343.0 (45)	1.4	47	53
NAGal	252.6 (56)[d]	253.4 (44)	0.8	65	35
MA·HCl	344.2 (40)	351.6 (60)	7.4	43	57
NAM	255.6 (60)	262.3 (40)	6.7	57	43
NBG	260.8 (90)	261.2 (10)	0.4		

[a] In parts per million upfield from external nitric acid. [b] Relative peak height. [c] Determined by ^1H NMR. Data from ref 3. [d] If the integrated peak area is used, a ratio of 63:37 is obtained. [e] Registry no. are, respectively, 14131-62-5, 10036-64-3, 14131-59-0, 14215-68-0, 14131-65-8, 14131-64-7, 61949-16-4. [f] Registry no. are, respectively, 14131-63-6, 14131-68-1, 14257-79-5, 14131-60-3, 14131-67-0, 7772-94-3, 6847-14-9.

Table II. ^{15}N Shielding Differences (ppm) between Epimeric 2-Aminohexoses Derivatives[a]

α-GalA·HCl–α-GA·HCl	+1.3
β-GalA·HCl–β-GA·HCl	+1.1
α-NAGal–α-NAG	+0.2
β-NAGal–β-NAG	+0.3
α-MA·HCl–α-GA·HCl	+3.9
β-MA·HCl–β-GA·HCl	+9.7
α-NAM–α-NAG	+3.2
β-NAM–β-NAG	+9.2

[a] Obtained from data in Table I; positive values correspond to upfield shift differences in parts per million.

stituents in β relative to α anomers is responsible for these shielding effects. Moreover, a number of different modes of hydrogen bonding are possible and the stereoelectronic effects that influence ^{15}N shifts of aminohexopyranoses are complicated and not well understood.

Table II illustrates the effect which results from the introduction of an axial substituent to the 2-amino-2-deoxy-D-hexose derivatives, using GA·HCl and NAG epimers as reference compounds. Shielding effects of +1.3 and +1.1 ppm are observed in the comparison with the analogous anomers of GalA·HCl. We assume that the orientation of the hydroxyl group is responsible for these upfield shifts, because the C-2 ammonium group remains unchanged with respect to the remaining substituents on the oxane ring, at least as a first approximation. However, there may be slight differences in bond angles in the galactosamine derivatives as a consequence of ring flattening to relieve 1,3-nonbonded interactions with the axial C-4 hydroxyl group. The shielding effects associated with change in stereochemistry of a C-4 hydroxyl group (δ substituent), although opposite in direction, are comparable in magnitude to those involving γ substituents, as can be seen from the shifts of the anomeric aminoglucose and aminogalactose derivatives in Table I. This is a large effect for a substituent far removed from the nitrogen in question. The orientation in space of the 4-OH group should not affect the steric environment of the equatorial C-2 ammonium function directly, and thus should have very little influence on its chemical shift. Furthermore, hydrogen bonding from the ammonium group in these 2-deoxyhexopyranoses to O-4 is sterically impossible.[14] These shielding differences may reflect some distant stereoelectronic perturbation of the ^{15}N chemical

Table III. Nitrogen-15 Shieldings of the 4-*tert*-Butylcyclohexylamines and Their Derivatives[a]

Derivative (solvent)	Trans[d]	Cis[e]	$\Delta\delta$[b]
$-NH_2$[c] (cyclohexane)	334.6	343.4	8.8
–NHAc (chloroform)	240.5	248.8	8.3
$-NH_3^+Cl^-$ [c] (CH_3OH)	329.5	335.4	5.9

[a] In parts per million from external nitric acid. [b] $\Delta\delta = \delta_N^{cis} - \delta_N^{trans}$. [c] Unpublished research by Dr. R. Duthaler. [d] Registry no. are, respectively, 2163-34-0, 2163-33-9, 31023-36-6. [e] Registry no. are, respectively, 31023-35-5, 54572-02-0, 61886-14-4.

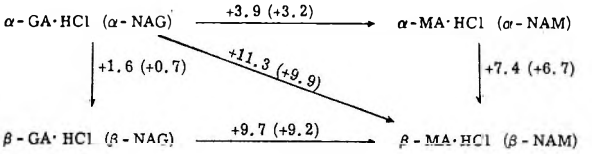


Figure 1. Nitrogen-15 chemical shift (ppm) relationships between aminoglucose and aminomannose derivatives.

shift, and it is conceivable that the spatial configuration between the hydroxyl substituent, C-4 and C-2, has an important bearing on the mechanism of these shift changes. The ^{19}F chemical-shift data for 4-substituted 1,1-difluorocyclohexanes[15] and 4-substituted 1-fluorobicyclo[2.2.2]octanes[16] have similar downfield shifts of the ^{19}F shieldings when polar substituents are oriented in a W arrangement. When the ^{15}N shifts of α- and β-NAGal are compared with those of analogous anomers of NAG, considerably smaller $\Delta\delta$ values are derived. If such shift effects are inductive effects of the electronegative C-4 hydroxyl group, then these smaller differences may, in part, reflect a change in polarization of the C-2–N bond for the change in substituent $-NH_3^+Cl^- \rightarrow -NHCOCH_3$.

Considerably larger shielding differences are observed between derivatives of mannosamine and glucosamine. To evaluate ^{15}N shielding differences for axial and equatorial C-2 amino groups for amino sugars in the absence of any additional perturbations caused by the changing relationships of γ-OH groups, experimental shifts of the β-mannosamine derivatives can be compared with expected shifts derived from the anomeric aminoglucose derivatives. Axial–equatorial differences of +12.9 and +10.6 ppm were obtained for the amino sugar hydrochlorides and their acetyl derivatives.[17] Analogous shift comparisons are reported in Table III for the amine nitrogen in *cis*- and *trans*-4-*tert*-butylcyclohexylamines as well as the hydrochloride salts and *N*-acetates, for which values are +8.8, +5.9, and +8.3, respectively. In every case, the axial nitrogen absorbs at higher field. For the cyclohexyl series, nonbonded interactions of the axial hydrogens at C-3 and C-5 are sufficient to perturb the electron distribution about the axial nitrogen nucleus such that its shielding is increased. The larger shielding differences between epimeric aminohexopyranose structures are not likely to arise solely from an interaction of a single axial hydrogen, and consequently, it seems likely that a substantial part of this effect can be ascribed to the gauche interaction of the ring oxygen in the axial compounds.

In Figure 1, data from Tables I and II are combined to illustrate the various chemical-shift relationships among anomeric aminomannose and aminoglucose derivatives. Much larger $\Delta\delta$ values are observed between β-mannosamine and β-glucosamine derivatives—+9.7 (+9.2) ppm compared with +3.9 (+3.2) ppm for the α derivatives. As noted previously, $\Delta\delta$ between anomers of either 2-deoxymannose derivative illustrates the pronounced γ-shielding effect associated with

Table IV. ^{13}C Chemical Shifts of NBG in Me_2SO[a]

Anomer (rel signal inten)	C_1	C_2	C_3	C_4	C_5	C_6	C=O
α (90)	91.3	46.2	71.9	71.0	72.9	62.1	167.4
β (10)	96.3	58.6	75.0	[b]	77.7	62.1	167.4

[a] In parts per million from external Me_4Si. [b] This signal must coincide with another reported.

the gauche form. The relief of this gauche interaction accounts for the smaller $\Delta\delta$ values between the α-aminomannoses and their epimeric gluco brethren. That is, the shielding effect associated with the change in the bonding relationship of the C-2 amino group with respect to the ring is partially cancelled by a concomitant (but opposing) effect resulting from the relief of the gauche interaction with the 1-OH substituent.

To observe both anomers of NBG in dimethyl sulfoxide solution, the original sample was maintained at room temperature for a period of 2 months, at which time the α-D anomer was preponderant. The ^{13}C NMR spectrum confirmed the ^{15}N NMR results which indicated that both anomers were present in an α:β ratio of 90:10. The ^{15}N chemical-shift difference between anomers of NBG is 0.4 ppm, compared with values of 1.6 and 0.7 ppm, respectively, for anomers of GA·HCl and NAG; thus $\Delta\delta_{-NH_3^+} > \Delta\delta_{-NHAc} > \Delta\delta_{-NHCOPh}$.

The shielding differences in these 2-amino-2-deoxy-D-hexoses could well be a function of the orientation of the nitrogen about the N–C-2 bond and, because the shielding differences are often larger than 1 ppm, they could be a source of stereochemical information.

Experimental Section

All the 2-amino-2-deoxy-D-hexose derivatives were purchased from Sigma Chemical Co., Inc., and were used without further purification. The ^{15}N NMR spectra were recorded in 25-mm sample tubes at temperatures of ca. 30–40 °C on a Bruker WH-180 spectrometer equipped with a Nicolet B-NC 12 computer with 24K memory (16K for spectrum accumulation), operating at 18.25 MHz in a pulsed Fourier transform mode with complete broad-band, proton noise decoupling. The computer allowed acquisition of 8192 data points for a spectrum having a sweep width of 10 000 Hz. A typical experiment required 1–2 h of data acquisition, using a pulse width of 20 μs (20° flip angle) at pulse intervals of 2.0 s. Chemical shifts are reported in parts per million (ppm) upfield from external nitric acid (1 M 98% ^{15}N-enriched nitric acid in deuterium oxide) capillary in which deuterium oxide was used to produce the field lock signal. Spectra of 25% solutions of the 2-acetamido-2-deoxy-D-hexoses and the 2-amino-2-deoxy-D-hexose hydrochlorides in water were recorded after reaching their mutarotational equilibria. A 20% solution of *N*-benzoyl-2-amino-2-deoxy-α-D-glucose in dimethyl sulfoxide mutarotated to ca. 10% of the β anomer after standing at room temperature for 2 months.

The ^{13}C NMR spectrum of NBG was recorded for the same sample used for the ^{15}N spectrum with the Bruker WH-180 spectrometer operating at 45.28 MHz. The chemical shifts of the skeletal carbons of the pyranose ring and the carbonyl carbon in both anomers are reported in Table IV.

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(17) In derivatives of β-mannosamine, the axial amino function has a cis-bonding relationship to both the C-1 and C-3 hydroxyl groups; therefore, a shift value must be estimated for a system in which an equatorial amino function retains the same bonding relationships to these hydroxyl groups. In the latter case, the C-1 and C-3 hydroxyl groups have an axial-bonding relationship with respect to the pyranose ring. A value of −1.6 (−0.7) ppm can be derived from the structural change 1-OH_e → 1-OH_a from the chemical shifts of the α and β forms of 2-amino-2-deoxyglucose. If an analogous change in the bonding of the 3-OH results in a similar shift difference, an additional factor of −1.6 (−0.7) ppm should be introduced into the shielding values of the α-aminoglucose derivatives. Thus, $\Delta\delta = \delta_{\beta\text{-MA·HCl}} - (\delta_{\alpha\text{-GA·HCl}} - 1.6) = +12.9$ ppm; $\Delta\delta = \delta_{\beta\text{-NAM}} - (\delta_{\alpha\text{-NAG}} - 0.7) = +10.6$ ppm.

^{15}N Nuclear Magnetic Resonance Spectroscopy. Natural-Abundance ^{15}N Nuclear Magnetic Resonance Spectra of Enamines[1]

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The ^{15}N chemical shifts of 18 cyclic enamines have been determined at the natural-abundance level of ^{15}N using the Fourier transform technique. The shifts depend on the size of both the cycloalkene and nitrogen-containing rings. Methyl substituents on the cycloalkene ring also influence the chemical shifts of enamines. Tertiary amines formed on hydrogenation of cyclic enamines are found to have ^{15}N chemical shifts 3.9–19.7 ppm upfield of the shift for the corresponding unsaturated compound. A carbonyl group in conjugation with an enamine group results in a large downfield shift of approximately 30–40 ppm for the nitrogen resonance of the enamine.

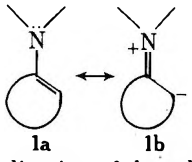
The nitrogen lone-pair electrons of an enamine can interact with the π electrons of the enamine double bond, enhancing the electron density of the β-alkenic carbon and making this position available for introduction of a substituent by a wide variety of electrophilic reagents.[2] The reactivities of enamines formed from cyclic ketones depend on the ring size and substitution pattern of both the ketone and amine parts.[3-7]

Table I. ^{15}N Chemical Shifts of Cyclic Enamines[a]

R	2	3	4	5	6	7
a —N⟨	304.1	300.7	299.3	301.2	317.6	302.9
b —N⟨	304.0	301.1	298.6		319.9	307.4
c —N⟨	306.5	305.7				
d —N⟨O	308.8	305.4	303.2			
e —N(Et)$_2$	304.5	304.0				

[a] Upfield with respect to external 1.0 M D^{15}NO$_3$ for 20 mol % solutions in cyclohexane.

The conformation and the degree of p–π overlap in cyclic enamines have been studied by ^1H and ^{13}C NMR spectroscopy.[5-9] It has been postulated[5,7,9] that the chemical shifts of the alkenic proton and β-alkenic carbon reflect the degree of p–π overlap in these molecules, i.e., the relative contributions of resonance forms **1a** and **1b** to the structure.



1a **1b**

In principle, an indication of the relative contributions of these canonical forms should also be available through consideration of ^{15}N chemical shifts for these compounds. For this reason, we have studied the natural-abundance ^{15}N NMR spectra of 18 cyclic enamines and a number of closely related compounds. We have also obtained ^{15}N NMR spectra of the 16 tertiary amines formed on hydrogenation of the above enamines, to ascertain how the removal of p–π overlap influences the ^{15}N chemical shifts.

Experimental Section

The cyclic enamines were synthesized and purified by the method of Stork and co-workers.[10] Physical properties and ^1H NMR spectral parameters were consistent with reported data.[5,8,10,11] *N,N*-Diethylenamines were prepared as described by Blanchard.[12]

Cyclic enamines were hydrogenated in ethanol at room temperature and 50 psi pressure of hydrogen, over 5% palladium on charcoal. Uptake of hydrogen was complete after 20 min, at which time shaking was discontinued and the catalyst removed by filtration. The solvent was evaporated and the residue distilled under reduced pressure. Physical and spectral properties for each tertiary amine were consistent with reported values.[4,13]

Cyclic enamino ketones were prepared by the method of Panouse and Sannié.[14] All other compounds used were commercial materials.

Proton noise-decoupled ^{15}N NMR spectra were recorded at the natural-abundance level with a Bruker WH-180 NMR spectrometer operating at 18.25 MHz. Measurements were made on large sample volumes (25-mm o.d. tubes, using 15–22-mL samples) with quadrature detection and Fourier-transform mode operation. Each spectrum was obtained with a repetition rate of 4.5 s, an acquisition time of 0.819 s, and a total accumulation of 2000 transients. The pulse angle was 20° (20-μs pulse width) at a decoupling power of 4 W. The chemical shifts are reported in parts per million upfield from external 1.0 M H^{15}NO$_3$ in D$_2$O (5-mm o.d. NMR tube).

Results and Discussion

The ^{15}N chemical shifts of cyclic enamines for cyclohexane solutions are reported in Table I. The results show that the ^{15}N shifts for cyclic enamines occur in the range 298.6–319.6 ppm upfield of D^{15}NO$_3$. If the compounds with a methyl ring substituent are excluded from consideration the range is much smaller (10.2 ppm).

That the alkenic proton and β-alkenic carbon-13 chemical shifts in pyrrolidine enamines are upfield by approximately 0.3 and 4–6 ppm, respectively, of the corresponding shifts in piperidine enamines has been attributed to a greater contribution of canonical form **1b** in the resonance hybrid of the structure of pyrrolidine enamines compared with piperidine enamines. This explanation is consistent with the greater reactivity of the pyrrolidine enamines in electrophilic substitution at their β-alkenic carbons. Comparison of the ^{15}N chemical shifts in pyrrolidine enamines with the shifts in the corresponding piperidine enamines reveals no systematic trends. For compounds **2a** and **2b** as well as **3a** and **3b** there are no significant chemical-shift differences while for **4a** and **4b** a small downfield shift is observed. Of **6a** and **6b,** and **7a** and **7b,** the piperidine enamines have shifts at higher field.

The relative degree of nitrogen lone-pair overlap with the alkene group has been estimated for ketone enamines corresponding to **a**–**e** by the ^{13}C carbonyl chemical shifts,[9] but the values so obtained do not correlate with the ^{15}N chemical shifts for the analogous compounds of either series **2** or **3.**

Table I shows that there is an upfield shift of about 3 ppm for enamines of cyclopentanone compared with the corresponding enamine of cyclohexanone. Because a double bond exo to a five-membered ring is more stable than the related double bond which is exo to a six-membered ring, we might have predicted that the dipolar resonance form **1b** of the enamines would have a greater contribution in the cyclopentanones compared to the cyclohexanones examined. The upfield shifts of both the β-alkenic carbon[9] and alkenic proton[7] signals in the former series are in agreement with this notion, but the upfield shift of the ^{15}N signals is not.

For ^{15}N chemical shifts, a decrease in electron density at a particular atom does not necessarily result in a downfield shift as is generally the case for ^1H and ^{13}C chemical shifts. Upfield shifts in the resonances of sp^2-hybridized nitrogens and downfield shifts for sp^3-hybridized nitrogens are well established for protonation of nitrogen atoms in organic molecules.[15] Apparently with sp^2-hybridized nitrogens carrying a lone pair, the second-order paramagnetic effect which is associated with the energy of the $n \rightarrow \pi^*$ transition is an important influence on the shift and will usually dominate simple electron density effects.

The data of Table I show that the shifts in cycloheptanone enamines are generally downfield by 1.4–2.5 ppm of the shifts in related cyclohexanone enamines. Again the relative order of the alkenic proton chemical shifts[7] corresponds to that of nitrogen shifts. It has been argued[7] that the maximum conformational hindrance to form **1b** in five- to seven-membered cycloalkanone enamines is offered by the seven-membered ring and consequently the cycloheptanone enamine should have the lowest field signal for the alkenic proton. If the resonances of sp^3-hybridized nitrogens move downfield with decreasing electron density, then the observed order of nitrogen shifts in Table I is not consistent with this reasoning.

The nitrogen resonances of 1-(pyrrolidino)cyclooctene is upfield of the corresponding cycloheptene derivative by 1.9 ppm. The relative alkenic proton shifts are the same for these two compounds.

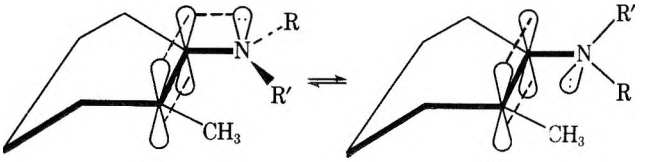
The ^{15}N shifts in morpholine enamines are upfield of the shifts in related piperidine enamines by about 4 ppm. The oxygen in the morpholine ring probably should not greatly affect the degree of interaction of the nitrogen with the double bond in the enamine and the ^1H and ^{13}C NMR data support this assertion.[7,9] If so, then the observed upfield shifts must have a different origin. The same shift difference is in fact displayed by morpholine (342.7 ppm) and piperidine (336.2

ppm), both measured in cyclohexane under comparable conditions (20 mol %). A similar upfield shift is observed[16] in butylamine on replacement of the γ-methylene group with an oxygen atom. It is possible that the observed shift difference for these enamines is a consequence of the inductive effect of the substituted 3-oxapentamethylene group [$(-CH_2CH_2)_2O$, $\sigma^* = +0.67$] compared with the pentamethylene group [$-(CH_2)_5$, $\sigma^* = -0.18$], although again the relative order is the opposite of that anticipated on the basis of simple electron-density considerations. Irrespective of its origin, there is a counterpart in the upfield ^{13}C shift which occurs through replacement of a γ-methylene or methyl group with a γ-oxygen or nitrogen of the same spatial disposition (Chart I of ref 17).

$CH_3OCH_2CH_2NH_2$ 361.7 ppm $CH_3CH_2CH_2CH_2NH_2$ 352.3 ppm

In Table II we have summarized methyl-substituent parameters for 1-(cycloalkylamino)-6-methylcyclohexenes and 1-(cycloalkylamino)-2-methylcyclohexenes. The assignment of resonances in the two isomeric 1-(pyrrolidino)methylcyclohexenes was made on the basis of the relative signal intensities and the reported isomer ratios.[5,9] The two piperidine isomers are present in approximately equal amounts,[5,9] so by analogy with the relative order of the signal in the pyrrolidine case, it was assumed that the upfield signal resulted from 1-(piperidino)-2-methylcyclohexene.

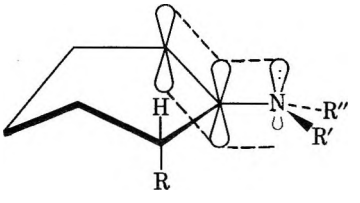
The data in Table II show that a 2- or 6-methyl substituent on the cyclohexene ring causes an upfield shift in the ^{15}N resonance of 1-(cycloalkylamino)cyclohexenes. The greater shifts are found for piperidine than pyrrolidine compounds, and much larger for a 2-methyl than a 6-methyl substituent. The steric and electronic factors which influence the isomer ratio of these four compounds have been discussed on the basis of ^{13}C and ^{1}H NMR data.[5,9] It has been argued[5] that in 2-methyl substituted 1-(*N,N*-dialkylamino)cyclohexenes **8**, the large steric interactions between R and R′ and the methyl substituent precludes their coplanarity and any substantial high degree of p–π overlap in the molecule. Consequently, the



8 **9**

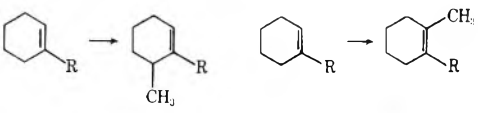
replacement of the alkenic proton by a 2-methyl group should result in an increase in steric interactions and a twisting of the R and R′ groups out of plane, thus increasing the proportion of conformations such as **9**. Because the nitrogen atom in **9** is more like an ordinary tertiary amine nitrogen (cf. Table III), the observed upfield shift caused by a 2-methyl substituent is expected. The larger shift changes for piperidine derivatives compared to pyrrolidine derivatives on 2-methyl substitution results from greater steric interactions in structures such as **8** with six-membered rings.

The methyl group of the 6-methyl derivatives of Table II is pseudoaxial[5,9] and relatively free from the steric interactions described above, so a large degree of overlap can be maintained on changing R = H to R = CH_3 in structure **10**. Consequently, a smaller change in ^{15}N chemical shifts takes place when a 6-methyl is introduced.



10

Table II. Methyl Effects on ^{15}N Chemical Shifts in Cyclic Enamines

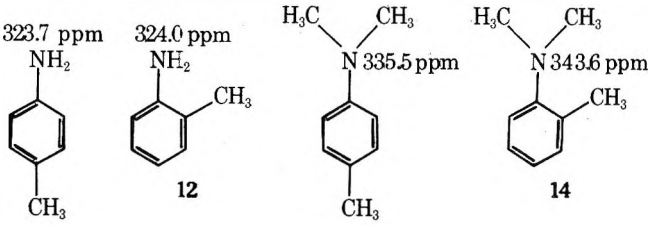


3 7 3 6

	R	$\Delta\delta_{^{15}N}$[a]	$\Delta\delta_{^{15}N}$[a]
a	—N⬠	2.2	16.9
b	—N⬡	6.3	18.5

[a] $\Delta\delta_{^{15}N} = [\delta(6 \text{ or } 7) - \delta(3)]$.

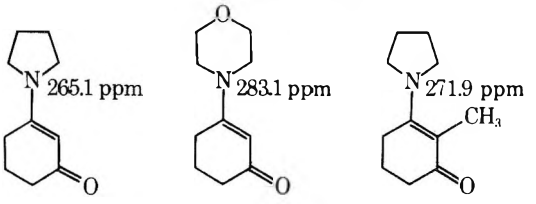
This analysis of enamine shifts is supported by the ^{15}N spectra of several aniline derivatives (**11–14**). The effect of introducing two *N*-methyl substituents on the shift of *p*-toluidine (that is, **11** → **13**) is a *diamagnetic* shift of 11.8 ppm.



11 **12** **13** **14**

The same substitutions change the ^{15}N shift of *o*-toluidine (**12** → **14**) upfield by 19.6 ppm. This larger upfield shift results from steric interactions preventing nonplanarity of the $N(CH_3)_2$ group with the benzene ring in **14**. It is unlikely that there is any corresponding steric inhibition of resonance in either **11** or **13**. Comparison of the shifts in **11** and **12** show the equality of *o*- and *p*-methyl substituent effects in the ^{15}N shift of aniline. The ^{13}C shifts of *o*-toluidine and *N,N*-dimethyl-*o*-toluidine also support these conclusions.[9]

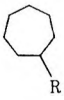
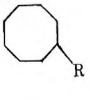
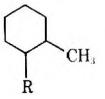
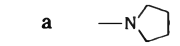
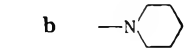
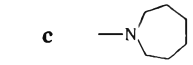
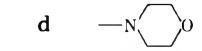
The ^{15}N shifts of enamino ketones **15** and **16** occur at 265.1 and 283.1 ppm, respectively, in agreement with earlier ^{14}N



15 **16** **17**

measurements of compounds containing the same functional group.[18] Thus, a carbonyl group in conjugation with the double bond of an enamine induces a large downfield shift in the ^{15}N resonance of an enamine (compare $\delta_{^{15}N}$ in **3a** and **3b** with $\delta_{^{15}N}$ in **15** and **16**, respectively). The observed shift can be associated either with (1) increased electron withdrawal of the nitrogen lone-pair electrons by the strongly electron-withdrawing carbonyl group or (2) the expected decrease in the $n \rightarrow \pi^*$ transition energy associated with introduction of the carbonyl group thus increasing the second-order paramagnetic effect at the nitrogen, and (3) a possible change in geometry of the nitrogen from pyramidal in enamines to planar in enamino ketones. Whatever the relative importance of each factor, there are corresponding ^{1}H and ^{13}C chemical shift differences between enamines and enamino ketones.[6,9] The ^{15}N shift of **17** shows that the effect of a 2-methyl substituent on the shift of **15** is smaller than the effect of a 2-methyl group on the shift of the enamine **3a**. The upfield shift

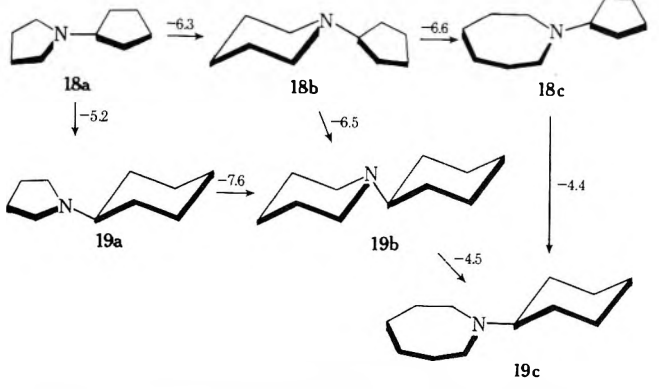
Table III. ^{15}N Chemical Shifts of Cyclic Tertiary Amines[a]

	R	 18	 19	 20	 21	 22
a		308.0 (3.9)	313.2 (12.5)	313.3 (14.0)	311.5 (10.3)	312.9 (−4.7)
b		314.3 (10.3)	320.8 (19.7)	317.9 (19.3)		319.6 (−0.3)
c		320.9 (14.4)	325.3 (19.6)			
d		318.5 (9.7)	323.9 (18.5)	322.5 (19.3)		
e	—N(Et)$_2$	321.1 (16.6)	321.0 (17.0)			

[a] See corresponding footnote in Table I. Numbers in parentheses are the shift differences between tertiary amines and the related enamines. $\Delta\delta = \delta(\text{amine}) - \delta(\text{enamine})$.

produced by a 2-methyl group in **15** could result from both torsional distortion about the C (alkene)–N bond, smaller than that postulated in the corresponding enamine, or a change in the nitrogen configuration from planar to pyramidal.

The ^{15}N chemical shifts for tertiary amines resulting from hydrogenation of cyclic enamines are summarized in Table III. This table shows that chemical shifts for compounds **18–21** occur in the range 308.0–325.3 ppm or 3.9–19.6 ppm upfield of shifts in the corresponding enamines. The increased shielding, although not large, is in the direction expected for an increase in electron density in the nitrogen atom as a result of the removal of p–π overlap of the nitrogen lone pair with the double bond. For two cases, **22a** and **22b,** the resonance of the tertiary amine is downfield of the shift in the corresponding enamine. Comparisons of shifts for **22a,b** and **19a,b** show that the 2-methyl substituent has little influence on the shifts for **19a** and **19b.** The downfield shift changes thus result from the unusually high-field resonances of enamines **6a** and **6b** and hydrogenation removes the factors responsible for these high-field shifts. It is evident from Table III that the cycloalkyl group and the heterocyclic ring size influence the ^{15}N chemical shifts of compounds **18–21,** as can be seen from the following diagram:



Introducing a γ-methylene group into either ring of 1-cyclopentylpyrrolidine (**18a**) produces an upfield shift of 5–6 ppm. The effect is additive so that a γ-methylene group in each ring causes an approximately double upfield shift (12.8 ppm). Two adjacent methylene groups added to the five-membered ring of pyrrolidine in either **18a** or **19a** move the nitrogen shift upfield by 12.9 and 12.1 ppm, respectively.

The ^{15}N shifts in the tertiary amines of Table III which are morpholine derivatives are upfield of the shifts in their piperidine analogues by 3–4 ppm.

One difference between tertiary amines and enamines is the large shift difference between diethylamine derivatives and the related pyrrolidine compounds. Conversion of an *N,N*-diethylamino group to a five-membered ring causes 13.1 and 7.8 ppm downfield shifts in the ^{15}N signals of compounds **18e** and **19e,** respectively, but no change in the corresponding enamine compounds. The explanation for this observation and others noted above awaits further clarification of the conformations of compounds **18–21,** as well as increased understanding of the other factors which might influence ^{15}N chemical shifts.

Registry No.—**2a,** 7148-07-4; **2b,** 1614-92-2; **2c,** 7374-91-6; **2d,** 936-52-7; **2e,** 34969-48-7; **3a,** 1125-99-1; **3b,** 2981-10-4; **3c,** 23430-63-9; **3d,** 670-80-4; **3e,** 10468-24-3; **4a,** 14092-11-6; **4b,** 19353-04-9; **4d,** 7182-08-3; **5a,** 942-81-4; **6a,** 5049-40-1; **6b,** 6128-00-3; **7a,** 5049-51-4; **7b,** 6127-99-7; **18a,** 18707-33-0; **18b,** 7335-04-8; **18c,** 5024-91-9; **18d,** 39198-78-2; **18e,** 34969-56-7; **19a,** 7731-02-4; **19b,** 3319-01-5; **19c,** 19797-11-6; **19d,** 6425-41-8; **19e,** 91-65-6; **20a,** 18707-34-1; **20b,** 62059-30-7; **20d,** 39198-79-3; **21a,** 18707-36-3; **22a,** 18707-25-0; **22b,** 55905-10-7.

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Synthesis of Dehydroalanine Peptides from β-Chloroalanine Peptide Derivatives

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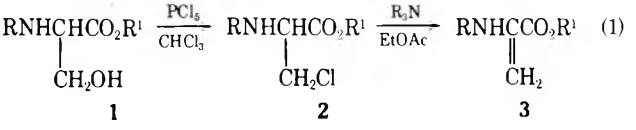
A series of N-protected di- and tripeptides containing the dehydroalanine unit has been prepared from the corresponding serine-containing peptides by a sequence of chlorination, using phosphorus pentachloride in chloroform, followed by base-catalyzed elimination. In two instances where *N*-benzyloxycarbonyl-L-phenylalanine was the N-terminal unit of a tripeptide, oxazoline hydrochlorides were obtained in the chlorination step. The chlorinated peptides also were obtained by direct incorporation of a β-chloro-L-alanine residue into the peptide by use of the carbodiimide method.

The dehydroalanine moiety has been and is of current interest in peptide chemistry. Dehydroamino acids are important constituents of the peptide antibiotics nisin,[1,2] subtilin,[2] thiostrepton,[3a] tentoxin,[3b] and alternariolide,[3c] for which the activity of the former two antibiotics has been proposed[4] to be related to the presence of unsaturated amino acids. Studies have been made to convert existing amino acids to dehydroalanine units with subsequent cleavage at the positions of the unsaturated residues.[5] The conversion of a serine to a dehydroalanine unit was used in a study[6] of the active site in chymotrypsin.

Dehydroalanine derivatives have been prepared by condensation of pyruvic acid with amides[7] and alkyl-α-halonitriles.[8] Azlactones, prepared by treatment of an *N*-acylglycine with an aromatic aldehyde, yielded dehydroamino acids upon hydrolysis;[9] more recently, oxidation of azlactones has led to the formation of dehydroamino acids.[10] Elimination reactions involving sulfonium[11] and sulfinyl[12] derivatives of cysteine and *O*-tosyl derivatives of serine[13] have found general use for preparation of dehydroalanine and peptides containing this unsaturated unit. Application of elimination reactions on β-chloroalanine derivatives for preparation of dehydroalanines has been reported.[14]

We were interested in the preparation of di- and tripeptides containing a dehydroalanine residue. We have found that reaction of serine-containing peptide derivatives with phosphorus pentachloride in chloroform readily effected chlorination of serine to yield a β-chloroalanine unit. Subsequent elimination, using a tertiary amine as base, gave the unsaturated peptide derivative in good yield (eq 1, Table I). An al-



(1)

1 2 3

ternative, but related, method is to introduce directly into the peptide the β-chloroalanine unit,[15] either as *N*-benzyloxycarbonyl-β-chloro-L-alanine or β-chloro-L-alanine methyl ester, followed by elimination.

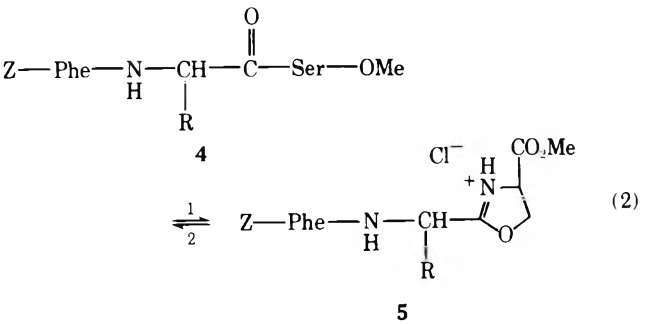
The conversion of alcohols to alkyl halides by use of phosphorus halides is a common reaction; indeed, serine and threonine ester hydrochlorides have been reported[16] to give the corresponding β-chloro derivatives upon treatment with phosphorus pentachloride. From our experience, the advantages of the above method are manifest in the consistent yields and clean nature of the reactions. We have successfully applied the method on protected serine as on di- and tripeptide derivatives containing serine or β-chloroalanine in various positions of the peptide. The amino protective groups used were benzyloxycarbonyl and, in two instances, trifluoroacetyl, while methyl and ethyl esters were employed as carboxyl protective groups. We have observed that dipeptides having a *N*-benzyloxycarbonyldehydroalanine unit in the N-terminal position are prone to undergo polymerization. Triethylamine effected elimination when the β-chloroalanine residue was at the C-terminal position in the peptide; when the above residue was at an internal or N-terminal position, it was necessary to employ 1,4-diazabicyclo[2.2.2]octane (Dabco) as base. The dehydroalanine group was readily characterized by the presence of vinyl proton absorptions in the NMR spectrum of the olefinic products.

The di- and tripeptides containing serine employed in this study were prepared by coupling the appropriate *N*-benzyloxycarbonyl-L-amino acid or dipeptide, using the carbodiimide procedure, with L-serine methyl ester or a peptide containing L-serine; new compounds prepared are listed in Table II.

The peptides containing β-chloroalanine (Table III) were prepared by chlorination of the seryl hydroxyl group using PCl_5 in chloroform or by the direct incorporation of β-chloro-L-alanine into the peptide. Chlorination of serine methyl ester appears[15,17] to occur without racemization. In this study, chlorination of Z-Gly-Ser-OMe gave product with a specific rotation of −7.0° (lit. −7.5°), while the specific rotations for Z-Gly-Phe-βClAla-OMe, prepared by chlorination of the tripeptide or by introduction of H-βClAla-OMe, were the same. Thus, racemization in the chlorination step does not appear to be occurring to a significant extent.

Comparison of the NMR spectra of the serine peptides with that of the corresponding β-chloroalanine derivatives in trifluoroacetic acid showed, upon chlorination, a downfield shift of approximately 0.3 ppm for the seryl α hydrogen and an upfield shift of similar magnitude for the seryl β hydrogens (see Tables II and III).

Chlorination of Z-Phe-Gly-Ser-OMe and Z-Phe-Ala-Ser-OMe gave products that were shown to be oxazoline hydrochlorides[19] (eq 2). In these two instances, the products precipitated from the reaction solution in contrast to the homogeneous nature of those reactions that yielded the desired β-chloroalanine derivatives. The oxazolines gave a positive



(2)

R = H or Me 1 PCl_5, $CHCl_3$ 2 Et_3N, H_2O R = H or Me

Table I. Preparation of Dehydroalanine Derivatives from β-Chloroalanine Derivatives via Elimination[a]

Reactant	Registry no.	Product[b,c]	Registry no.	Yield, %	Recrystn solvent[d]	Mp, °C	NMR, δ[e]	$[\alpha]_D$ (concn)[f]
Z-βClAla-OMe	62107-38-4	Z-ΔAla-OH[g]	39692-63-2	68	A	108–109	5.92, 6.35[h]	
TFA-βClAla-OMe	62076-45-3	TFA-ΔAla-OMe	58137-35-2	91		Oil	6.12, 6.67[h]	
TFA-Gly-βClAla-OMe	62085-24-9	TFA-Gly-ΔAla-OMe	62076-54-4	83		Oil	5.96, 6.55[h]	
Z-Gly-βClAla-OMe	14131-96-5	Z-Gly-ΔAla-OH[i]	62076-55-5	55	B	188–189	6.46, 6.74	
Z-Ala-βClAla-OMe	19525-94-1	Z-Ala-ΔAla-OH	62076-56-6	52	C	118–119	6.40, 6.70	−17.9 (2.2)
Z-Phe-βClAla-OMe	62076-46-4	Z-Phe-ΔAla-OH	62076-57-7	49	A	149–150	6.36, 6.65	−8.4 (2.3)
Z-Val-βClAla-OMe	62076-47-5	Z-Val-ΔAla-OMe	62076-58-8	90	A	116–117	5.92, 6.62[h]	+3.6 (2.1)
Z-βClAla-Gly-OEt	7625-66-3	Z-ΔAla-Gly-OEt[j]	55477-82-2	63	E	76–78	5.25, 6.13[h]	
Z-βClAla-Ala-OEt	62076-48-6	Z-ΔAla-Ala-OEt	62076-59-9	80		Oil[k]	5.25, 6.10[h]	
Z-βClAla-Leu-OMe	62076-49-7	Z-ΔAla-Leu-OH	62076-60-2	40		Oil	5.32, 6.10[h]	
Z-Gly-Gly-βClAla-OMe	62076-50-0	Z-Gly-Gly-ΔAla-OMe	62076-61-3	86	D	156–157	6.36, 6.64	
Z-Gly-Phe-βClAla-OMe	62076-51-1	Z-Gly-Phe-ΔAla-OMe	62076-62-4	90	A	159–160	6.31, 6.58	−9.0 (2.2)
Z-Phe-Gly-βClAla-OMe	62076-52-2	Z-Phe-Gly-ΔAla-OMe	62076-63-5	60	A	114–115	6.37, 6.61	−23.1 (1.3)
Z-Gly-βClAla-Gly-OEt	7678-33-3	2-Gly-ΔAla-Gly-OEt[l]	36935-08-7	50	F	129–131	5.45, 6.47[h]	
Z-Phe-βClAla-Gly-OEt	62076-53-3	Z-Phe-ΔAla-Gly-OEt	62076-64-6	91		Oil	5.43, 6.45[h]	

[a] See Experimental Section for general reaction conditions. [b] Acceptable analytical data (±0.4% for C, H, N) were obtained for all new compounds except the oils listed (entries 2, 3, 9, and 10). Satisfactory NMR and TLC data were obtained on all compounds. Literature references are given for known compounds. [c] The acids listed were obtained by alkaline hydrolysis (1 N NaOH in EtOH) of the corresponding ester. [d] A = EtOAc–petroleum ether (bp 30–60 °C), B = EtOH, C = benzene–petroleum ether, D = EtOAc, E = ethyl ether–petroleum ether, F = $CHCl_3$–petroleum ether. [e] Chemical shift values for vinyl protons recorded in trifluoroacetic acid with an internal Me_4Si standard, unless noted otherwise. [f] Optical rotations recorded in DMF at 24 °C. [g] Reference 13a. [h] Recorded in $CDCl_3$. [i] Reference 28. [j] Reference 13a. [k] Oil polymerized upon attempted purification. [l] Reference 13b.

Table II. Data on Serine-Containing Peptides[a,b]

Registry no.	Peptide	Yield, %	Recrystn solvent[c]	Mp, °C	NMR, δ[d]	$[\alpha]_D$ (concn)[e]
34078-88-1	Z-Val-Ser-OMe	57	A	162–163	4.90, 4.22[f]	+10.4 (1.5)
62076-41-9	Z-Phe-Gly-Ser-OMe	41	B	136–137	4.91, 4.24	−18.3 (1.7)
62076-42-0	Z-Phe-Ala-Ser-OMe	37	B	176–177	4.93, 4.26	+7.5 (2.5)
62076-43-1	Z-Gly-Gly-Ser-OMe	58	B	69–70	4.90, 4.25	+1.8 (1.4)
62076-44-2	TFA-Gly-Ser-OMe	80	C	136–137	4.95, 4.31[f]	

[a] Only new compounds are listed in this table. References to known compounds used in this study are given in the Experimental Section. Acceptable analytical data (±0.4% for C, H, N) were obtained on all new compounds except for entry 5 above. Satisfactory NMR and TLC data were obtained on all compounds. [b] See Experimental Section for general reaction conditions. [c] A = EtOAc–petroleum ether (bp 30–60 °C), B = EtOAc, C = diethyl ether. [d] Chemical shift values for α-methine and β-methylene protons, respectively, in trifluoroacetic acid with internal Me_4Si, unless noted otherwise. [e] Measured in DMF at 24 °C. [f] Chemical shift values in $CDCl_3$.

silver nitrate test for ionic chlorine, while treatment with triethylamine followed by aqueous workup gave the original serine-containing tripeptide.[19c] Chlorination of Z-Gly-Gly-Ser-OMe and Z-Gly-Phe-Ser-OMe proceeded normally to yield the desired β-chloroalanine tripeptides. The reasons for obtaining oxazoline derivatives when phenylalanine is at the N-terminal position are not clear. The desired tripeptide, Z-Phe-Gly-β-ClAla-OMe, was obtained by coupling the appropriate protected dipeptide with β-chloroalanine methyl ester using *N,N'*-dicyclohexylcarbodiimide. The above chlorotripeptide underwent elimination in the normal fashion to yield the corresponding dehydroalanine tripeptide derivative.

Experimental Section

All new compounds reported in this paper gave satisfactory analytical data for C, H, and N to within ±0.4% of the calculated values, except as noted in tables. NMR spectra were obtained for all compounds with Varian EM 360 or XL-100-12 spectrometers; partial data are given in the tables. Recrystallized products were shown to be homogeneous by TLC on Brinkmann silica gel F_{254} plates developed in chloroform–methanol–acetic acid (85:10:5). Evaporations in vacuo were carried out with a Buchler rotary evaporator. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Elemental analyses were performed by M-H-W Laboratories, Garden City, Mich. The *N*-benzyloxycarbonyl-L-amino acids and L-serine methyl ester used were from commercial sources.

General Procedure for Preparation of Di- and Tripeptides Containing Serine. New compounds prepared in this work are listed in Table II. Known compounds employed are listed below with literature references: Z-Gly-Phe-OH,[20] Z-Phe-Gly-OH,[20] Z-Phe-Ala-OH,[21] Z-Gly-Gly-OH,[22] Z-Gly-Ser-OMe,[23,24] Z-Ala-Ser-OMe,[24] Z-Phe-Ser-OMe,[13a] Z-Gly-Phe-Ser-OMe,[25] TFA-Gly-OH,[26] TFA-Ser-OMe.[27]

The *N*-benzyloxycarbonyl or *N*-trifluoroacetylamino acid or dipeptide (5–15 mmol) and 1 equiv of L-serine methyl ester hydrochloride in chloroform were treated with 1 equiv of triethylamine and *N,N'*-dicyclohexylcarbodiimide. The reaction mixture was stirred at room temperature for 8–12 h. The dicyclohexylurea was removed by filtration and the filtrate was washed with dilute HCl, 5% $NaHCO_3$, and water. The organic phase was dried over Na_2SO_4. Evaporation in vacuo gave the peptide product which was recrystallized from the appropriate solvent (see Table II or appropriate literature reference). TFA-Gly-Ser-OMe proved to be water soluble; therefore, the above washing procedures were omitted.

General Procedure for Chlorination of Serine Peptide Derivatives. The β-chloroalanine peptide derivatives were prepared

Table III. Data for β-Chloroalanine Peptide Derivatives

Product[a]	Yield %[b]	Solvent[c]	Mp, °C	NMR, δ[d]	$[\alpha]_D$ (concn)[e]
Z-Gly-βClAla-OMe[f]	81	A	123–125	5.12, 3.96	
Z-Ala-βClAla-OMe	76	A	131–133	5.14, 3.96	+1.7 (1.5)
Z-Phe-βClAla-OMe	73	B	127–129	4.88, 3.97[g]	−11.1 (1.4)
Z-Val-βClAla-OMe	55	B	151–152	5.01, 3.97	+7.6 (1.5)
Z-βClAla-Gly-OEt	(78)	C	131–132.5	4.73, 4.05[i,g]	
Z-βClAla-Ala-OEt	50 (87)	D	149–150.5	4.78, 4.08[g]	−4.1 (1.5)
Z-βClAla-Leu-OMe	(88)	B	87–88.5	4.63, 3.86[g]	−7.3 (1.5)
Z-Gly-Gly-βClAla-OMe	78 (37)	B	147–148	5.01, 3.91	−6.6 (1.8)
Z-Gly-Phe-βClAla-OMe	63 (63)	B	140–141	5.08, 3.95	−5.5 (1.4)
Z-Phe-Gly-βClAla-OMe	0 (51)	B	148–149	5.08, 4.00	−12.1 (2.3)
Z-Gly-βClAla-Gly-OEt[h]	(68)	C	116–119	5.02, 4.00[i,g]	
Z-Phe-βClAla-Gly-OEt	(50)	E	184–186	5.00, 4.00[i]	−6.7 (1.4)
TFA-βClAla-OMe	37		Oil	4.96, 4.00[g]	
TFA-Gly-βClAla-OMe	77	A	133–134	5.23, 4.04[g]	

[a] See Experimental Section for general reaction conditions. Acceptable analytical, NMR, and TLC data were obtained on all compounds except for the last two entries. [b] Numbers in parentheses refer to yields obtained by DCC condensation with appropriate β-chloroalanine moiety. [c] A = benzene–petroleum ether (bp 30–60 °C), B = EtOAc–petroleum ether, C = EtOAc, D = $CHCl_3$–petroleum ether, E = $CHCl_3$–EtOH–petroleum ether. [d] Chemical shift values in trifluoroacetic acid for α and β protons, respectively, unless otherwise noted. Values given correspond to center of multiplet for each set of protons. [e] Recorded in DMF at 24 °C. [f] Reference 18. [g] Chemical shift values in $CDCl_3$. [h] Reference 15. [i] Approximate value as multiplet superimposed upon peaks due to glycyl methylene and ethyl ester methylene.

from the corresponding serine derivatives (0.2–20 mmol) by treatment with 1 equiv of PCl_5, added in portions, to a solution of the peptide in $CHCl_3$. The reaction mixture was stirred at room temperature for 12–16 h, washed with water, and dried over sodium sulfate. Evaporation in vacuo yielded the product as an oil which normally solidified upon standing. The solid product was recrystallized from the appropriate solvent listed in Table III.

Preparation of Di- and Tripeptides Containing β-Chloroalanine by Carbodiimide Method. The tripeptides, Z-Phe-Gly-βClAla-OMe, Z-Gly-Gly-βClAla-OMe, and Z-Gly-Phe-βClAla-OMe, were prepared by condensation of the appropriate *N*-benzyloxycarbonyldipeptide (5 mmol) with 1 equiv of β-chloro-L-alanine methyl ester hydrochloride[28] in 30 mL of chloroform–dimethylformamide (2:1) containing 1 equiv each of triethylamine and *N,N'*-dicyclohexylcarbodiimide. After 8 h, the urea was removed by filtration. The filtrate was diluted with chloroform, washed successively with dilute HCl, 5% $NaHCO_3$, and water, and dried over Na_2SO_4. Evaporation of the solvent in vacuo gave the tripeptide (see Table III).

The dipeptides (entries 5, 6, and 7, Table III) were prepared by the above procedure by condensation of *N*-benzyloxycarbonyl-β-chloro-L-alanine[15] with the appropriate amino acid ester in chloroform. The tripeptides (entries 11 and 12, Table III) were prepared in a similar fashion by condensation of the appropriate *N*-benzyloxycarbonylamino acid with β-chloro-L-alanylglycine ethyl ester hydrobromide.[15]

General Procedure for Preparation of Peptides Containing Dehydroalanine. The β-chloroalanine peptide derivative (1–5 mmol) in EtOAc was treated with 1 equiv of triethylamine or Dabco and the reaction mixture was stirred for 8–12 h at room temperature. The precipitated solid was removed by filtration and the filtrate was washed with water and dried over Na_2SO_4. The solvent was removed in vacuo to yield the dehydroalanine derivative (see Table I).

For those cases in Table I for which the acid is listed rather than the methyl ester, the ester was hydrolyzed according to the procedure of Photaki[13a] in a mixture of alcohol and 1 N sodium hydroxide.

Formation of Oxazoline Derivatives upon Chlorination. To a suspension of Z-Phe-Gly-Ser-OMe (**4**, R = H) (0.91 g, 2.0 mmol) in 10 mL of $CHCl_3$ was added PCl_5 (0.42 g, 2.0 mmol). A slightly exothermic reaction soon subsided whereupon a white solid was deposited. The mixture was stirred for 6 h and the solid was removed by filtration, washed with ether, and dried. Recrystallization of the solid from acetone yielded 0.75 g (75%) of oxazoline **5** (R = H), mp 159–160 °C, $[\alpha]^{24}_D$ −18.7° (c 1.0, DMF). This material gave an immediate precipitate with silver nitrate solution.

To a suspension of **5** (500 mg, 1 mmol) in 5 mL of ethyl acetate was added 1 equiv of triethylamine and the resulting mixture was stirred overnight at room temperature. The solid material was removed by filtration and the filtrate was washed with water, dried over Na_2SO_4, and removed in vacuo to yield 250 mg of a solid, mp 135–137 °C. This material was shown to be Z-Phe-Gly-Ser-OMe by comparison of melting point, NMR spectra, and TLC data.

In a similar manner, Z-Phe-Ala-Ser-OMe (**4**, R = Me) gave the oxazoline **5** (R = Me), mp 172–174 °C from acetone–ether, $[\alpha]^{24}_D$ −6.2° (c 2.0, DMF), in 81% yield. **5**, upon treatment with triethylamine followed by aqueous workup, gave **4** (R = Me).

Acknowledgment. Appreciation is expressed to the National Institutes of Health (Grants CA 10653 and AI 11978) for support of this work.

Registry No.—Z-Gly-Phe-OH, 1170-76-9; Z-Phe-Gly-OH, 13122-99-1; Z-Phe-Ala-OH, 21881-18-5; Z-Gly-Gly-OH, 2566-19-0; Z-Gly-Ser-O-Me, 10239-27-7; Z-Ala-Ser-O-Me, 19542-34-8; Z-Phe-Ser-O-Me, 860-55-9; Z-Gly-Phe-Ser-O-Me, 23828-12-8; TFA-Gly-OH, 383-70-0; TFA-Ser-O-Me, 1604-45-1; Z-Val-OH, 1149-26-4; L-Ser-O-Me-HCl, 5680-80-8; β-chloro-L-alanine methyl ester HCl, 17136-54-8; *N*-benzyloxycarbonyl-β-chloro-L-alanine, 7625-65-2; oxazoline **5** (R = H), 62076-65-7; oxazoline **5** (R = Me), 62078-95-9.

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Conversion of Threonine Derivatives to Dehydroamino Acids by Elimination of β-Chloro and *O*-Tosyl Derivatives

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DL-Threonine methyl ester was converted by chlorination with phosphorus pentachloride followed by N-acylation to *erythro*-α-acylamino-β-chloro-DL-butyric acid methyl esters, which upon elimination with Dabco as base yielded 2-acylaminocrotonates as a mixture of *E* and *Z* isomers. Elimination with DBU as base furnished predominantly the *E* isomer. The *Z* isomers formed from the above erythro compounds were shown to arise by isomerization of the corresponding *E* isomer. In comparison, *N*-acyl-*O*-tosyl-DL-threonine methyl esters (threo configuration) yielded only the *Z* isomer upon elimination. *N*-Tosylthreonine derivatives, regardless of configuration, undergo elimination to give *N*-tosylaminocrotonates of *Z* configuration. Evidence is given that aziridines are intermediates in the formation of olefin from *N*-tosylthreonine derivatives.

Dehydroamino acids are constituents of certain peptide antibiotics.[1] Considerable attention[2] has been given recently to the preparation of dehydroamino acids, particularly of the dehydroalanine unit, which unit is generally derived from serine or cysteine derivatives. In this paper, we report studies on elimination reactions of threonine to give 2-acylaminocrotonate derivatives.

Threonine derivatives have been converted to 2-acylaminocrotonates by dehydration[3] and tosylate elimination.[4] Other methods not directly involving threonine for preparation of 2-acylaminocrotonates have been by elimination reactions of sulfonium salts,[2b] sulfoxides,[2c] *N*-chloro-α-amino acid esters,[2f] α-(*N*-acylhydroxyamino) acid esters,[2g] and by amide condensation with α-keto esters.[2h] We recently have prepared peptides containing dehydroalanine by conversion of serine to a β-chloroalanine unit with subsequent elimination.[2i] In this paper, we report application of this method, and also elimination reactions of tosylate derivatives. for preparation of dehydroamino acids from derivatives of threonine.

DL-Threonine methyl ester hydrochloride (**1**) was transformed to *erythro*-β-chloro-DL-α-aminobutyric acid methyl ester hydrochloride (**2**)[5] by chlorination with phosphorus pentachloride, a reaction known to occur with inversion of configuration.[5] Acylation of **2** gave the *N*-acyl-*erythro*-β-chloro-DL-α-aminobutyrates **4**.

Treatment of the *erythro*-β-chlorobutyrates **4** with 1,4-diazabicyclo[2.2.2]octane (Dabco) in ethyl acetate effected elimination to yield the 2-acylaminocrotonates **5**. In all cases, a mixture of geometrical isomers was obtained, though the relative amounts of the *E* and *Z* isomers varied depending upon the *N*-acyl group (Table I). The proportion of geometrical isomers formed and assignment of configuration were determined by NMR spectroscopy[6] (see Table IV). The *E* isomer would be the product expected to be formed from the *erythro*-β-chlorobutyrates if a trans E_2 elimination was occurring. The *Z* isomer formed in these reactions likely arises from isomerization of the *E* isomer. Evidence for this was obtained by treatment of an 87:13 *E*:*Z* mixture of **5a** under the conditions of elimination for an additional 16 h, whereupon NMR analysis showed the composition to be 75:25 *E*:*Z*. Likewise, **4c** and **4e** each gave predominantly the *Z* isomer upon elimination, a result consistent with enhanced *E* to *Z* isomerization due to the electron-withdrawing effects of the *N*-benzyloxycarbonyl and trifluoroacetyl groups, respectively. Poisel and Schmidt[2f] have reported that, under acidic conditions, the *Z* isomer of 2-acylaminocrotonates is the thermodynamically controlled product, a result consistent with our observations.

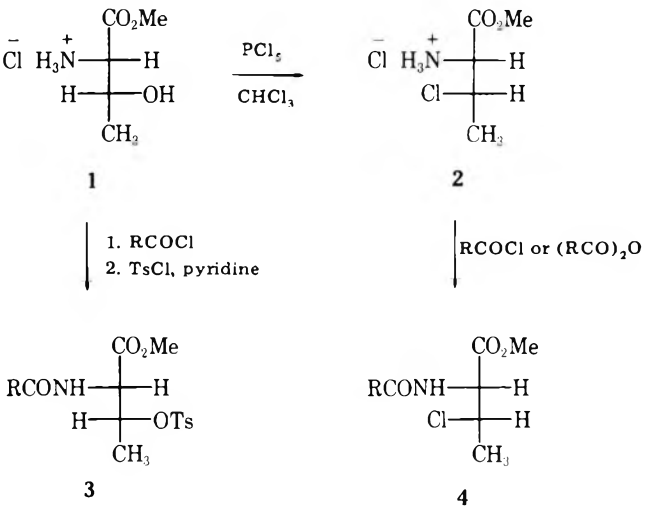
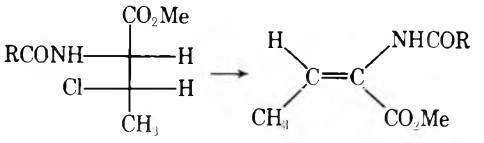
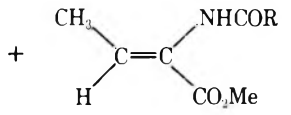


Table I. Elimination Reactions Using Dabco as Base

Reactant 4	R	Product 5 yield, %	Ratio E	Ratio Z
a	C_6H_5	90	66	33
b	$C_6H_5CH_2$	79	59	41
c	$C_6H_5CH_2O$	80	43	57
d	CH_3	46	77	23
e	CF_3	81	13	87
f	Z-$NHCH_2$	81	66	33



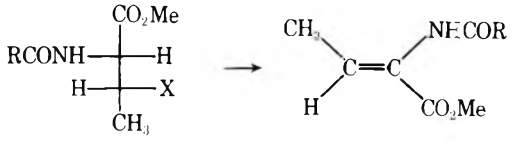
4 5-*E*



5-*Z*

Interestingly, treatment of the β-chlorobutyrate **4a** with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) effected elimination to give, as measured from the NMR spectrum of the product mixture, a 95:5 *E*:*Z* ratio; similar results were obtained for **4c** (entries 3 and 5, Table II). Thus, use of DBU as base affords a synthetically useful method for preparation of 2-acylaminocrotonates of *E* configuration. The elimination reactions with DBU proceed at a much faster rate than with Dabco and were complete within 1 h. In comparison, reaction of **4a** with Dabco was only 75% complete after a reaction period of 6 h. Treatment of **4a** with DBU for 72 h led to a 64:36 mixture of *E* and *Z* isomers; this result again is consistent for isomerization of the *E* to the *Z* isomer.

N-Acyl-*O*-tosyl-DL-threonine methyl esters (**3a–d**) of natural threo configuration underwent elimination to yield only *N*-acylaminocrotonates **5** of *Z* configuration, as expected for a trans E_2 elimination leading directly to the more stable *Z* isomer. *N*-Benzyloxycarbonyl-*threo*-β-chloro-DL-α-aminobutyric acid methyl ester (**3e**), prepared by chlorination of *allo*-threonine methyl ester, also yielded only the *Z* isomer upon elimination. The tosylates **3a–d** were prepared by tosylation of the corresponding *N*-acyl-DL-threonine methyl ester. Yields of the *Z* crotonates **5** obtained in the elimination reactions are given in Table III.



3a, R = Ph; X = OTs
b, R = $PhCH_2$; X = OTs
c, R = $PhCH_2O$; X = OTs
d, R = *Z*-$NHCH_2$; X = OTs
e, R = $PhCH_2O$; X = Cl

5-*Z*a, R = Ph
b, R = $PhCH_2$
c, R = $PhCH_2O$
f, R = *Z*-$NHCH_2$

Oxazolines are known[7,8] to be formed from serine and threonine derivatives upon chlorination. The possibility exists, therefore, that tosylate **3** and β-chlorobutyrate **4** could form oxazolines as intermediates in the elimination reaction leading to olefin. The formation of olefin from oxazolines has been reported.[9] We prepared the oxazoline hydrochloride **7** from **6** according to the procedure of Tishler and co-workers;[8] however, when **7** was treated to the conditions for elimination, no elimination to yield crotonate occurred and only the neutralized oxazoline **8** was obtained.

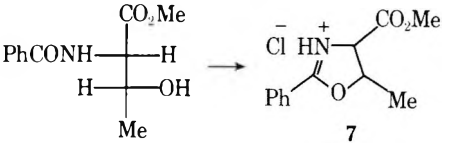
Table II. Variation of Isomer Distribution with Reaction Time and Base Used

Reactant	Base	Reaction time, h	Product 5, % E	Product 5, % Z
4a	Dabco	16	87	13
4a	Dabco	32	75	25
4a	DBU	1	95	5
4a	DBU	72	64	36
4c	DBU	1	85	15

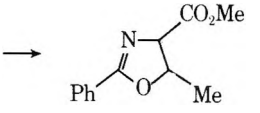
Table III. Elimination Reactions of *N*-Acyl-*O*-tosylthreonine Derivatives

Reactant	Product Z isomer	Yield, %	Mp, °C	Solvent[a]
3a	5a	81	78–79	A
3b	5b	76	79–81	A
3c	5c	85	65.5–67	B
3d	5f	89	56–59	A
3e	5c	64	65.5–67	B

[a] A = ethyl acetate–petroleum ether, B = benzene–petroleum ether.

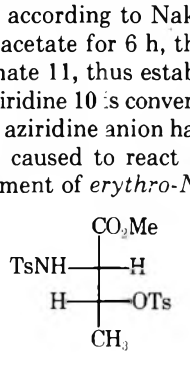


6 7



8

The elimination reaction of *N*-tosyl-DL-threonine methyl ester (**9**) appears to proceed by a diferent mechanism than the above elimination reactions, in that the aziridine **10** is implicated as an intermediate leading to at least a portion of the *Z* crotonate **11** formed in the reaction. Nakagawa et al.[4] have reported obtaining a mixture of **10** and **11**, as ethyl esters, when the ditosylate **9** was treated with *N*-ethylpiperidine in benzene. When a 40:60 mixture of **10** and **11**, which we prepared according to Nakagawa,[4] was treated with Dabco in ethyl acetate for 6 h, the only product obtained was the *Z* crotonate **11**, thus establishing that under these conditions the aziridine **10** is converted to crotonate **11**. The ring opening of the aziridine anion has been discussed.[10] When ditosylate **9** was caused to react with Dabco, only **11** was obtained. Treatment of *erythro*-*N*-tosyl-β-chloro-DL-α-aminobutyric



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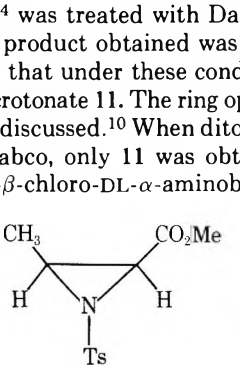

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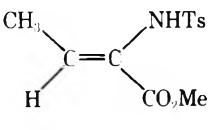
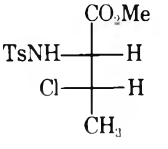
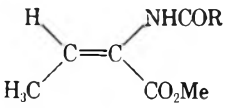


11

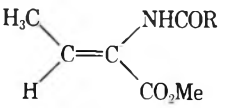


12

Table IV. NMR Data of 2-Acylaminocrotonates[a, b]



5-*E*



5-*Z*

Compd	Confign	R group			NH	Vinyl	β-Methyl	Methyl ester
		Ph	CH_2	CH_3				
5a	*E*	7.3–7.9			8.31	7.18	2.05	3.77
5a	*Z*	7.3–7.9			7.80	6.80	1.78	3.67
5b	*E*	7.32	3.57		7.10	7.03	1.97	3.62
5b	*Z*	7.32	3.65		6.90	6.68	1.65	3.66
5c	*E*	7.30	5.15		7.30	6.71	2.05	3.73
5c	*Z*	7.30	5.15		7.30	6.68	1.77	3.67
5d	*E*			2.00	7.62	6.90	2.02	3.75
5d	*Z*			2.00	7.40	6.72	1.71	3.68
5e	*E*				*c*	7.15	2.07	3.93
5e	*Z*				9.74	6.92	1.73	3.87
5f	*E*	7.32	5.12, 3.90[d]		8.12, 5.95	6.99	2.03	3.78
5f	*Z*	7.32	5.12, 3.85[d]		7.87, 5.95	6.83	1.71	3.70

[a] Spectra were recorded in $CDCl_3$ with shift values given in parts per million relative to Me_4Si. [b] Multiplicities for the various proton groupings in the order listed above are as follows: Ph (s or m), CH_2 (s), CH_3 (s), NH (brd), vinyl (q), β-methyl (d), methyl ester (s). [c] Intensity too weak to observe. [d] Shift values for glycine methylene.

acid methyl ester (12) with Dabco also furnished only *Z* crotonate 11. Attempts to observe formation of an aziridine in these reactions with Dabco as the base were not successful; if an aziridine intermediate is formed, it must rapidly undergo ring opening to form olefin. We also did not observe formation of the *E* crotonate from 12; however, if the *E* isomer were formed, either by direct elimination or via an aziridine, it may be rapidly isomerized to the *Z* isomer 11, though this isomerization would have to occur at a much faster rate, as might be expected, than for isomerization of the less acidic *N*-acylcrotonates 5.

The *Z* configuration was assigned to crotonate 11 on the basis that N-methylation of 11 with methyl iodide–sodium hydride in DMF gave a single product in which the vinyl proton showed a small downfield shift as compared to the vinyl proton position in 11. This result is consistent for a *Z* isomer of an *N*-acylaminocrotonate; in contrast, the corresponding *E* isomer would be expected to have undergone a substantial upfield shift upon N-methylation.[6]

Experimental Section

All new compounds that were crystalline gave satisfactory analytical data for C, H, and N to within ±0.4% of the calculated values. NMR spectra were obtained for all compounds with a Varian XL-100-12 spectrometer. Recrystallized products and products obtained as oils were shown to be homogeneous by TLC on Brinkmann silica gel F_{254} plates developed in chloroform–methanol–acetic acid (85:10:5), ethyl acetate–ligroin, bp 60–90 °C (1:1), or chloroform. Evaporations in vacuo were carried out with a Buchler rotary evaporator. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Elemental analyses were performed by M-H-W Laboratories, Garden City, Mich.

Preparation of *erythro*-α-Acylamino-β-chloro-DL-butyric Acid Methyl Esters 4a–e. For the preparation of **4a–c**, *erythro*-α-amino-β-chloro-DL-butyric acid methyl ester hydrochloride (**2**,[5] 5–10 mmol) in water–$NaHCO_3$ (2 equiv) was treated with the appropriate acid chloride (1 equiv) and the reaction mixture was stirred at room temperature for 4–6 h. The mixture was extracted with ethyl acetate, and the extracts were washed with 5% $NaHCO_3$ and water and dried (Na_2SO_4). In the case of **4a**, the product precipitated during the reaction and was collected by filtration.

4a: mp 77–78 °C from ethyl acetate–petroleum ether (bp 60–90 °C); 91% yield; NMR ($CDCl_3$) δ 1.67 (d, 3 H, β-methyl), 3.80 (s, 3 H, methyl ester), 4.41 (m, 1 H, β hydrogen), 4.91 (m, 1 H, α hydrogen), 6.98 (brd, 1 H, NH), 6.30–6.81 (m, 5 H, phenyl).

4b: oil; 62% yield; NMR ($CDCl_3$) δ 1.47 (d, 3 H, β-methyl), 3.56 (s, 2 H, benzyl), 3.70 (s, 3 H, methyl ester), 4.22 (m, 1 H, β hydrogen), 4.81 (m, 1 H, α hydrogen), 6.71 (brd, 1 H, NH), 7.30 (s, 5 H, phenyl).

4c: mp 53.5–55.5 °C from ether–petroleum ether; 74% yield; NMR ($CDCl_3$) δ 1.51 (d, 3 H, β-methyl), 3.70 (s, 3 H, methyl ester), 4.26 (m, 1 H, β hydrogen), 4.80 (m, 1 H, α hydrogen), 5.17 (s, 2 H, benzyl), 6.70 (brd, 1 H, NH), 7.31 (s, 5 H, phenyl).

Compounds **4d** and **4e** were prepared by treatment of **2** (5–10 mmol) with 1 equiv of triethylamine in ethyl acetate, followed by addition of 1.2 equiv of acetic anhydride and trifluoroacetic anhydride, respectively. The reaction mixture was stirred at room temperature for 6 h and filtered, and the filtrate was washed with saturated NaCl solution and dried over Na_2SO_4.

4d: oil; 56% yield; NMR ($CDCl_3$) δ 1.55 (d, 3 H, β-methyl), 2.00 (s, 3 H, acetyl), 3.72 (s, 3 H, methyl ester), 4.24 (m, 1 H, β hydrogen), 4.79 (m, 1 H, α hydrogen), 6.88 (brd, 1 H, NH).

4e: oil; 81% yield; NMR ($CDCl_3$) δ 1.70 (d, 3 H, β-methyl), 3.88 (s, 3 H, methyl ester), 4.37 (m, 1 H, β hydrogen), 4.91 (m, 1 H, α hydrogen), 7.55 (brd, 1 H, NH).

***N*-Benzyloxycarbonylglycyl-*erythro*-β-chloro-DL-α-aminobutyric Acid Methyl Ester (4f).** To a solution of **2** (1.88 g, 0.01 mol) and Z-Gly-OH (2.09 g, 0.01 mol) in chloroform–dimethylformamide (2:1) were added equimolar amounts of triethylamine and *N*,*N*[1]-dicyclohexylcarbodiimide and the reaction mixture was stirred for 8 h. Following filtration, the filtrate was washed with 2 N HCl, 5% $NaHCO_3$, and water and dried over Na_2SO_4. Removal of the solvent in vacuo furnished **4f** as a viscous oil: 50% yield; NMR ($CDCl_3$) δ 1.54 (d, 3 H, β-methyl), 3.78 (s, 3 H, methyl ester), 3.95 (d, 2 H, glycyl methylene), 4.31 (m, 1 H, β hydrogen), 4.73 (m, 1 H, α hydrogen), 5.21 (s, 2 H, benzyl), 5.80 (brd, 1 H, NH), 7.21 (brd, 1 H, NH), 7.31 (s, 5 H, phenyl).

Preparation of *N*-Acyl-DL-threonine Methyl Esters. The *N*-acyl-DL-threonine methyl esters used in the tosylation reactions described in the following section were prepared from DL-threonine methyl ester hydrochloride (**1**)[5] by acylation using the procedure described above for preparation of **4a–c**. The following compounds were prepared: *N*-benzyloxycarbonyl-DL-threonine methyl ester, oil, 80%; *N*-benzoyl-DL-threonine methyl ester, mp 83–84 °C (lit.[8] mp 82–84 °C), 73%; *N*-phenylacetyl-DL-threonine methyl ester, oil, 61% yield.

N-Benzyloxycarbonylglycyl-DL-threonine methyl ester was prepared from *N*-benzyloxycarbonylglycine and DL-threonine methyl ester hydrochloride using the carbodiimide procedure described above for **4f**, mp 104–105 °C from benzene, 50% yield.

Preparation of *O*-Tosyl-DL-threonine Derivatives 3a–d. The appropriate *N*-acyl-DL-threonine methyl ester (2–5 mmol) was dissolved in dry pyridine and the resulting solution was cooled to −5 °C. *p*-Toluenesulfonyl chloride (2 equiv) in dry pyridine was added dropwise at a rate to maintain the temperature below −5 °C. The reaction mixture was kept at 0 °C for 2 h and then was allowed to stand overnight in the refrigerator. The reaction mixture was poured

into water and the product, which precipitated as a solid, was collected by filtration and air dried. **3d** was an oil, which was isolated by extraction of the aqueous phase with chloroform.

3a: mp 89–90 °C from benzene–petroleum ether; 51% yield; NMR ($CDCl_3$) δ 1.26 (d, 3 H, β-methyl), 2.33 (s, 3 H, tolyl methyl), 3.50 (s, 3 H, methyl ester), 4.86 (m, 1 H, α hydrogen), 5.09 (m, 1 H, β hydrogens), 6.70 (brd, 1 H, NH), 7.18–7.80 (m, 9 H, phenyl hydrogens).

3b: mp 74–75 °C from ethyl acetate–petroleum ether; 40% yield; NMR ($CDCl_3$) δ 1.21 (d, 3 H, β-methyl), 2.43 (s, 3 H, tolyl methyl), 3.53 (s, 3 H, methyl ester), 3.61 (s, 2 H, $PhCH_2$), 4.73 (m, 1 H, α hydrogen), 5.06 (m, 1 H, β hydrogen), 6.14 (brd, 1 H, NH), 7.30 (s, 5 H, phenyl), 7.17–7.71 (A_2B_2, 4 H, tolyl).

3c: mp 74–75 °C from benzene–petroleum ether; 71% yield; NMR ($CDCl_3$) δ 1.33 (d, 3 H, β-methyl), 2.40 (s, 3 H, tolyl methyl), 3.55 (s, 3 H, methyl ester), 4.51 (m, 1 H, α hydrogen), 5.12 (s) superimposed upon m at 5.13 (3 H, benzyl and β hydrogen), 5.51 (brd, 1 H, NH), 7.30 (s, 5 H, phenyl), 7.15–7.80 (A_2B_2, 4 H, tolyl).

3d: oil; 57%yield; NMR ($CDCl_3$) δ 1.41 (d, 3 H, β-methyl), 2.49 (s, 3 H, tolyl methyl), 3.66 (s, 3 H, methyl ester), 4.01 (d, 2 H, glycyl methylene), 4.81 (m, 1 H, α hydrogen), 5.19 (s) superimposed upon m at 5.20 (3 H, benzyl and β hydrogen), 5.71 (brd, 1 H, NH), 6.98 (brd, 1 H, NH), 7.40 (s, 5 H, phenyl), 7.20–7.78 (A_2B_2, 4 H, tolyl).

***N*-Benzyloxycarbonyl-*threo*-β-chloro-DL-α-aminobutyric Acid Methyl Ester (3e).** *threo*-β-Chloro-DL-α-aminobutyric acid methyl ester hydrochloride[5] (0.75 g, 0.4 mmol) was treated with carbobenzoxy chloride as described above for **4c.** The product was obtained as a viscous oil in 57% yield: NMR ($CDCl_3$) δ 1.41 (d, 3 H, β-methyl), 3.65 (s, 3 H, methyl ester), 4.57 (m, 2 H, α and β hydrogens), 5.18 (s, 2 H, benzyl), 5.70 (brd, 1 H, NH), 7.32 (s, 5 H, phenyl).

General Procedure for Elimination Reaction of Threonine Derivatives. The respective *N*-acyl-*O*-tosylthreonine esters **3a–d** and *N*-acyl-*erythro*-β-chloro-α-aminobutyrates **4a–f** were dissolved in ethyl acetate and 2 equiv of 1,4-diazabicyclo[2.2.2]octane (Dabco) was added. The reaction mixture was stirred overnight at room temperature. Water was added to the reaction mixture and the organic phase was separated, washed with water, and dried over Na_2SO_4. The solvent was removed in vacuo to yield the dehydroamino acid derivatives **5.** The erythro derivatives **4** yielded a mixture of *E* and *Z* isomers of **5** (see Table I); the product mixture of *E* and *Z* isomers was analyzed by use of reported NMR spectral data;[6] complete NMR data are given in Table IV. The threonine derivatives **3** gave only the *Z* isomers of **5** (see Table III).

For the elimination reactions using 1,5-diazabicyclo[5.5.0]undec-5-ene (DBU) as base, the *N*-acyl-*erythro*-β-chloro-α-aminobutyrates **4a** and **4c** were dissolved in chloroform, DBU was added, and the reaction mixture was stirred for 1 h. The mixture was washed with 2 N HCl, saturated $NaHCO_3$, and water. The solvent was dried over $MgSO_4$ and removed in vacuo to yield product (Table II).

Reaction of Oxazoline 7 with Dabco. The oxazoline hydrochloride **7** (1.27 g, 5 mmol), prepared according to Tishler,[8] was treated with Dabco according to the general procedure described above. After the usual workup, 1.0 g (90%) of the neutral oxazoline **8** was obtained as an oil: NMR ($CDCl_3$) δ 1.32 (d, 3 H, methyl), 3.73 (s, 3 H, methyl ester), 4.90 (m, 2 H, H-4 and H-5), 7.22–8.00 (m, 5 H, phenyl).

The oxazoline **8**, upon treatment with ethereal HCl, furnished the oxazoline hydrochloride **7**, mp 117–119 °C (lit. 117–119 °C),[8] mixture melting point undepressed.

***N,O*-Ditosyl-DL-threonine Methyl Ester (9).** DL-Threonine methyl ester hydrochloride (3.4 g, 0.02 mol) in 20 mL of dry pyridine cooled to −5 °C was treated with 15.2 g (0.08 mol) of tosyl chloride in 30 mL of pyridine at a rate to maintain the temperature below −5 °C. The reaction mixture was kept at 0 °C for 2 h, stored overnight in the refrigerator, and poured into water. The solid was collected by filtration and air dried to yield 7.0 g (79%) of **9:** mp 120.5–122 °C from benzene–petroleum ether; mp of L isomer[11] 146–149 °C; NMR ($CDCl_3$) δ 1.41 (d, 3 H, β-methyl), 2.50 (s, 6 H, tolyl methyl), 3.51 (s, 3 H, methyl ester), 4.02 (m, 1 H, α hydrogen), 5.06 (m, 1 H, β hydrogen), 5.46 (brd, 1 H, NH), 7.21–8.00 (m, 8 H, tolyl aromatic).

***N*-Tosyl-*erythro*-β-chloro-DL-α-aminobutyric Acid Methyl Ester (12).** A solution of **2**[5] (3.4 g, 0.02 mol) in pyridine was treated with 1 equiv of tosyl chloride as described above. The reaction mixture was poured into crushed ice, and the solid was collected by filtration, washed with water, and air dried. Recrystallization from benzene–petroleum ether gave 4.9 g (81%) of **12:** mp 95–97 °C; NMR ($CDCl_3$) δ 1.49 (d, 3 H, β-methyl), 2.36 (s, 3 H, tolyl methyl), 3.48 (s, 3 H, methyl ester), 4.60 (m, 2 H, α and β hydrogens), 5.51 (brd, 1 H, NH), 7.18–7.62 (m, 4 H, tolyl aromatic).

Elimination Reactions for *N*-Tosyl Threonine Derivatives. The ditosyl derivative **9** (2.2 g, 5 mmol) was treated with *N*-ethylpiperidine according to the procedure of Nakagawa[4] to yield a mixture of aziridine **10** and (*Z*)-*N*-tosyl-α-aminodehydrobutyric acid methyl ester (**11**) in a ratio of 40:60. In other experiments, the percentage of aziridine **10** varied from 40 to 91%; similar erratic yields have been reported by Atherton and Meienhofer.[11] The above mixture of **10** and **11** was treated with Dabco (1 equiv according to the amount of aziridine) in ethyl acetate at room temperature for 6 h. Workup of the reaction mixture in the usual manner yielded 1.12 g (81%) of the dehydrobutyric acid **11**, mp 117–119 °C (lit.[4] mp 118–120 °C).

N,O-Ditosyl-DL-threonine (**9**) was treated with Dabco (2 equiv) in ethyl acetate and the reaction mixture stirred overnight at room temperature. Workup in the usual manner gave the *Z* isomer **11** in 85% yield.

Treatment of *N*-tosyl-*erythro*-β-chloro-α-aminobutyric acid methyl ester (**12**) with Dabco as above gave the *Z* isomer **11** in 79% yield. Reaction of **12** with *N*-ethylpiperidine also yielded only **11**; the aziridine **10** was not detected even when shorter reaction periods were used.

***N*-Methyl-*N*-tosyl-α-aminodehydrobutyric Acid Methyl Ester.** To a solution of **11** (270 mg, 1.0 mmol) in 2 mL of dimethylformamide was added 30 mg (1.2 mmol) of sodium hydride. After the evolution of hydrogen had ceased, 0.2 mL of methyl iodide was added. The mixture was stirred at room temperature for 2 h, poured into water, and extracted with chloroform. The extract was washed with water and dried over Na_2SO_4. Removal of the solvent in vacuo gave an oil that solidified upon standing. Recrystallization from petroleum ether gave 170 mg (60%) of product: mp 54–55 °C; NMR ($CDCl_3$) δ 1.91 (d, 3 H, β-methyl), 2.36 (s, 3 H, tolyl methyl), 2.94 (s, 3 H, *N*-methyl), 3.46 (s, 3 H, methyl ester), 7.09 (s, 1 H, vinyl), 7.18–7.60 (m, 4 H, tolyl aromatic). The position of the vinyl proton in **11** (ethyl ester) occurs at δ 6.93.[4]

Acknowledgment. Appreciation is expressed to the National Institutes of Health (Grant AI 11978) for support of this work.

Registry No.—**1,** 62076-66-8; **2,** 62076-67-9; **3a,** 62076-68-0; **3b,** 62076-69-1; **3c,** 62078-71-1; **3d,** 62076-70-4; **3e,** 62076-71-5; **4a,** 62076-72-6; **4b,** 62076-73-7; **4c,** 62076-74-8; **4d,** 62076-75-9; **4e,** 62076-76-0; **4f,** 62076-77-1; *Z*-**5a,** 60027-58-9; *E*-**5a,** 26927-54-8; *Z*-**5b,** 60027-60-3; *E*-**5b.** 60027-54-5; *Z*-**5c,** 60027-61-4; *E*-**5c,** 60027-55-6; *Z*-**5d,** 60027-59-0; *E*-**5d,** 60027-53-4; *Z*-**5e,** 60027-63-6; *E*-**5e,** 60027-57-8; *Z*-**5f,** 60027-62-5; *E*-**5f,** 60027-56-7; **7,** 62107-39-5; **8,** 62107-40-8; **9,** 62076-78-2; **11,** 62076-79-3; **12,** 62078-72-2; benzoyl chloride, 98-88-4; benzeneacetyl chloride, 103-80-0; carbonochloridic acid phenyl methyl ester, 501-53-1; trifluoroacetic anhydride, 407-25-0; Z-Gly-OH, 1138-80-3; *N*-benzyloxycarbonyl-DL-threonine methyl ester, 62076-80-6; *N*-benzoyl-DL-threonine methyl ester, 28415-16-9; *N*-phenylacetyl-DL-threonine methyl ester, 62078-73-3; *N*-benzyloxycarbonylglycyl-DL-threonine methyl ester, 19898-19-2; *p*-toluenesulfonyl chloride, 98-59-9; *threo*-β-chloro-DL-α-aminobutyric acid methyl ester HCl, 62076-81-7; *N*-methyl-*N*-tosyl-α-aminodehydrobutyric acid methyl ester, 62076-82-8.

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Displacement Reactions of Cyclic Sulfites and Phosphates by Salts of Weak Acids Applicable to the Synthesis of Phospholipids and Other Natural Substances

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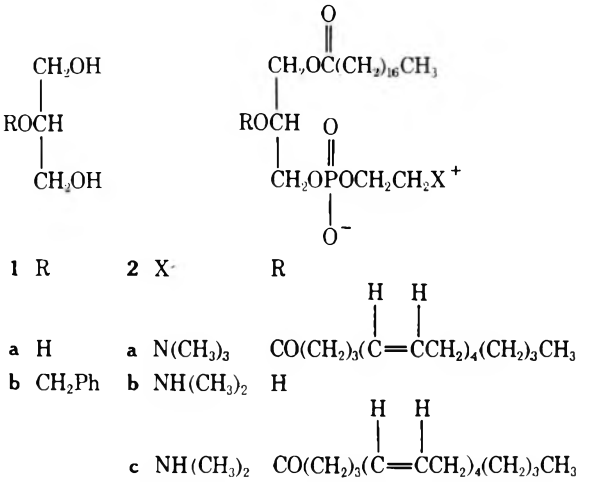
Six-membered ring cyclic sulfites **7a** derived from 2-*O*-benzylglycerol react in Me_2SO with salts of weak acids such as carboxylate and *p*-chlorophenoxide to yield 1-acyl- or 1-*O*-*p*-chlorophenoxy-2-*O*-benzylglycerols **8a**, **8b**, **8c**, and **8d** in good yields. In an analogous manner, the cyclic phenylphosphate **7b** reacts with carboxylate or phenylphosphate to yield the 1-acyl- or 1-phosphoryl-2-*O*-benzylglycerol 3-phosphates **8f** and **8h**. The potential applicability to the synthesis of glycerolphospholipids, e.g., the 2-arachidonoylphosphatidyldimethylethanolamine **2c**, and dinucleotides is demonstrated or discussed.

The structural feature present in glycerol (**1a**), i.e., the 1,3-diol system having at least one primary alcohol group, is present in natural products such as the glycerolphospholipids, sphingolipids, and also in carbohydrates that are found in oligosaccharides, glycolipids, and nucleotides. This paper describes a method which adds to other known and useful methods,[1] for the esterification and phosphorylation of the glycerol moiety.[2]

One of the purposes of this investigation was to facilitate the large-scale synthesis of glycerolphospholipids which would be esterified at C-1 and C-2 with a saturated and a polyunsaturated fatty acid, respectively. Such glycerolphospholipids play an important functional role in cell membranes in maximizing the activity of enzymes.[3] In addition, certain glycerolphospholipids, e.g., **2b**, esterified at C-2 with arachidonic acid, have been postulated as the immediate precursors of the fatty acids which are subsequently converted to prostaglandins.[4,5]



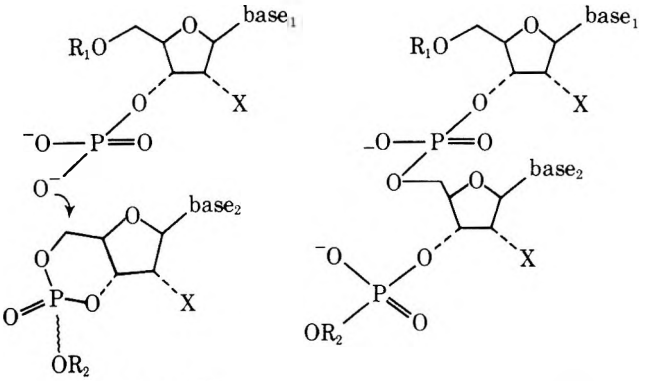
1 R: **a** H; **b** CH_2Ph

2 X⁻: **a** $N(CH_3)_3$; **b** $NH(CH_3)_2$; **c** $NH(CH_3)_2$

R: **a** $CO(CH_2)_3(C{=}CCH_2)_4(CH_2)_3CH_3$; **b** H; **c** $CO(CH_2)_3(C{=}CCH_2)_4(CH_2)_3CH_3$

Another purpose of this study was to find a model reaction which may serve to indicate the potential that a nucleotide monophosphate ester may have in displacing a second cyclic 3′,5′-phenyltriphosphate ester to form a dinucleotide under relatively neutral conditions. This reaction which is under investigation may formally be represented by the general equations in Scheme I.

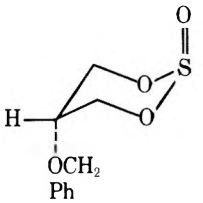
Scheme I



The result of this investigation is a new method for the selective acylation or phosphorylation of the 1,3-diol system, typified by glycerol (**1a**). The method involves a new ring opening reaction of cyclic esters, which are derived from sulfurous and phenylphosphoric acid and 2-*O*-benzylglycerol (**1b**), by salts of weak acids, such as carboxylic acids, *p*-chlorophenol, and phenylphosphoric acid.

Synthesis and Stereochemistry of Cyclic Sulfite and Phosphate Esters from 2-*O*-Benzylglycerol. For the purpose of this study, 2-*O*-benzylglycerol (**1b**), which possesses a suitably protected secondary hydroxyl group, was utilized to study the formation of the corresponding cyclic esters derived from sulfurous, phenylphosphoric, and sulfuric acid.

When 2-*O*-benzylglycerol was heated with dimethyl sulfite it was converted to a mixture of diastereomeric cyclic sulfite esters which were separated by chromatography into the 1,3,2-dioxathiane 2-oxides **3** and **4**. A comparison of the NMR spectra of the isomers indicated that the predominant isomer and conformer, present as 67% of the mixture, was **3** in which the bulkier 5-benzyloxy group is in the axial position. In



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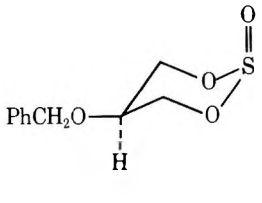
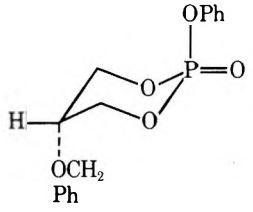


4

contrast to the values for the absorption frequencies in the NMR spectra for equatorial and axial hydrogen atoms in a cyclohexane ring, equatorial hydrogen atoms in 1,3,2-dioxathiane 2-oxides absorb at higher fields than their axial counterparts.[6] The C_5 hydrogen atom in the predominant isomer **3** exhibits a pentet centered at δ 3.46, which is at higher fields than its axial counterpart in **4**. The small coupling constant (J = 2 Hz) for the pentet of H_5e in **3** is that expected of an equatorial hydrogen coupled to the axial and equatorial hydrogens at C_4 and C_6. The results and assignment of configurations are also consistent with earlier observations that the S=O bond prefers the axial configuration in cyclic sulfite esters in the solution and the solid state, even when the 5 position of a 1,3,2-dioxathiane 2-oxide is occupied by a bulky substituent such as *tert*-butyl.[7]

Preparation of the cyclic sulfate ester from the corresponding sulfite by methods known to convert sulfites to cyclic sulfates,[8,9] e.g., by oxidation with peroxide or calcium permanganate, failed. For this reason, the reactions of the cyclic sulfate were not studied.

The phenylphosphates **5** and **6** were obtained as a mixture when 2-*O*-benzylglycerol was esterified with phenyl phosphodichloridate in pyridine. When the diastereomeric cyclic phosphates were separated by chromatography, the 5-benzyloxy-1,3-dioxa-2-phosphorinanes **5** and **6** were obtained in



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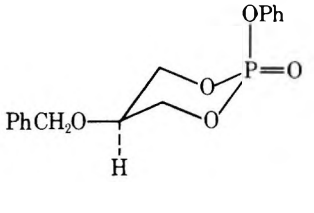


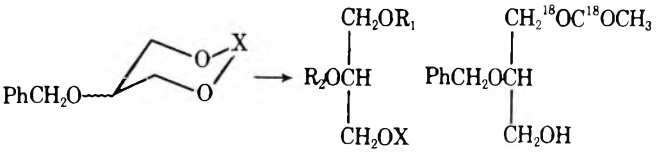
6

a ratio of 2:1, respectively. Their stereochemistry was assigned on the basis of spectral evidence. It has been established that in 2-oxo-2-phenoxy-1,3,2-dioxaphosphorinanes, unlike the sulfite (S=O) counterpart, the P=O bond is more stable in a conformation in which it is equatorial.[10,11] The NMR spectrum of the phosphate **5** parallels the spectrum of the analogous sulfite **3** and shows the absorption of the C-5 hydrogen at higher fields than its diastereomer. The shift (δ 3.60) to higher fields and the small coupling constants for the sextet (J = 1.5 Hz) are those expected of an equatorial proton in a six-membered ring cyclic phosphate having a chairlike conformation.[12]

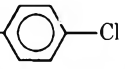
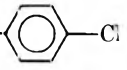
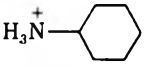
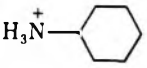
The derived cyclic sulfite and phosphate esters described above were then studied in regard to their nucleophilic displacement by salts of carboxylic acids and *p*-chlorophenoxide in order to achieve a reaction represented formally by **7** → **8**.

Reaction of Carboxylate and *p*-Chlorophenoxide with the Cyclic Sulfite Esters. The reaction of acyclic and cyclic aliphatic sulfites with nucleophiles such as hydroxide and alkoxide anions is known to take place with S–O bond cleavage.[13] On the other hand, nucleophiles such as tertiary amines, chloride and sulfide ions, and phosphines react with sulfites to give products of C–O cleavage.[8,9]

In our studies with carboxylate anions as nucleophiles, when the mixture of cyclic sulfite esters **7a** was heated in Me_2SO at

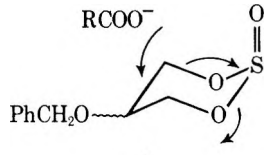


7 X
a S=C
b P=O(OPh)

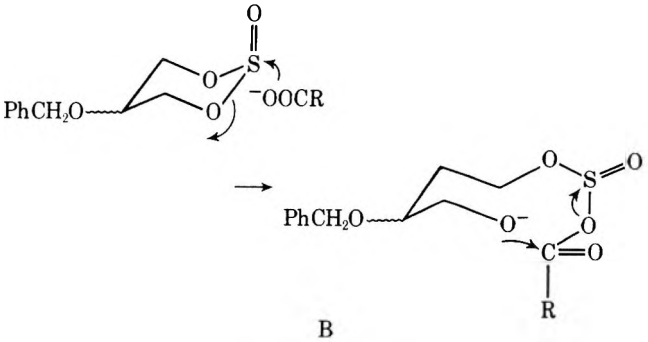
8	R_1	R_2	X
a	$COCH_3$	CH_2Ph	H
b	$COC_{15}H_{31}$	CH_2Ph	H
c	$COC_{17}H_{35}$	CH_2Ph	H
d		CH_2Ph	H
e		H	H
f	$COC_{17}H_{35}$	CH_2Ph	$P(OPh)O_2^-K^+$
g	$COC_{17}H_{35}$	CH_2Ph	$P(OPh)O_2^-Ag^+$
h	$P(OPh)O_2^-N^+(CH_3)_4$	CH_2Ph	$P(OPh)O_2^-N^+(CH_3)_4$
i	$P(OPh)O_2^-$	CH_2Ph	$P(OPh)O_2^-$
			
j	$COC_{17}H_{35}$	CH_2Ph	tosyl

130 °C with potassium acetate, palmitate, or stearate, the esters were converted in high yield to *rac*-1-acetyl-, 1-palmitoyl-, and 1-stearoyl-2-*O*-benzyl-*sn*-glycerol, **8a**, **8b**, and **8c**, respectively. No reaction occurred when the sulfites were heated with lithium stearate in THF solution.

Two mechanisms were considered for the ring opening of the cyclic sulfites. In the reaction with acetate ion, nucleophilic attack on the carbon atom could proceed with C–O cleavage and form an unstable sulfite as illustrated by mechanism A. Alternatively, attack by acetate could occur on the sulfur atom with S–O cleavage. An intermediate mixed anhydride would then form and internally acylate the resulting anion as represented by mechanism B.



A



B

In order to establish the mechanism of the reaction, isotopically labeled **8a** (**9**) was prepared from the sulfite **7a** using acetate in which both oxygen atoms were labeled with ^{18}O. The fragmentation patterns in the mass spectra of unlabeled and labeled acetate **8a** and **9** were studied, focusing on fragments resulting from the cleavage of the oxygen–acyl bond In the unlabeled acetate **8a** these are fragments *m/e* 181 and 43. In the product obtained with labeled acetate **9**, the fragment *m/e* 45 should be obtained regardless of which mechanism is op-

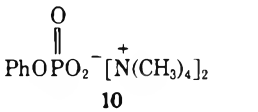
erating. However, the second fragment *m/e* 181 appears as fragment *m/e* 183 in the product only when mechanism A operates, i.e., when C–O bond cleavage occurs. This is true regardless of whether scrambling of the acetyl group occurs during the reaction or mass spectral analysis. The results show that the ratio of the mass peaks 183 and 181 in the labeled and unlabeled product is about 66:1. Thus, fission of the sulfite ester with carboxylate anion must occur predominantly by C–O cleavage, possibly with the assistance of the polar solvent Me_2SO.

In analogous manner to the reaction with carboxylate ion, *p*-chlorophenoxide ion reacted with the cyclic sulfites **7a** and gave **8d** in high yield.[14] When subjected to hydrogenolysis **8d** yielded chlorophenesin (**8e**),[15] a suppressor of humoral antibody response.

Reaction of Carboxylate and Phenylphosphate with the Cyclic Phosphate Esters 7b. Studies on the reaction of nucleophiles and cyclic phosphate triesters have shown that displacement with hydroxide or alkoxide occurs on the phosphorus atom.[16,17] Cyanide ion is known to attack the five-membered ring ethylene phosphate at the carbon atom with subsequent elimination of acrylonitrile.[18] Only recently has the displacement of a cyclic phosphate with trimethylamine been observed.[19] Nucleophilic displacement by carboxylate anion on cyclic phosphates has not been reported.

In our experiments when a mixture of 1,3-dioxa-2-phosphoranes **7b** was heated with potassium stearate in Me_2SO, the acyl and phosphoryl group were introduced in the desired positions in a single step to yield potassium 1-stearoyl-2-*O*-benzyl-3-phenylphosphorylglycerol (**8f**), isolated in 70% yield as the crystalline silver salt **8g**.

A second type of nucleophile which was prepared and utilized in a reaction with the cyclic phosphates **7b** was the bistetramethylammonium salt of phenylphosphoric acid (**10**). This substance was chosen because of its solubility in organic solvents. Also, being a salt of the weak acid, it would be expected to be a superior nucleophile when compared with a salt derived from diphenylphosphoric acid and, therefore, a more suitable model for the nucleophile in the reaction Scheme I. When the phosphate salt **10** was reacted with the cyclic phosphate **7b** in Me_2SO, a glycerol diphosphate was obtained which was isolated as the bistetramethylammonium glyceroldiphosphate **8h**. It was then converted by ion exchange chromatography to the cyclohexylammonium salt **8i**. A ^{13}C NMR spectrum of **8h** confirmed its symmetrical structure. A phosphorus analysis, ^{31}P NMR, and ^1H NMR spectra were consistent with the structural assignment for **8i**.



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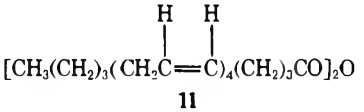

11

Synthesis of the 2-Arachidonoylglycerolphospholipid 2c. Compounds **8b** and **8c** were demonstrated by others[2,20,22] to be useful intermediates in the synthesis of glycerolphospholipids, possessing a saturated fatty acyl group at C-1 and polyunsaturated fatty acyl group at C-2. The 1-stearoyl-2-*O*-benzylglycerol (**8c**) was converted by way of the monotosylate **8j** to the lysophosphatidyldimethylethanolamine (**2b**), and arachidonic acid was converted to its anhydride **11** with dicyclohexylcarbodiimide in carbon tetrachloride. Reaction of **2b** with **11** in the presence of pyridine and a small amount of 4-dimethylaminopyridine, to facilitate the acylation, yielded the *rac*-2-arachidonoylglycerolphospholipid **2c**.

Experimental Section

Microanalyses were performed by Mr. Emmanuel Zielinski and associates, and spectra were run by Mr. John Damascus and associates of Searle Laboratories.

TLC runs were on 7.6-cm microscope slides covered with a 0.25-mm thickness of Woelm F silica, with a magnesium aluminum silicate binder. Visualization of spots was by phosphomolybdic acid, 5% in EtOH (w/v), followed by heat. Column chromatography used Mallinckrodt SilicAR CC-4 or CC-7 silicic acid. The weight ratio of adsorbent to material was 100:1. Materials were applied as benzene solutions and, unless indicated otherwise, eluted with benzene containing increasing amounts of EtOAc.

NMR spectra were taken on a Varian A-60A, T-60, or XL-100. All spectra are 60 MHz unless specified otherwise. Location of peaks are in parts per million using Me_4Si as an internal standard. The ^{31}P NMR spectrum was obtained through the courtesy of J. N. Shoolery of Varian Associates.

The mass spectral analyses were performed by J. Hribar and W. Aksamit using an AEI MS-30 mass spectrometer (70 eV, 4 kV accelerating volts) by direct insertion probe (source 220 °C).

Dimethyl sulfoxide (distilled in glass) was obtained from the Burdick-Jackson Laboratories, Inc. Melting points were taken on a Fisher-Johns hot-stage apparatus and are uncorrected. Hydrogenations were done by Mr. M. Scaros and Ms. J. Serauskas and chromatography by B. Smith and R. Nicholson and their associates at Searle Laboratories.

2β-Oxo-5α-benzyloxy-1,3-dioxa-2-thiane (3) and 2β-Oxo-5β-benzyloxy-1,3-dioxa-2-thiane (4) or 7a. A mixture of 50 g (0.29 mol) of 2-*O*-benzylglycerol[21] and 32.5 g (0.33 mol) of dimethyl sulfite was heated so that the temperature of the mixture was brought up slowly to 128 °C over a period of 3 h. The reaction was followed by using TLC plates and elution of the plates with ethyl acetate–benzene (30:70). The mixture was heated for an additional 4 h at 128 °C and then distilled slowly to yield product **7a**, bp 148–152 °C (0.7 mm), which was a mixture of two isomers, in average yield of 40.5 g (61%). An NMR spectrum of the product indicated a ratio of **3** and **4** to be 2:1. The mixture of diastereomers (530 mg) in ethyl acetate–benzene (3:7) was separated by dry column chromatography on CC-7 silica gel (150 g) equilibrated with 12 mL of water on a 3.7 cm (width) column and developed with 200 mL of ethyl acetate–benzene (3:7). The column was divided into four fractions of silica gel after sampling by TLC. The first fraction was extracted with 125 mL of methylene chloride and yielded 118 mg of **3**: δ 3.46 (pentet, $J_{5e,4e} \sim J_{5e,6e} \sim J_{5e,4a} \sim J_{5e,6a}$ = 2 Hz, 1 H, C_{5e} H), 3.93 (J_{gem} = −12.5 Hz, broad doublets, $J_{4e,5e} \sim J_{6e,5e} \sim J_{4a,5e} \sim J_{6a,5e}$ = 1.5 Hz, 2 H, $C_{4e,6e}$ H), 4.91 (J_{gem} = −12.5 Hz, broad doublets, $J_{4a,5e} \sim J_{6a,5e} \sim J_{4e,5e} \sim J_{6e,5e}$ = 1.5 Hz, 2 H, $C_{4a,6a}$ H), 4.67 (s, 2, OCH_2), and 7.34 (s, 5, Ph).

Anal. Calcd for $C_{10}H_{12}O_4S$: C, 52.67; H, 5.27. Found: C, 52.97; H, 5.25. The fourth fraction was extracted with 125 mL of methylene chloride and yielded 16 mg of **4**: δ 3.80–4.10 (m, 3, C_{5e} H and $C_{4e,6e}$ H), 4.35–4.75 (m, 2, C_{5a} H, $C_{4a,6a}$ H), 4.58 (s, 2, OCH_2), and 7.32 (s, 5, C_6H_5); the C_{5a} H in **4** was too difficult to resolve and its absorption band was found overlapping, at higher fields than the C_{5e} H in **3**, with bands for the C_4 and C_6 hydrogen atoms.

Anal. Calcd for $C_{10}H_{12}O_4S$: C, 52.67; H, 5.27. Found: C, 53.01; H, 5.44.

Attempts at oxidation of cyclic sulfite ester **7a** with calcium permanganate in acetic acid–chloroform (1:1), with 30% aqueous hydrogen peroxide in acetone, or with chromium trioxide–sulfuric acid yielded mostly starting material as evidenced by TLC.

2α-Oxo-2β-phenoxy-5α-benzyloxy-1,3-dioxa-2-phosphorane (5) and 2α-Oxo-2β-phenoxy-5β-benzyloxy-1,3-dioxa-2-phosphorane (6) or 7b. To a solution of 11.25 g (61.8 mmol) of 2-*O*-benzylglycerol,[21] 75 mL of acetone (AR grade which was distilled from molecular sieves), and 7.6 g of pyridine, which was cooled in an ice bath, was added in 25 min a solution of 12.7 g of dichlorophenyl phosphate. A precipitate of pyridine hydrochloride appeared and the mixture stood at room temperature for 18 h. A TLC on silica gel developed with ethyl acetate–benzene (30:70) indicated that the reaction was complete. The mixture was filtered and the collected solid was washed with acetone. The filtrate was distilled to dryness under reduced pressure and the residue was dissolved in ethyl acetate–benzene. The solution was washed with three 150-mL portions of water, dried over magnesium sulfate, and distilled to dryness. Recrystallization of the crude product **7b** by removal of the ethyl acetate by distillation at low temperatures and pressure gave 5.8 g (45%) of **5**. Crystallization of the product from ethyl acetate gave pure **5**: mp 120–123 °C; δ 3.60 (sextet, $J_{5e,4e} \sim J_{5e,6e} \sim J_{5e,4a} \sim J_{5e,6a} \sim J_{5ep}$ = 2 Hz, 1 H, C_{5e} H), 4.33, measured from center of band (J_{gem} = −12, $J_{4e,5e} \sim J_{6e,5e} \sim J_{4a,5e} \sim J_{6a,5e}$ = 1.5 Hz, 2 H, $C_{4e,6e}$ H), 4.72, measured from center of band (J_{gem} = −12, $J_{4e,5e} \sim J_{6e,5e} \sim J_{4a,5e} \sim J_{6a,5e}$ = 1.5 Hz, 2 H, $C_{4a,6a}$ H), 4.67 (s, 2, OCH_2), and 7.30, 7.37 (2 s, 10, 2 C_6H_5).

Anal. Calcd for $C_{16}H_{17}O_5P$: C, 60.00; H, 5.35. Found: C, 59.96; H, 5.37.

The mother liquor from the recrystallization of **5**, which was rich in **6**, was evaporated to dryness. The 2.5 g of the mixture was dissolved in ethyl acetate–benzene (1:7) and separated by dry column chromatography on CC-7 silica gel (150 g) equilibrated with 12 mL of water and developed with 150 mL of ethyl acetate–benzene (1:7). The column was divided into six parts. The third fraction containing **6** was extracted with ethyl acetate and methylene chloride to yield 818 mg of product **6**, mp 40–45 °C: δ 3.91–4.67 (m, 5, C_{5a} H, C_4 and C_6H_2), 4.50 (s, OCH_2), and 7.30, 7.34 (2 s, 10, 2 C_6H_5). The C_{5a} H in **6** was too difficult to resolve and its absorption band was found overlapping, at higher fields than the C_{5e} H in **3**, with bands for the C_4 and C_5 hydrogen atoms.

Anal. Calcd for $C_{16}H_{17}O_5P$: C, 60.00; H, 5.35. Found: C, 59.95; H, 5.37.

***rac*-1-Acetyl-2-*O*-benzyl-*sn*-glycerol (8a).** When 73.8 g (0.32 mol) of **7a** was reacted with 32 g (0.326 mol) of anhydrous potassium acetate in Me_2SO at temperatures of 132–145 °C according to the procedure outlined for the preparation of **8b**, 67 g of crude acetate **8a** was obtained containing traces of sulfite ester or 2-*O*-benzylglycerol. The substance was purified by column chromatography on CC-7 silica gel and elution with methylene chloride–hexane (1:1) with increasing amounts of ethyl acetate. The pure acetate was obtained when the column was eluted with ethyl acetate–methylene chloride–hexane (15:42.5:42.5): IR 3600 (OH) and 1745 cm^{-1} (Ac); δ (D_2O exchanged) 2.07 (s, 3, $COCH_3$), 3.65–3.78, 4.20–4.28 (m, 5 H, $-OCH_2CHCH_2O-$), 4.67 (s, 2, OCH_2), and 7.35 (s, 5 H, $-C_6H_5$); mass spectrum *m/e* 224 (M^+), 183/181 (M − 43/M − 45) (16:1), 165 (M − acetoxy), 167 (no peak), and 43/45 ($CH_3CO/CH_3C^{18}O$) (11:1).

***rac*-1-Di^{18}-*O*-Acetyl-2-*O*-benzyl-*sn*-glycerol (9).** To a solution of 250 mg (3.9 mmol) of [^{18}O]acetic acid (90%, Bio-Rad Laboratories) in 25 mL of anhydrous toluene was added 438 mg (3.9 mmol) of potassium *tert*-butoxide. The mixture was heated at reflux for 1 h and then distilled to dryness at 120 °C under reduced pressure. Me_2SO (15 mL) was added to the potassium acetate in an atmosphere of nitrogen and the mixture was heated to 104 °C. Then 890 mg (3.9 mmol) of sulfite ester was added and the mixture was stirred at 130–135 °C for 3.5 h. The Me_2SO was removed by distillation and the residue was extracted with methylene chloride. The mixture was filtered and the filtrate was distilled to dryness. The crude product was purified by dry column chromatography on CC-7 silica gel (150 g) equilibrated with 12 mL of water for 16 h and developed with 200 mL of ethyl acetate–benzene (3:17). The second of four fractions upon extraction with ethyl acetate and removal of solvent yielded 125 mg of pure **9**. An NMR ($CDCl_3$) was identical with that of **8a**; mass spectrum *m/e* 183/181 (M − 43/M − 45) (1:4.1), 165 (M − acetoxy) 167 (no peak), and 43/45 ($CH_3CO/CH_3C^{18}O$) (1:4.5).

***rac*-1-Palmitoyl-2-*O*-benzyl-*sn*-glycerol (8b).** Potassium palmitate was prepared by adding 33.7 g (0.3 mol) of potassium *tert*-butoxide to 76.9 g (0.3 mol) of palmitic acid in 3.5 L of dry toluene in a drybox. The mixture was heated at reflux for 1 h in an atmosphere of nitrogen and then concentrated by distillation to 2 L in 2 h. The potassium palmitate, which was collected by filtration, washed with toluene, and dried in an atmosphere of nitrogen, weighed 83.3 g (93%).

A mixture of 83.3 g of potassium palmitate and 1250 mL of Me_2SO was heated to 105 °C in an atmosphere of nitrogen and then 63.7 g (0.28 mol) of the unseparated mixture **7a** was added in 15 min. The potassium palmitate dissolved as the reaction proceeded. The mixture was heated at 130 °C for 4–6 h, and then concentrated by distillation at 80 °C (<1 mm) to remove the Me_2SO. The residue was dissolved in 4 L of methylene chloride. Some insoluble material was removed in a slow filtration through a layer of Supercel. The methylene chloride solution was washed with three 400-mL portions of water, dried over a mixture of sodium and magnesium sulfate, filtered through a layer of Supercel, and distilled to dryness. The crude product, which weighed 102.2 g (86%), was purified by crystallization from 500 mL of methanol cooled in a dry ice–isopropyl alcohol bath for 1 h. The product was collected in an insulated glass sintered funnel and then heated at 40 °C under reduced pressure to remove residual methanol. The product **8b**[20] remained solid when stored at 0 °C and was analytically pure: δ 0.83–0.90, 125 [m, 35, $(CH_2)_{14}CH_3$], 2.20–2.47 (m, CH_2CO, OH), 3.48–3.55 and 4.18–4.27 (m, 5, OCH_2CHCH_2O), 4.65, 4.67 (d, 2, OCH_2Ph), and 7.37 (s, 5, C_6H_5).

Anal. Calcd for $C_{26}H_{44}O_4$: C, 74.24; H, 10.54. Found: C, 74.20; H, 10.31.

***rac*-1-Stearoyl-2-*O*-benzyl-*sn*-glycerol (8c).** When 63.2 g (0.277 mol) of **7a** was treated with 87.2 g (0.3 mol) of potassium stearate in 1.2 L of Me_2SO according to the procedure outlined for the preparation of **8b**, 121 g (100%) of crude **8c** and 104.4 g of pure **8c**[20] were obtained after crystallization from very cold methanol (−20 to −60 °C). The product **8c** was converted with excess *p*-toluenesulfonyl chloride in pyridine at 0 °C to its tosylate **8j**. The NMR spectra of **8c** and **8j**, like **8b**, were consistent with the assigned structures reported previously.[20,22,24]

***rac*-1-*O*-*p*-Chlorophenyl-2-*O*-benzylglycerol (8d).** A solution of 4.1 g (0.018 mol) of the cyclic sulfite **7a**, 50 mL of Me_2SO, and 3.25 g (0.0194 mol) of the potassium salt of *p*-chlorophenol was heated with stirring in an atmosphere of nitrogen at 127–130 °C for 1 h. The mixture was concentrated by distillation under reduced pressure (0.1 mm) and then added to 250 mL of an ice–water mixture. The aqueous mixture was extracted with two 100-mL portions of methylene chloride. The methylene chloride solution was washed with 30 mL of water and 30 mL of 3% aqueous sodium bicarbonate, dried over sodium sulfate, and distilled to dryness. The crude product weighed 4.6 g. It was purified by low-pressure column chromatography utilizing 250 g of Woelm silica gel under 200 psi pressure and a flow rate of 10 mL/min. Elution with ethyl acetate–benzene (3:17) gave fractions which when combined yielded 2.28 g of analytically pure **8d**: δ 3.7–4.1 (m, 5, OCH_2CHCH_2O), 4.70 (s, 2, OCH_2Ph), 6.71–7.2 (m, 4 H, $-C_6H_4Cl$), and 7.38 (s, 5 H, C_6H_5).

Anal. Calcd for $C_{16}H_{17}ClO_3$: C, 65.64; H, 5.85. Found: C, 65.32; H, 5.83.

1-*O*-*p*-Chlorophenylglycerol (8e). A mixture of 2.58 g of **8d**, 140 mL of benzene, 260 mg of 10% Pd/C, and 0.5 mL of a saturated solution of HCl in isopropyl alcohol was shaken in an atmosphere of hydrogen (atmospheric pressure). After 8.5 h an additional 260 mg of catalyst was added and the hydrogenation was continued for 1.5 h. The mixture was diluted with 100 mL of benzene and separated by filtration. The benzene solution was washed with aqueous sodium bicarbonate solution and water, dried over sodium sulfate, and evaporated to dryness. The crude product weighed 1.58 g. It was purified by column chromatography on Woelm silica gel (250 g) under 200 psi pressure and a flow rate of 10 mL/min. Elution with ethyl acetate gave fractions which yielded 501 mg of crude **8e**. Crystallization of the crude product from hexane yielded 365 mg of **8e**, mp 80–81 °C.

Anal. Calcd for $C_9H_{11}ClO_3$: C, 53.34; H, 5.47. Found: C, 53.41; H, 5.41.

Silver *rac*-1-Stearoyl-2-*O*-benzyl-*sn*-glycerol 3-Phenylphosphate (8g). A crude mixture of 1.38 g (4.3 mmol) of cyclic phosphates **7b** in 25 mL of Me_2SO was added dropwise with stirring to a mixture of 1.49 g of potassium stearate and 40 mL of Me_2SO maintained at 124 °C. The mixture was heated at 130 °C for 2 h and then concentrated by distillation at 80 °C (0.3 mm) to remove Me_2SO. The residue, a yellow-brown solid, was dissolved in ether. A small amount of remaining precipitate was removed by filtration and the filtrate was evaporated to dryness. An NMR of the product, which weighed 2.3 g, was consistent with the structure of **8f**: δ 0.831–1.33 [m, 35, $(CH_2)_{16}CH_3$], 1.93–2.13 (m, CH_2CO), 3.67–4.16 (m, 5, OCH_2CHCH_2O), 4.43 (s, 2, $PhCH_2O$), and 7.07–7.28 (m, 10, 2 C_6H_5). The salt was dissolved in 137 mL of acetone and the slightly hazy solution was filtered and warmed to about 50 °C. To this solution, protected from light, were added a warm solution of 663 mg (3.9 mmol) of silver nitrate, 19 mL of water, and 38 mL of acetone. A precipitate appeared which on further warming to 53 °C dissolved. The solution upon cooling in an ice–salt mixture yielded colorless crystals, 2.3 g (74%), of analytically pure **8g**.

Anal. Calcd for $C_{34}H_{52}O_7AgP$: C, 57.43; H, 7.37. Found: C, 57.31; H, 7.37.

Tetramethylammonium and Dicyclohexylammonium Salts of 2-*O*-Benzylglycerol 1,3-Bisphenylphosphate (8h and 8i). The bistetramethylammonium salt of phenylphosphoric acid was prepared in the following way. To a cold solution of 500 mg (2.87 mmol) of phenylphosphoric acid[23] in 3 mL of distilled water was added a solution of 2.1 mL of 2.69 N tetramethylammonium hydroxide in methanol. The solution was evaporated to dryness at 35 °C (0.1 mm) to yield 918 mg of the amorphous salt **10**, which was used without further purification. When 1 equiv of base was used to neutralize the phenylphosphoric acid, a crystalline monoammonium salt was obtained. The NMR spectrum of the monoammonium salt exhibited maxima which indicated the presence of one tetramethylammonium group for each phenyl group.

A solution of 860 mg (2.68 mmol) of **10** and 780 mg (2.44 mmol) of cyclic phosphates **7b** in 25 mL of Me_2SO was heated at 125–130 °C for 1.8 h. The Me_2SO was removed at 75–80 °C (0.1–0.3 mm). The residue was extracted with four portions of 30 mL of ether and then dissolved in 25 mL of distilled water. A small amount of precipitate (37 mg) which remained was the cyclic phosphate ester. The aqueous solution containing the product was distilled to dryness at 45 °C (0.1 mm) to yield 990 mg of the crude product **8h**: ^{1}H NMR (Me_2SO) δ 3.10

[s, 24 $^{+}N(CH_3)_4$], 4.50 (s, 2, OCH_2Ph), and 7.10–7.27 (m, 15, 3 C_6H_5); ^{13}C NMR [D_2O-dioxane (67:41)] decoupled, δ 56.1 (CH_3), 65.7 (OCH_2), 72.7 (OCH_2Ar), 77.8 (OCH), 120.8, 121 (C-2, 6 of PhO), 1.8 (C-4 of PhO), 128.8, 129, 129.2 (C-2, 4, 6 of Ph), 130.5 (C-3 of Ph), 138.2 (C-1 of Ph), and 152.9 (C-1 of PhO).

Anal. Calcd for $C_{30}H_{46}N_2O_9P_2$: H, 7.24; N, 4.37. Found: H, 7.49; N, 4.25.[22]

A 3-mL sample of Dowex 50 W-X8 (1.7 mg/mL resin bed, 20–50 mesh) hydrogen form was exchanged with cyclohexylamine and then washed with distilled water. A solution of 500 mg of **8h**, obtained above, in 5 mL of water was passed through a column of the cyclohexylamine treated resin. The column was eluted with an additional amount of water to collect the salt **8i**. The aqueous fractions containing the product were collected and evaporated to dryness under reduced pressure. Crystallization of the residue from methanol and acetone yielded crystals, mp 174–178 °C: R_f 0.26 [NaOAc–EtOH–H_2O (0.05:1:1)]; ^1H NMR δ 1.13–2.18 [m, 20, $2(CH_2)_5$], 3.78–4.20 (m, 5, OCH_2CHCH_2O), 4.62 (s, 2, OCH_2Ph), and 7.07–7.35 (m, 15, 3 C_6H_5); ^{31}P NMR (D_2O) (H_3PO_4, δ 56.46) δ 54.94 (1400 transients with proton decoupling), a partially resolved triplet was found when decoupler was turned off.

Anal. Calcd for $C_{34}H_{50}N_2O_9P_2$: C, 58.95; H, 7.28; N, 4.04; P, 8.95. Found: C, 56.60; H, 7.38; N, 4.30; P, 8.79.[24]

***rac*-1-Stearoyl-2-arachidonoyl-*sn*-glycerol-3-phosphoryl-(*N*,*N*-dimethyl)ethanolamine (2c).** Arachidonic acid anhydride was prepared in the following way. A solution of 10.7 g (35 mmol) of arachidonic acid (90% purity from Hormel Institute) in 200 mL of dry carbon tetrachloride was added, with stirring over a period of 5 min and in an atmosphere of nitrogen, to a solution of 3.72 g (18 mmol) of dicyclohexylcarbodiimide in 110 mL of carbon tetrachloride. After stirring in the dark for 6 h, the mixture was filtered through a Celite filter pad. The filtrate was distilled to dryness under reduced pressure at 50 °C. The oil **11** which remained weighed 10.7 g [R_f 0.89, MeOH–$CHCl_3$ (1:19)] and was utilized without further purification.

A mixture of 3.90 g (8.1 mmol) of the lysolipid **2b**, prepared from **8j** by the method of Van Deenan,[22,24] 10.7 g (17 mmol) of freshly prepared **11**, 29 mL of pyridine (distilled over CaH), and 290 mg of 4-dimethylaminopyridine was stirred at 23 °C for 18 h. A TLC indicated that the reaction was complete. The solution was poured into 250 mL of toluene and concentrated by distillation to remove the pyridine. The concentrated solution was evaporated to dryness at 50 °C (0.3 mm). The crude product weighed 16.1 g. It was dissolved in methanol–chloroform (1:19) and purified by chromatography on 1400 g of CC-7 silica gel. Elution with methanol–chloroform (1:19) gave a forefraction which was discarded. Elution with methanol–chloroform (1:9) yielded **2c** weighing 4.38 g (70%); TLC R_f 0.47 on CC-7 silica gel; 95 $CHCl_3$: 35 MeOH:6 H_2O δ 0.80–1.02 (t, 6, 2 CH_3), 1.30 [s, broad $(CH_2)_{13}$, $(CH_2)_4$, $(CH_2)_3$], 1.67–2.41 (m, 10, C=CCH_2, 2 CH_2CO), 4.43–4.64, [m, s, 12, (C=CCH_2C=C)$_3$, $N(CH_3)_2$], 3.20–3.33 (m, hidden with D_2O, NCH_2), 3.97–4.43 (m, 7, OCH_2CHCH_2O, OCH_2O), and 5.33, 5.41, 5.50 (m, 8, 4 cis CH=CH).

Anal. Calcd for $C_{45}H_{82}NO_8P$: H, 10.24; N, 1.82. Found: H, 10.03; N, 1.66.[24]

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Registry No.—**1b,** 14690-00-7; **2b,** 19491-37-3; **2c,** 62085-19-2; **3,** 62067-16-7; **4,** 62067-17-8; **5,** 42320-93-4; **6,** 42320-37-6; **8a,** 62067-18-9; **8b,** 62106-90-5; **8c,** 18679-03-3; **8d,** 62067-19-0; **8e,** 62067-20-3; **8f,** 62067-21-4; **8g,** 62085-20-5; **8h,** 62085-22-7; **8i,** 62067-23-6; **9,** 62067-24-7; **10,** 62067-25-8; **11,** 55726-28-8; dimethyl sulfite, 616-42-2; dichlorophenyl phosphate, 770-12-7; palmitic acid, 57-10-3; potassium stearate, 593-29-3; *p*-chlorophenol, 106-48-9; phenylphosphoric acid, 701-64-4; tetramethylammonium hydroxide, 75-59-2; cyclohexylamine, 108-91-8; arachidonic acid, 506-32-1.

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Sesquiterpene Lactones of *Eupatorium perfoliatum*[1,2]

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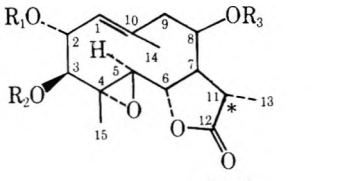
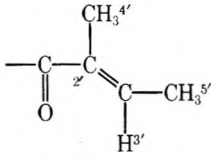
Structures of four new sesquiterpene lactones isolated from *Eupatorium perfoliatum* L. were determined by a combination of chemical and physical techniques. Three are esters of tiglic acid with the lactone ring closed to C-6. Two, euperfolin and euperfolitin, are 8-tigloyl-4,5-epoxy-1(10)-germacranolides with hydroxyl groups at the 3 and the 2 and 3 positions of the ring, respectively. The third, eufoliatin, is a 3-tigloyl-4,5,9,10-diepoxyguianolide with the lactone ring closed to C-6. The fourth, eufoliatorin, is a novel dilactone of the guaiane series whose stereochemistry was established by x-ray crystallography.

In the present paper we continue our reports on the constituents of *Eupatorium* species sensu stricto,[5] which have produced a number of cytotoxic and antitumor sesquiterpene lactones,[6] and describe the isolation of four polar new

sesquiterpene lactones in rather small quantity from *Eupatorium perfoliatum* L.[7] Two of these were the germacranolide euperfolitin (**1a**), of interest as a possible precursor of the secogermacradienolide pycnolide (**7**) from *Liatris pycnostachya* Michx.,[8] and the related germacranolide **4a** (euperfolin). The other two substances were the diepoxyguaianolide eufolitin (**5a**) and the interesting dilactone eufoliatorin (**6**), which appears to represent a new type of sesquiterpene dilactone.

We discuss first the structure elucidation of euperfolitin

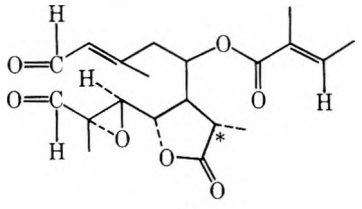


1a, $R_1, R_2 = H$; $R_3 =$ 

b, $R_1, R_2 =$ Ac; R_3 same as in **1a**

c, $R_1, R_2, R_3 = H$

d, $R_1, R_2 =$  ; R_3 same as in **1a**



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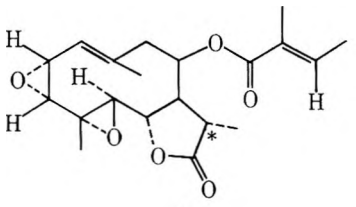

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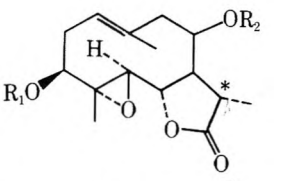
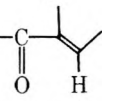
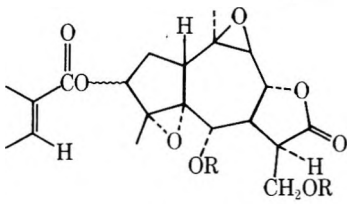


4a, $R_1 = H$; $R_2 =$ 

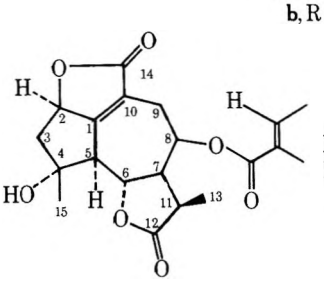
b, $R_1 =$ Ac; R_2 same as in **4a**

c, $R_1, R_2 = H$



5a, R = H

b, R = Ac



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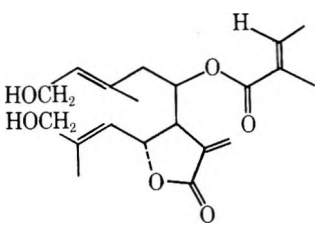

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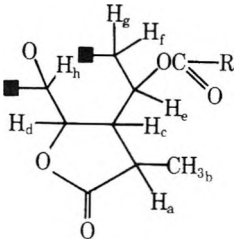
* Assignment dubious. Methyl may be β by analogy with **6**.[8]

(**1a**), $C_{20}H_{28}O_7$ (high-resolution mass spectrum and elemental analysis), mp 190–192 °C (amorphous), $[\alpha]_D$ −5.81°, which we have so far been unable to convert to a substance suitable for x-ray analysis. It was a γ-lactone of the type partially shown in A (IR band at 1765 cm^{-1}, presence of a methyl doublet at 0.95 ppm instead of the usual two doublets characteristic of an exocyclic methylene group). The remaining part structure shown in A (where ■ represents a quaternary

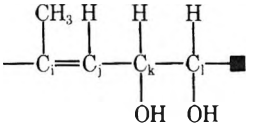


A

center) was evident from spin-decoupling experiments in Me_2SO-d_6 (Table I). H_d was conveniently located at 4.57 ppm as a doublet of doublets. Irradiation at the frequency of H_d converted a doublet at 3.05 ppm (H_h) to a singlet and a slightly broadened triplet at 2.80 ppm (H_c) to a broadened doublet. In the reverse experiment, irradiation at the frequency of H_h collapsed H_d to a doublet. Irradiation at the frequency of H_c converted H_d to a doublet, affected a multiplet at 2.81 ppm (H_a), and sharpened a broadened doublet at 5.28 ppm (H_e); conversely, irradiation at the frequency of H_a reduced H_c to a broadened doublet and collapsed the methyl doublet at 0.95 ppm to a singlet. Irradiation at the frequency of H_e slightly sharpened the signal of H_c and simplified what was obviously the AB part of an ABX system at 2.58 (H_f) and 2.22 ppm (H_g) ($J_{AX} = 6$, $J_{BX} < 1$, $J_{AB} = 14$ Hz), as could be demonstrated further by the results when H_f and H_g were irradiated. Chemical shift and multiplicity of H_h suggested that it was on carbon vicinal to a quaternary center and carrying an epoxidic oxygen; similarly, the behavior of the ABX system indicated that H_f and H_g represented a methylene group next to a quaternary center and that H_e was on carbon carrying an ester function which, because of the empirical formula, the NMR spectrum (vinyl multiplet at 6.87 ppm, two superimposed methyl multiplets at 1.74 ppm), and the mass spectrum [prominent peak at *m/e* 280 ($M^+ - C_5H_8O_2$), base peak at *m/e* 83 (C_5H_7O)], was a tiglate. The presence of a five-carbon ester was also established by hydrolysis of **1a** (NaOMe, MeOH)[9] to **1c**, $C_{15}H_{22}O_6$.

The assignments of H_d, H_e, and H_h were confirmed by single frequency decoupling of the off-resonance ^{13}C NMR spectrum of **1a** (Table II) which displayed the doublets of C_d, C_e, and C_h at 77.5, 72.8, and 83 ppm, respectively. The other terminus of the epoxide group attached to C_h was represented by a carbon singlet at 64.2 ppm.

The ^1H NMR spectrum of euperfolitin also displayed a doublet at 5.39 ppm (H_j of partial structure B). Irradiation at



B

this frequency sharpened a somewhat broadened methyl resonance at 1.57 ppm and collapsed a doublet of doublets at 4.08 ppm (H_k) to a doublet. Conversely, irradiation at the frequency of H_k collapsed the doublet of H_j to a broad singlet and a doublet at 2.90 (H_l) to a singlet which must be adjacent to a quaternary center. Since acetylation of **1a** gave a diacetate **1b** (new double strength IR band at 1740 cm^{-1}, new 3-proton

Table I. ^{1}H NMR Spectra of Sesquiterpene Lactones from *Eupatorium perfoliatum* and Derivatives[a]

Compd	H-1	H-2	H-3	H-5	H-6	H-7	H-8	H-9	H-11	H-13	H-14	H-15	H-3′	H-4′, H-5′[h]	Misc
1a[b]	5.39 dbr (9,1)	4.57 dd (9,9)	2.89 d (9)	3.05 d (9)	4.57 dd (9,9)	2.80 m	5.28 dbr (5, <1, <1)	2.58 dd (14,5) 22.2 dbr (14, <1)	2.80 m	0.95 d[g] (7)	1.55	1.20	6.87 m	1.74 m	
1b	5.30 dbr (10,1)	5.60 dd (10,10)	4.82 d (9)	3.03 d (9)	4.54 dd (9,9)	2.75 m	5.43 dbr (5, <1, <1)	2.94 dd (14,5) 2.27 dbr (14, <1)	2.75 m	1.12 d[g] (7)	1.82 m	1.42	6.86 m	1.82 m	2.90 (Ac) 2.14 (Ac)
1c[c]	5.80 dbr (9,1)	5.00 dd (9,9)	3.85 d (9)	3.25 d (9)	4.90 dd (9,9)	2.37 m	4.50 dbr (5, <1, <1)	2.72 dd (14,5) 2.37 dbr (14, <1)	3.07 m	1.33 d[g] (7.5)	2.01	1.70			
1e	5.30 d (9)	5.91 dd (9,9)	5.45 d	3.17 dbr	4.61 br	2.86 m	5.45 d	2.86 m 2.30 dbr (14,<1)	2.86 m	1.16 d[g] (7)	1.99	1.60	6.89	1.87 m	10 arom protons
2	5.80 d (8)	9.92 d (8)	8.87	3.25 d (4.5)	4.80 dd	2.65 m	5.33 m	2.65 m	2.65 m	1.20 d[g] (7.5)	2.28 br (1)	1.58	6.81 m	1.77 m	
3	5.42 m[e]	4.57 m[e]	3.46 d (9)	3.00 d (9)	4.57 m	2.80 m	5.42 dbr	2.90 dd (14,6) 2.30 dbr (14, <1)	2.80 m	1.15 d[g] (7)	1.73	1.40	6.8 m	1.84 m	
4a	5.20 dbr (12,1)	2.40 m[f]	3.46 dd (10, 7)	2.87 d (9)	4.57 dd (9,9)	2.72 m	5.40 dbr (6, <1, <1)	2.72 m 2.16 dbr (15, <1)	2.72 m	1.10 d[g] (8)	1.61	1.34	6.84	1.77 m	2.87 bs[j] (−OH)
4b	5.24 dbr (12,1)	2.30 m[f]	4.52 dd (10, 6)	2.89 d (9)	4.58 dd (9,9)	2.78 m	5.40 dbr (6, <1, <1)	2.78 m 2.22 dbr (14, <1)	2.78 m	1.13 d[g] (7)	1.65	1.43	6.86 m	1.84 m	2.10 (Ac)
4c	5.26 dbr (12,1)	2.67 m[f]	3.76 dd (10,7)	3.05 d	4.78 dd (9,9)	2.31 m	4.48 dbr (4, <1, <1)	2.67 m 2.31[e]	3.05[e]	1.39 d[g] (7)	1.99	1.58			
5a[b]	2.40 m	2.11 ddd (15,5,2 1.90 ddd (15,5,2))	5.30 br		3.34	2.74 m	4.81 dd (10,10)	2.74 m	2.40 m	3.83 m	1.44	1.05	6.93 m	1.80 m	6.97 br (OH)[j] 5.96 br (OH)[j]
5b	2.71 m	2.30 ddd (15,5,2) 1.83[e]	5.50 br		4.2	2.90 m	4.68 dd (12,9)	2.93 d (10)	2.90 m	4.10[i]	1.62	1.32	6.81	1.80 m	2.04 (Ac) 2.11 (Ac)
5b[d]	2.41 m (4,3)	1.88 ddd (15,4,3) 1.09 ddd (15,3,2)	5.47 br (~3,2)		4.53	2.98 dd (12,10) 10)	4.66 dd (12,9)	2.95 d (9)	2.41 m	3.95[i]	1.61[e]	1.53	6.54	1.30 m	1.68 (Ac) 1.61 (Ac)
6		5.40 m	2.39[e] 1.36 dd (12,12)	3.19 d (9)	4.62 dd (9,9)	2.70 m	5.54 m	2.98 dd (17.4) 2.44 m	2.70 m	1.14 d[g] (8)		1.61	6.70 m	1.74 m	

[a] Run in $CDCl_3$ at 270 MHz on a Brucker HFX-270 instrument with Me_4Si as internal standard unless otherwise specified. Values are in parts per million: d, doublet; t, triplet; br, broadened singlet; m, multiplet. Unmarked signals are singlets. Figures in parentheses are coupling constants in hertz. [b] Run in Me_2SO-d_6. [c] Run in pyridine-d_5. [d] Run in benzene-d_6. [e] Signal partially obscured or superimposed. [f] Intensity two protons. [g] Intensity three protons. [h] Intensity six protons. [i] Center of AB of an ABX system. [j] Exchanges with D_2O

Table II. ^{13}C NMR Spectra of Lactones from *E. perfoliatum*

Carbon atom	1a[a]	4a[b]	6[b]
1	130.6 d	125.1 d	165.9
2	72.6 d	33.0 t	81.5 d
3	65.6 d	64.9 d	29.8 t
4	64.2	65.1	83.1
5	83.0	77.0 d	38.8 d
6	77.5 d	76.2 d	75.8 d
7	47.9 d	47.4 d	48.2 d
8	72.8 d	72.0 d	66.9 d
9	44.1 t	43.5 t	45.6 t
10	133.3	133.2	128.3
11	40.9 d	40.3 d	56.9 d
12	178.5	178.3	177.7
13	12.0 q	11.1 q	11.6 q
14	20.5 q	19.7 q	175.0
15	12.8 q	12.2 q	26.2 q
1′	166.8	166.3	166.7
2′	129.1	128.3	122.7
3′	139.3 d	138.8 d	138.8 d
4′	14.5 q	14.5 q	14.4 q
5′	12.3 q	11.8 q	12.0 q

[a] Run in Me_2SO-d_6 on a Bruker HFX-270 instrument operating at 67.905 MHz. Unmarked signals are singlets. Assignment of all multiplets made by single frequency off-resonance spin decoupling. Assignments of C-4, C-5, C-10, and C-2[1] based on predicted shifts and other spectra in our files. [b] Run in $CDCl_3$. Assignments based on comparison with spectrum of **1a** and predicted shifts.

NMR signals at 2.00 and 2.10 ppm) in whose NMR spectrum the resonances at 4.08 and 2.90 ppm were shifted downfield to 5.60 and 4.82 ppm, the presence of partial structure B was inferred and confirmed by the single frequency off-resonance decoupled ^{13}C NMR spectrum, which showed C_i and C_j as a singlet and a doublet at 133 and 131 ppm, respectively, and C_k and C_l as two doublets at 72.6 and 65.6 ppm.

The remaining signal in the NMR spectrum of **1a** was a methyl resonance at 1.21 ppm. Combination of A and B with this information led to gross structure **1a.**

As for the stereochemistry, if it be assumed that H-7 of euperfolitin is α as in all sesquiterpene lactones of established absolute stereochemistry, the large values of $J_{6,7}$ (9 Hz) and $J_{5,6}$ (8 Hz) require that H-6 be β- and that H-5 be α-oriented. Hence the lactone ring is trans fused. The magnitude of $J_{7,11}$ (9 Hz) is somewhat more appropriate for H-11β (models), but does not completely exclude α orientation of H-11.[10] The very small value of $J_{7,8}$ (<1 Hz) requires that the tigloyl side chain be β oriented.

We now consider the stereochemistry of the 1,10 double bond and the 4,5-epoxide. Oxidation of **1a** with sodium metaperiodate in methanol yielded a dialdehyde **2a,** thereby furnishing chemical proof for the presence of the vicinal diol system. The NMR spectrum of **2a** exhibited a doublet at 9.92 ppm due to the aldehyde proton of C-2 and the resonance of H-1 now appeared at 5.80 ppm. Furthermore, the C-14 methyl resonance was shifted downfield to 2.28 ppm due to deshielding by the aldehyde carbonyl; hence the 1,10 double bond is trans.[11] As for the stereochemistry of the epoxide ring, Dreiding models demonstrated that the large value of $J_{5,6}$ cannot be satisfied by a cis epoxide whereas the values of $J_{5,6}$ and $J_{6,7}$ are appropriate for a trans 4,5-epoxide derived from a trans,trans germacradiene as shown in the formulas.

In discussing the remaining problem, i.e., the configurations of euperfolitin at C-2 and C-3, we assume first that, as has been shown in numerous instances,[12] those conformations of trans-1(10),trans-4,5 germacradienes or the corresponding

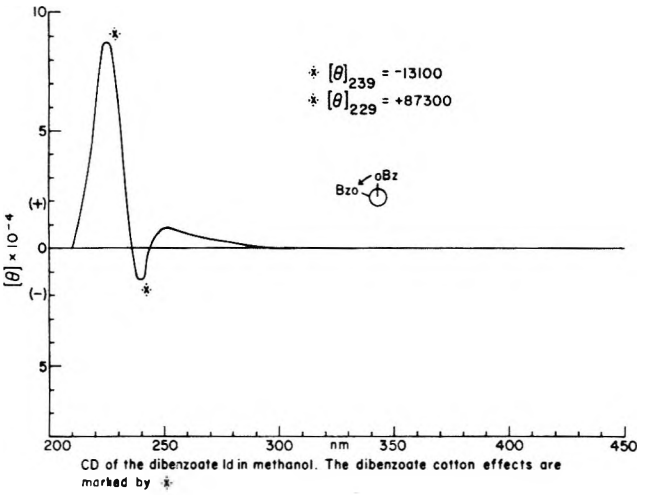
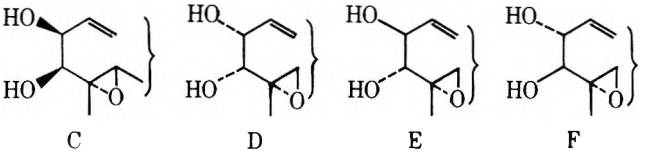


Figure 1. Application of dibenzoate rule to **1d.**

4,5-epoxides are preferred in which the 1,10 double bond is crossed with the 4,5 bond so that the C-4 and C-10 methyl groups are syn to each other. Support for this inference was the absence of an NOE between H-5 and the C-14 methyl group; other experiments along this line confirmed that the 1,10 double bond was trans (no NOE between H-1 and H-14) and suggested that H-3 was α oriented (no NOE between H-3 and H-15).

If this last bit of evidence be neglected, four possible arrangements, C, D, E, and F, are possible for the diol moiety.



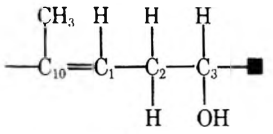
Preparation of the dibenzoate **1a,** determination of the CD curve (Figure 1), and application of the dibenzoate rule[13] show that the glycol system possesses negative chirality. Inspection of the Dreiding models then eliminated partial formulas C and D which give rise to positive chirality. Lastly, while the model of E displays negative chirality, the H-2, H-3 dihedral angle approximates 90° which clashes with the observed large value of $J_{2,3}$ (9 Hz). Consequently, the correct stereochemistry is that of F which gives rise to negative chirality and an H-2, H-3 dihedral angle of ~170° as well as satisfying all the other requirements.

Treatment of **1a** with $SOCl_2$–pyridine surprisingly effected transformation to a 2,3-epoxide **3** which $J_{2,3}$ and inspection of Dreiding models required to be α-cis.[14] We suggest that this is the result of S_Ni displacement of C-3 hydroxyl by $SOCl_2$–pyridine followed by intramolecular displacement of the β-oriented halogen by the α-oriented hydroxyl group on C-2.

The C-2, C-3 stereochemistry deduced for euperfolitin (**1a**) is identical with that of 2β,3α-dihydroxy-1(10),4,5,11,13-germacatriene, a stress metabolite isolated[15] from *Datura stramonium* infected with various fungi. The observed coupling constants for the diol systems are remarkably similar and further support our assignments. Unfortunately, the crystals of euperfolitin or its derivatives were unsuitable for x-ray analysis which is needed to settle the stereochemistry at C-11.

The second substance euperfolin (**4a**), $C_{20}H_{28}O_6$ (high-resolution mass spectrum, elemental analysis), mp 173 °C, $[\alpha]_D$ − 13.9°, exhibited IR, UV, and NMR absorption similar to that of **1a,** thus suggesting a close structural relationship. Spin-decoupling experiments (Table I) reinforced this conclusion, partial structure A being established in the manner

discussed for euperfolitin. On the other hand, the C-2 hydroxyl group of euperfolitin was missing in **4a**; the vinylic proton (H-1) of **4a** appeared as a broad doublet at 5.20 ppm which was allylically coupled to a vinyl methyl group and vicinally coupled to a two-proton multiplet centered at 2.40 ppm (H-2a and H-2b). These in turn were coupled to a doublet of doublets at 3.46 ppm which moved downfield to 4.52 ppm on acetylation of **4a** to **4b**. Hence **4a** contains partial structure G where C-3 is again joined to a quaternary carbon atom.

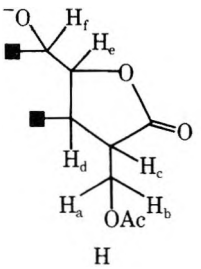


G

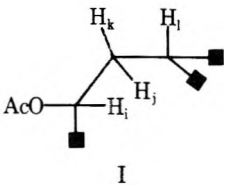
Comparison of the ^{13}C NMR spectrum of **4a** with that of **1a** (Table II) confirmed the absence of the 2-hydroxyl group (Δ C-2 = 4.26 ppm).[16] Since the various coupling constants of **1a** and **4a** were very similar (Table I), the stereochemistry of euperfolitin and euperfolin at the various centers must be the same. The C-3 hydroxyl group of euperfolin was deduced to be β as in **1a** because of the absence of an NOE between H-3 and H-15,[11] by analogy with **1a**, and by the correspondence of $J_{2a,3}$ and $J_{2b,3}$ (10, 7 Hz) with those of 11,13-dihydronovanin, which has a β-oriented acetate function at C-3.[10f,17] Hydrolysis (NaOMe, MeOH)[9] furnished **4c** which exhibited the expected spectroscopic properties; but further work was negated by lack of material.

The third substance, eufoliatin (**5a**) from *E. perfoliatum*, $C_{20}H_{26}O_8$ (high-resolution mass spectrum, elemental analysis), mp 227–229 °C (amorphous), $[\alpha]_D$ −27.5°, was available in small quantity only. Like euperfolin, it contained a hydroxyl group, a γ-lactone, and a tigloyl ester (IR bands at 3420, 1765, 1700, and 1640 cm^{-1}; NMR signals typical of tiglate—see Table I—and mass spectrum which exhibited significant peaks at *m/e* 311 ($M^+ - C_5H_7O$), 294 ($M^+ - C_5H_8O_2$), and 83 (base peak, C_5H_7O). However, two methyl singlets at 1.44 and 1.05 ppm suggested that at least one of the methyl groups was attached to carbon carrying an ether or hydroxyl; of two protons in the 4.8–5.3 ppm region, the one at lower field, a somewhat broadened singlet at 5.30 ppm, was provisionally assigned to the proton under the ester and the one at higher field, a doublet of doublets at 4.81 ppm, to hydrogen under the lactone.

Acetylation yielded a diacetate **5b** whose NMR spectrum in benzene-d_6 afforded excellent separation of signals and permitted deduction, by spin decoupling, of the sequence shown in partial structure H, where H_a, H_b, H_c, H_d, H_e, and H_f could be located at 4.14, 3.77, 2.41, 2.98, 4.66, and 2.95 ppm, respectively. H_a and H_b represented the AB part of an ABX system whose chemical shift, when compared with those in **5a**, indicated that the carbon atom to which they were attached carried one of the two new acetate groups. H_d, which was next to H_c, and H_e, the lactonic proton, was next to a quaternary center as was H_f whose chemical shift (compare with shift of H_c and H_f in $CDCl_3$) indicated that it was attached to carbon carrying an oxygen atom. A second sequence determined by spin decoupling was I, where H_i, H_j, H_k, and



H



I

H_e were found at 5.47 (hydrogen under tigloyl ester), 1.88, 1.09 (two geminate-coupled protons each coupled to H_i and H_e), and 2.41, respectively, the last apparently to two quaternary centers.

Since hydroxyl groups, double bonds, and carbonyl groups other than those represented in the ester and lactone functions were absent, the molecular formula of eufoliatin required a bicyclic carbon skeleton and the incorporation of two ether functions, one of which is included in H. In view of the chemical shift of the two methyl singlets, these requirements could be met most satisfactorily by writing gross structure **5b** for the diacetate, although scarcity of material prevented further verification by chemical methods. The tentative stereochemistry assigned to **5a** and **5b** is based on the usual assumption that the C-11 side chain is equatorial and β. In that case, the large coupling constants $J_{7,8}$ and $J_{8,9}$ require that H-8 be β and H-9 be α. The large coupling constant $J_{7,11}$ suggests but does not prove that H-11 is β[10] and the lack of coupling between H-6 and H-7 requires that H-6 be β oriented. In this arrangement the dihedral angle between H-6 and H-7 would be about 105°.

The further assumption can be made that H-1 is α as in all naturally occurring guaianolides produced by cyclization of a trans-1(10)-trans-4,5 germacradiene precursor[18] (this seems likely because of the cooccurrence of **1a** and **4a**) where subsequent epimerization due to the presence of a ketone at C-2 or a vinylogous ketone at C-3 is not possible.[19] However, the observed coupling constants $J_{1,2a}$, $J_{1,2b}$, $J_{2d,3}$, and $J_{2b,3}$ (~4, 3, 3, and 2 Hz) leave uncertain the orientation of the C-3 ester function even after the knotty question of the configuration of the two epoxide rings has been considered.

Models incorporating a trans-9,10- or an α-cis-9,10-epoxide did not satisfy the requirement for a large value of $J_{8,9}$; hence the 9,10-epoxide must be β-cis. Models incorporating a trans 4,5-epoxide could not be constructed; biogenetic considerations suggest that the 4,5-epoxide is α-cis, which satisfies the requirement that $J_{6,7}$ vanish, whereas models with the 4,5-epoxide β-cis display a H-5, H-7 dihedral angle such that $J_{6,7}$ should be appreciable. Consequently we prefer the stereochemistry shown in **5a** and **5b**, where the stereochemistry at C-3 remains in doubt. Unfortunately, we have so far been unable to obtain crystals suitable for x-ray analysis.

Only a small amount of the crystalline fourth substance eufoliatorin (**6**), $C_{20}H_{24}O_7$, mp 224 °C, was isolated. It had a γ-lactone function of the type present in **1a** and **4a** (IR band at 1780 cm^{-1}, methyl doublet at 1.14 ppm) and a tigloyl ester [IR bands at 1685 and 1640 cm^{-1}, typical NMR signals at 1.61 and 1.74 ppm (two vinyl methyl multiplets), significant mass spectral peaks at *m/e* 277 ($M^+ - C_5H_7O_2$), 276 ($M^+ - C_5H_8O_2$), and 83 (base peak, C_5H_7O)]. The IR spectrum suggested the presence of another α,β-unsaturated γ-lactone (band at 1753 cm^{-1}), especially since there was significant UV absorption at 219 and 210 nm (ϵ 26 100 and 24 600).

Spin decoupling experiments on eufoliatorin demonstrated the pattern shown in partial structure J. H_d was located as a doublet of doublets at 4.62 ppm. Irradiation at this frequency collapsed a doublet at 3.19 ppm (H_e) to a singlet and affected a two-proton multiplet at 2.70 ppm. Conversely, irradiation at the frequency of H_e collapsed the H_d signal to a doublet; hence H_e must be adjacent to two quaternary carbon atoms. Irradiation at the frequency of the 2.70-ppm multiplet collapsed H_d to a doublet and the methyl doublet (H_b) at 1.14 ppm to a singlet and affected a multiplet at 5.54 ppm (H_f), obviously the proton under the tiglate. Consequently, it became evident that the signals of H_a and H_c overlapped at 2.70 ppm. Irradiation at the frequency of H_f simplified what appeared to be the AB part of an ABX system where A, geminate-coupled to B, was a doublet of doublets at 2.98 ppm (H_g) and B a multiplet at 2.44 ppm (H_h). The reverse experiments

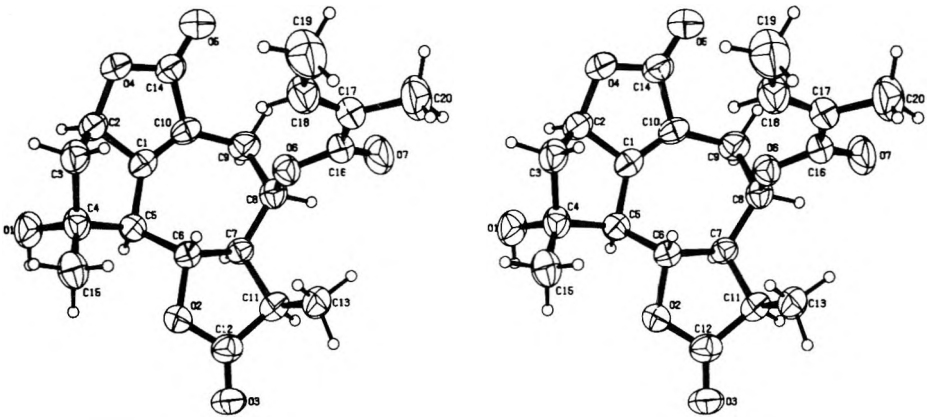
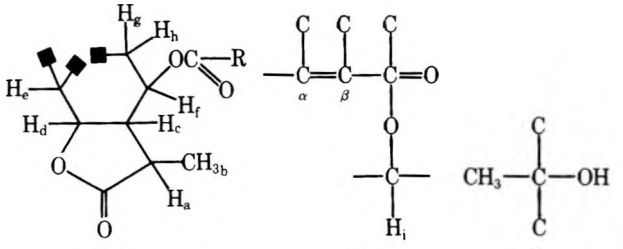


Figure 2. Stereoscopic view of **6**.

confirmed these conclusions and showed that the methylene group including H_g and H_h was next to a quaternary center.



J K L

The ^{13}C NMR off-resonance spectrum of **6** (Table II) displayed, as surmised, three carbonyl frequencies in the region characteristic of lactone and ester carbonyls, two of these being identifiable with the carbonyl groups of J; the third was assigned to the α,β-unsaturated lactone partially shown in K, since the off-resonance spectrum also displayed two vinylic carbon singlets at 128 (α) and 165.9 (β) in addition to the vinylic carbons of the tigloyl residue (122.7 and 138.8 d). Three doublets at 81.5, 75.8, and 66.9 ppm and a singlet at 83.1 ppm represented carbons carrying ethereal, alcohol, and ester oxygen. Failure to achieve acetylation by the acetic anhydride–pyridine method indicated that the hydroxyl group was tertiary and therefore attached to the carbon represented by the singlet at 83.1 ppm. Furthermore, since the ^1H NMR spectrum contained a methyl singlet at 1.61 ppm, the tertiary hydroxyl group was incorporated in partial structure L. Two of the three CHO doublets could be identified with C_d and C_f of J; hence K was closed to a secondary carbon as shown.

The ^1H NMR spectrum displayed three additional signals not so far accounted for. A multiplet at 5.40 ppm was logically assigned to H_i of K. Irradiation at the frequency of H_i changed a multiplet at 2.39 ppm (H_j) to a broad doublet and collapsed the third remaining signal, a doublet of doublets at 1.36 ppm (H_k), to a doublet. Conversely, irradiation at the frequency of H_j converted the H_i and K_k signals to doublets, while irradiation at the frequency of H_k affected the multiplets of H_i and H_j.

The molecular formula of eufoliatorin required that it must be bicyclic apart from its two lactone rings. A structure which incorporates J, K, and L and satisfies all requirements was **6**, exclusive of stereochemistry. If H-7 is α as usual, the large coupling constants $J_{6,7}$ and $J_{5,6}$ require that H-6 be β and H-5 be α oriented. Again while $J_{7,11}$ is large, a decision in favor of α or β orientation of C-13 was difficult and could not be achieved by attempts to assess the effect of paramagnetic shift reagents on the shift of C-13. The very small value of $J_{7,8}$ (<1 Hz) showed that the tigloyl ester was β. On biogenetic grounds, it was assumed that H-5 and the hydroxyl group at C-4 were α oriented, but since determination of the configuration at the various centers was limited by the amount of material available and since the structure was novel, eufoliatorin was submitted to x-ray analysis.

Table III. Crystal Data for 6

Formula:	$C_{20}H_{24}O_7$	
Orthorhombic		
Space group	$P2_12_12_1$	$Z = 4$
a = 8.124 (5) Å		
b = 13.041 (7) Å		
c = 17.840 (10) Å		
d_{calcd} 1.322 g cm^{-1}		

Crystal data for **6** are listed in Table III. Figure 2 is a stereoscopic drawing of the molecule which represents the absolute configuration if our inference about the absolute stereochemistry at H-7 is correct. It confirms our conclusions about the gross structure, the seven-membered ring being a deformed chair with C-6 as apex, and about the configurations at C-6, C-7, and C-8, supports our speculative assignment of stereochemistry on biogenetic grounds to C-4 and C-5, and establishes the previously unknown configurations at C-2 and C-11. Because of the cooccurrence of **1a**, **4a**, **5a**, and **6** in the same plant it is conceivable that the stereochemistry of **1a**, **4a**, and **5a** is the same as that of **6**. Tables IV, V, and VI containing bond lengths, bond angles, and torsion angles are available as supplementary material.

Experimental Section[20]

Extraction of *Eupatorium perfoliatum*. Above-ground parts of *E. perfoliatum* L., collected by Mr. R. Lazor (Lazor no. 1218) on Sept 20, 1968 at the intersection of Florida State Road 20 with a side road 7 miles east of Hosford, Fla., wt 45 lb, was extracted with $CHCl_3$ and worked up in the usual manner.[21] The dark brown gum, wt 180 g, was chromatographed over a column of 1.2 kg of silicic acid (Mallinckrodt 100 mesh) packed in benzene, the column being eluted with fractions of increasing polarity, 200-mL fractions being collected. Fractions 15–26 ($CHCl_3$), 27–54 ($CHCl_3$–MeOH, 49:1), and 55–67 ($CHCl_3$–MeOH, 19:1) eluted a complex mixture (TLC), mixed and evaporated to give a gum. This gum (80 g) was rechromatographed over a column of 1.2 kg of silicic acid, the column being eluted with solvent of increasing polarity beginning with benzene. The $CHCl_3$ eluates on preparative TLC (solvent system benzene–ethyl acetate, 1:2) gave solid euperfolir. (**4a**) which was recrystallized from ethyl acetate–hexane to give colorless material: wt 0.40 g; mp 173 °C; $[\alpha]^{22}D$ −13.9° (c 0.0228, MeOH); CD curve $[\theta]_{290}$ 0, $[\theta]_{260}$ + 554, $[\theta]_{250}$ +998, $[\theta]_{240}$ + 1164, $[\theta]_{231}$ +44 (last reading); IR bands (KBr) at 3410 (–OH), 1775 (γ-lactone), 1708 and 1642 cm^{-1} (α,β-unsaturated ester); strong UV end absorption. Elemental analysis consistently indicated what was probably stubborn retention of solvate, but the high-resolution mass spectrum and the derivatives (vide infra) confirmed the proposed empirical formula.

Anal. Calcd for $C_{20}H_{28}O_6$: mol wt, 364.1884. Found: mol wt (MS), 364.1896.

The high-resolution mass spectrum showed other significant peaks at *m/e* (composition, %) 349 ($M^+ - CH_3$, 3.2), 346 ($M^+ - H_2O$, 3.0), 334 ($M^+ - CH_2O$, 3.6), 333 ($C_{15}H_{22}O_5$, 10.5), 281 ($M^+ - C_5H_7O$, 1.6), 265 ($M^+ - C_5H_7O_2$, 3.3), 264 ($M^+ - C_5H_8O_2$, 14.9), 247 ($M^+ - C_5H_7O_2 - H_2O$, 6.2), 246 ($M^+ - C_5H_8O_2 - H_2O$, 13.4), 236 ($M^+ - C_5H_8O_2 - CO$, 1.4), 231 ($M^+ - C_5H_8O_2 - H_2O, CH_3$, 6.7), 221 ($M^+ - C_5H_8O_2 - CO - CH_3$, 17.9), 203 ($M^+ - C_5H_8O_2 - H_2O - CO$, 1.4), 191 ($C_{13}H_{15}O_3$, 52.7), 100 ($C_5H_8O_2$, 24.4), and 83 ($C_5H_7O$, base peak).

The $CHCl_3$–MeOH (19:1) eluate yielded a gum which showed a major spot on TLC. This component (eufoliatorin) was separated by repeated preparative TLC (solvent system benzene–ethyl acetate, 1:1) as a gum which eventually solidified and was recrystallized from ethyl acetate–hexane as colorless needles (**6**) which were suitable for x-ray analysis: wt 0.15 g; mp 224 °C; CD curve $[\theta]_{315}$ 0, $[\theta]_{300}$ +677, $[\theta]_{290}$ +1692, $[\theta]_{280}$ +2370, $[\theta]_{269}$ +2540, $[\theta]_{255}$ +6770, $[\theta]_{245}$ +11 340, $[\theta]_{237}$ 0, $[\theta]_{230}$ −54 950, $[\theta]_{220}$ −116 100, $[\theta]_{210}$ −63 400 (last reading); IR bands (KBr) at 3490 (–OH), 1780 (γ-lactone), 1753 (α,β-unsaturated γ-lactone), 1685 and 1640 cm^{-1} (α,β-unsaturated ester); UV spectrum (MeOH) λ_{max} 282 nm (ε 2990), 250 (6840), 219 (26 100), and 210 (24 600). As in most other compounds encountered in this work, the carbon analysis remained consistently low.

Anal. Calcd for $C_{20}H_{24}O_7$: C, 63.82; H, 6.43; O, 29.75; mol wt, 376.1521. Found: C, 63.06; H, 6.42; O, 29.71; mol wt (MS), 376.1525.

The high-resolution mass spectrum showed other significant peaks at *m/e* (composition, %) 277 ($M^+ - C_5H_7O_2$, 8.4), 258 ($M^+ - C_5H_8O_2 - H_O$, 13.4), 249 ($M^+ - C_5H_7O_2 - Co$, 3.6), 100 ($C_5H_8O_2$ 5.5), 99 ($C_5H_7O_2$, 5.6), and 83 (base peak, C_5H_7O).

Fractions 68–70 of the original chromatogram ($CHCl_3$–MeOH, 19:1) gave 10 g of a gum which showed two major spots on TLC. This was rechromatographed over 300 g of silica gel. $CHCl_3$–MeOH (3%) eluted solid material (eufoliatin) which was recrystallized from MeOH–$CHCl_3$ to give a colorless powder (**5a**): wt 0.10 g; mp 227–229 °C; $[\alpha]_D$ −27.5° (*c* 0.0121, MeOH); IR bands (KBr) 3420 (–OH), 1765 (γ-lactone), 1700 and 1640 cm^{-1} (α,β-unsaturated ester); UV spectrum λ_{max} 220 nm (ε 12 800). The carbon analysis was consistently low.

Anal. Calcd for $C_{20}H_{26}O_8$: C, 60.90; H, 6.64; O, 32.45; mol wt, 394.1627. Found: C, 60.18; H, 6.57; O, 33.02; mol wt (MS), 394.1618.

The high-resolution mass spectrum also exhibited significant peaks at *m/e* (composition, %) 311 ($M^+ - C_5H_7O$, 1.7), 295 ($M^+ - C_5H_7O_2$, 3.1), 294 $M^+ - C_5H_8O_2$, 2.4), 277 ($M^+ - C_5H_7O_2 - H_2O$, 1.7), 276 ($M^+ - C_5H_8O_2 - H_2O$, 1.4), 248 ($M^+ - C_5H_8O_2 - H_2O - H_2O - CO$, 2.3), 100 ($C_5H_8O_2$, 6.8), and 83 ($C_5H_7O$, base peak).

Fractions 71–73 of the original chromatogram ($CHCl_3$–MeOH, 8%) gave a gum which was rechromatographed over 200 g of silica gel. The $CHCl_3$–MeOH (5%) eluates gave euperfolitin (**1a**) as a solid which was recrystallized from ethyl acetate–hexane to give **1a**: mp 190–192 °C; $[\alpha]^{82}_D$ −5.81° (*c* 0.0119, MeOH); CD curve $[\theta]_{290}$ 0, $(\theta]_{265}$ +490, $[\theta]_{255}$ 982, $[\theta]_{243}$ +1470, $[\theta]_{235}$ +1150, $[\theta]_{230}$ 0, $[\theta]220$ −982, $[\theta]_{210}$ −1310 (last reading); IR bands (KBr) 3450 (–OH), 1765 (γ-lactone), 1700 and 1650 cm^{-1} (α,β-unsaturated ester); UV spectrum 220 nm (ε 7600). The carbon analysis remained consistently low.

Anal. Calcd for $C_{20}H_{28}O_7$: C, 63.14; H, 7.42; O, 29.44; mol wt, 380.1835. Found: C, 61.85; H, 7.49; O, 29.77; mol wt (MS), 380.1856.

Other significant peaks in the high-resolution mass spectrum which, except for the molecular ion (1%), showed only rather weak peaks above *m/e* 200 were at *m/e* (composition, %) 362 ($M^+ - H_2O$, 0.1), 280 ($M^+ - C_5H_8O_2$, 0.3), 262 ($M^+ - C_5H_8O_2 - H_2O$, 1.1), 244 ($M^+ - C_5H_8O_2 - 2H_2O$, 0.5), 100 ($C_5H_8O_2$, 2.5), and 83 (C_5H_7O, base peak).

Preparation of Acetates 1b, 4b, and 5b. A. Acetylation of 0.1 g of **1a** in 1 mL of pyridine and 0.5 mL of acetic anhydride at room temperature overnight followed by the usual workup gave a gummy diacetate which was purified by preparative TLC (silica gel, solvent system $CHCl_3$–MeOH, 6%), but could not be induced to crystallize: IR bands (film) 1780, 1740 (very strong), 1640, 1375, and 1240 cm^{-1}. The low-resolution mass spectrum exhibited no parent peak, but other significant peaks at *m/e* 422 ($M^+ - C_2H_2O$), 379 ($M - C_2H_2O - C_2H_3O$), 364 ($M^+ - C_5H_8O_2$), and 83 (base peak, C_5H_7O). The carbon analysis was consistently low.

Anal. Calcd for $C_{24}H_{32}O_9$: C, 62.06; H, 6.94; O, 31.00; mol wt, 422.1941. Found: C, 60.31; H, 6.96; O, 31.87; mol wt (MS), 422.1946.

B. Acetylation of 0.050 g of **4a** in the above manner and purification of the crude product by preparative TLC (silica gel, solvent system benzene–ethyl acetate, 1:2) followed by recrystallization from benzene–hexane gave **4b**: mp 130 °C; IR bands (KBr) 1778, 1738, 1709, 1640, 1255, 1190, and 1040 cm^{-1}.

Anal. Calcd for $C_{22}H_{30}O_7$: C, 65.01; H, 7.44; O, 27.55; mol wt, 406.1990. Found: C, 64.13; H, 7.55; O, 28.04; mol wt (MS), 406.1995.

Other significant peaks in the high-resolution mass spectrum were at *m/e* (composition, %) 364 ($M^+ - C_2H_2O$, 5.5), 346 ($M^+ - C_2H_4O_2$, 1.1), 306 ($M^+ - C_5H_8O_2$, 1.3), 264 ($M^+ - C_2H_2O - C_5H_8O_2$, 2.5), 246 ($M^+ - C_2H_4O_2 - C_5H_8O_2$, 10.4), and 83 ($C_5H_7O$, base peak).

C. Acetylation of 0.030 g of **5a** in the above manner and purification of the crude product by preparative TLC (silica gel, $CHCl_3$–MeOH, 5%) gave **5b** as a gum, wt 0.020 g, which had IR bands (film) at 1785, 1741, 1440, 1370, 1240, and 1015 cm^{-1}. The low-resolution mass spectrum exhibited significant peaks at *m/e* 436 ($M^+ - C_2H_2O$), 394 ($M - 2C_2H_2O$), 376 ($M - C_2H_4O_2 - C_2H_2O_2$), 294 ($M - 2C_2H_2O - C_5H_8O_2$), and 83 (base peak, C_5H_7O).

Anal. Calcd for $C_{24}H_{30}O_{10}$: mol wt, 478.1830. Found: mol wt (MS), 478.1839.

Hydrolysis of 1a and 4a. A. A solution of 0.1 g of **1a** in 10 mL of MeOH was stirred with 80 mg of NaOMe at room temperature (N_2 atmosphere) for 4 h. The reaction remained incomplete (TLC). The solution was acidified with dilute acetic acid, the methanol removed at reduced pressure, and the residue diluted with water. The mixture was extracted with ethyl acetate; the washed and dried extract was evaporated and the residue separated by preparative TLC (silica gel, $CHCl_3$–MeOH, 15%). The more polar band yielded a solid (**1c**) which was recrystallized from acetone–hexane to give a colorless powder: yield 10 mg; mp 210–211 °C; IR bands (KBr) 3400, 1760, 1640, 1445, 1380, 1180, 1000, and 850 cm^{-1}.

Anal. Calcd for $C_{15}H_{22}O_6$: mol wt, 298.1415. Found: mol wt (MS), 298.1392.

Other significant peaks in the high-resolution mass spectrum were *m/e* (composition, %) 280 ($M^+ - H_2O$, 9.3), 265 ($M^+ - CH_3 - H_2O$, 11.9), 262 ($M^+ - 2H_2O$, 24.5), 247 ($M^+ - 2H_2O - CH_3$, 6.1), 244 ($M^+ - 3H_2O$, 9.7), 219 ($M^+ - CH_3 - CO - 2H_2O$, 36.6).

The less polar band (wt 50 mg) represented starting material.

B. Hydrolysis of 0.050 g of **4a** in the above manner, purification of the crude product by preparative TLC (silica gel, benzene–ethyl acetate, 1:2), and recrystallization from acetone–hexane gave 8 mg of **4c** as an amorphous powder: IR bands (KBr) 3496, 3392, 1755, 1435, 1240, and 1125 cm^{-1}. The low-resolution mass spectrum exhibited the molecular ion at *m/e* 282 ($C_{15}H_{22}O$) and other significant peaks at *m/e* 264 ($M^+ - H_2O$, 246 ($M^+ - 2H_2O$), and 221 ($M^+ - H_2O - CH_3 - CO$).

Anal. Calcd for $C_{15}H_{22}O_5$: mol wt, 282.1467. Found: mol wt (MS), 282.1494.

Periodate Cleavage of 1a. A solution of 0.10 g in 2 mL of MeOH was stirred with a solution of 0.1 g of sodium metaperiodate in 2 mL of MeOH and 3 mL of water overnight, diluted with water, and extracted with ethyl acetate. The washed and dried extracts were evaporated at reduced pressure and purified by preparative TLC (silica gel, $CHCl_3$–MeOH, 10%) to give 46 mg of gummy **2** which had IR bands (film) at 1770, 1750, 1700 (br), 1645, 1450, and 1380 cm^{-1}. The low-resolution mass spectrum exhibited the molecular ion at *m/e* 378 ($C_{20}H_{26}O_7$) and other significant peaks at *m/e* 349 ($M^+ - CHO$), 295 ($M^+ - C_5H_7O$), 249 ($M^+ - CHO - C_5H_8O_2$), and 83 (base peak, C_5H_7O).

Anal. Calcd for $C_{20}H_{26}O_7$: mol wt, 378.1678. Found: mol wt (MS), 378.1684.

Dibenzoate of 1a. A solution of 0.025 g of **1a** in 0.5 mL of pyridine and 0.2 mL of benzoyl chloride was allowed to stand at room temperature for 24 h and worked up in the usual manner. The crude gummy product solidified on triturating with hexane. The amorphous product was filtered, washed with hexane, and dried, yield 0.020 g, mp 145–147 °C. The CD curve is reproduced in Figure 1. The low-resolution mass spectrum exhibited the molecular ion at *m/e* 588 ($C_{34}H_{36}O_9$) and other significant peaks at *m/e* 505 ($M^+ - C_5H_7O$), 488 ($M^+ - C_5H_8O_2$), 483 ($M^+ - C_7H_5O$), 383 ($M^+ - C_5H_8O_2 - C_7H_5O$), and 83 ($C_5H_7O$). The 270-MHz NMR spectrum was practically superimposable on that of **1b** (chemical shifts, coupling constants), except for additional signals due to the ten aromatic protons.

Anal. Calcd for $C_{34}H_{36}O_9$: C, 69.37; H, 6.16; O, 24.46. Found: C, 69.98; H, 6.29; O, 24.23.

Reaction of 1a with Thionyl Chloride. A solution of 0.10 g of **1a** in 2 mL of pyridine was cooled to 0 °C, mixed with 0.2 mL of thionyl chloride, and stirred, the reaction being monitored by TLC. After 2.5 h the mixture was decomposed with ice water and extracted with $CHCl_3$. The washed and dried extract was evaporated and purified by preparative TLC (silica gel, $CHCl_3$–MeOH, 10%). The gummy product **3**, wt 21 mg, had IR bands ($CHCl_3$) at 1770, 1705, 1640, 1380, and 1085 cm^{-1}. The high-resolution mass spectrum did not exhibit

the molecular ion, but a peak (1.5%) at *m/e* 279.1231 (calcd for $C_{20}H_{26}O_6$, C_5H_7O, 279.1243). Other significant peaks were at *m/e* (composition, %) 263 ($M^+ - C_5H_7O_2$, 22.8), 262 ($M^+ - C_5H_8O_2$, 26.8), 245 ($M^+ - C_5H_7O_2 - H_2O$, 3.4), 244 ($M^+ - C_5H_8O_2 - H_2O$, 49.6), 229 ($M^+ - C_5H_8O_2 - H_2O - CH_3$, 6.3), 100 ($C_5H_8O_2$, base peak), and 99 ($C_5H_7O_2$, 31.3).

X-Ray Analysis of Eufoliatorin. Intensity data were measured on a Hilger-Watts diffractometer (Ni filtered Cu Kα radiation, θ–2θ scans, pulse height discrimination). A crystal measuring approximately 0.15 × 0.4 × 0.5 mm was used for data collection; no absorption correction was made (μ = 8.4 cm^{-1}). A total of 2210 reflections were measured for $\theta < 76°$, of which 1992 were considered to be observed [$I > 2.5\sigma(I)$]. The structure was solved by a multiple solution procedure[22] and was refined by full-matrix least squares. In the final refinement anisotropic thermal parameters were used for the heavier atoms and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations but their parameters were not refined. The final discrepancy indices are R = 0.055 and wR = 0.076 for the 1992 observed reflections. The final difference map has no peaks greater than ±0.3 e Å^{-3}.

Acknowledgment. We wish to thank Mr. R. C. Rosanske for help with determination of the ^{13}C NMR spectra and the nuclear Overhauser effects.

Registry No.—**1a**, 62197-54-0; **1b**, 62197-55-1; **1c**, 62197-56-2; **1d**, 62197-57-3; **2**, 62197-58-4; **3**, 62197-59-5; **4a**, 62197-60-8; **4b**, 62197-61-9; **4c**, 62197-64-2; **5a**, 62197-62-0; **5b**, 62197-63-1; **6**, 62197-65-3.

Supplementary Material Available. Tables IV, V, and VI listing bond distances, bond angles, and torsion angles of compound **6** (3 pages). Ordering information is given on any current masthead page.

References and Notes

(1) This article is dedicated to the memory of S. Morris Kupchan, a long-time friend who published several noteworthy papers on constituents of *Eupatorium* species in the decade before his untimely death in 1976.
(2) Work at Florida State University supported in part by USPH Grant CA-13121 through the National Cancer Institute.
(3) W. Herz and R. P. Sharma, *J. Org. Chem.*, **41**, 1015 (1976).
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(6) For references to earlier work, on *Eupatorium* species, see ref 3, which also includes citations concerning the flavonoids of *E. perfoliatum* and related species.
(7) The crude extract as a whole was rather polar and difficult to separate. The four substances we were successful in purifying represented a relatively small portion of the total extract.
(8) W. Herz and R. P. Sharma, *J. Org. Chem.*, **41**, 1248 (1976).
(9) See ref 3 for reasons governing choice of this reagent combination.
(10) Use of paramagnetic shift methods which can occasionally be used to solve this vexing problem was ineffective in this case and that of the other substances described in this report because of line broadening, overlapping of signals, etc. The applicability of the solvent shift method of C. R. Narayanan and N. K. Venkatasubramaniam [*Tetrahedron Lett.*, 5865 (1966); *J. Org. Chem.*, **33**, 3156 (1968)], which gives good results with 11,13-dihydroeudesmanolides, to 11,13-dihydrogermacranolides and 11,13-dihydroguaianol des of known stereochemistry is currently being tested.
(11) For leading citations, see ref 8.
(12) See, for examp e, (a) N. S. Bhacca and N. H. Fischer, *Chem. Commun.*, 68 (1969); (b) F. Šorm, M. Suchý, M. Holub, A. Linek, I. Hadinec, and C. Novák, *Tetrahedron Lett.*, 1893 (1970); (c) S. K. Talapatra, A. Patra, and B. Talapatra, *Chem. Commun.*, 1534 (1970); (d) E. J. Gabe, S. Neidle, D. Rogers, and C. E. Nordman, *ibid.*, 559 (1971); (e) K. Tori, I. Horibe, Y. Tamura, and H. Tada, *J. Chem. Soc., Chem. Commun.*, 620 (1973); (f) M. A. Irwin and T. A. Geissman, *Phytochemistry*, **12**, 875 (1973); (g) R. W. Doskotch, S. L. Keely, and C. D. Hufford, *J. Chem. Soc., Chem. Commun.*, 1137 (1972); (h) A. T. McPhail and K. D. Onan, *J. Chem. Soc., Perkin Trans. 2*, 1798 (1975); (i) K. Tori, I. Horibe, Y. Tamura, K. Kuriyama, H. Tada, and K. Takeda, *Tetrahedron Lett.*, 387 (1976); (j) A. Quick and D. Rogers, *J. Chem. Soc., Perkin Trans. 2*, 465 (1976).
(13) N. Harada and K. Nakanishi, *J. Am. Chem. Soc.*, **91**, 3990 (1969). The exciton split CD curves of dibenzoates invariably have either a stronger first extremum and weaker second or they are equal. Figure 1 shows some anomalies: (1) the extrema are shifted by 7–8 nm to the red and (2) the second extremum is much more intense. A reviewer has commented that the strong intensity of the second Cotton effect is probably due to the overlap of the positive CD maximum arising from the tiglate group.
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(16) Since the ^{13}C NMR spectra of **1a** and **4a** were run in different solvents, no attempt is made to interpret the chemical shifts exhibited by C-1, C-5, and C-8, although that of C-1 is in the right direction.
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Grisabine and Grisabutine, New Bisbenzylisoquinoline Alkaloids from *Abuta grisebachii*

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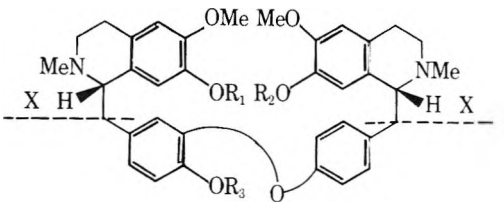
Grisabine and grisabutine, new bisbenzylisoquinoline alkaloids from *Abuta grisebachii*, Triana & Planchon, have been assigned structures **1** and **2**, respectively, on the basis of spectroscopic and chemical evidence.

Recent studies from our laboratory have led to the isolation of a number of new alkaloids from plants of the tropical American genus *Abuta* (Menispermaceae).[1] We now wish to report the isolation and structure determination of two new bisbenzylisoquinoline alkaloids, grisabine (**1**) and grisabutine (**2**), from the Amazonian species *Abuta grisebachii*.[2]

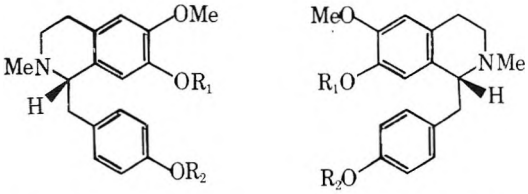
Grisabine (**1**) was obtained as white needles, mp 148–149 °C. The composition $C_{37}H_{42}N_2O_6$ was determined by high-resolution mass spectrometry.

The infrared spectrum (KBr) of grisabine showed a band at 3400 cm^{-1}, attributable to a nonassociated phenolic group. The NMR spectrum of grisabine showed the presence of three superimposed aromatic methoxyls at δ 3.83, two nonequivalent methylimino groups at δ 2.43 and 2.48, and a band of 11 unresolved aromatic protons in the range of δ 6.38–7.01.

The mass spectrum of grisabine is typical of that of a bisbenzylisoquinoline alkaloid containing only a single tail-to-tail ether bridge. Thus, the molecular ion at *m/e* 610 was quite weak (4%), while the two identical head fragments **13** formed the base peak at *m/e* 192.

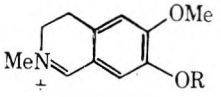


1, $R_1 = R_2 = H$; $R_3 = Me$
2, $R_1 = R_2 = R_3 = H$
3, $R_1 = R_2 = R_3 = Me$
4, $R_1 = R_2 = CD_3$; $R_3 = Me$
5, $R_1 = R_2 = R_3 = CD_3$



6, $R_1 = R_2 = Me$
7, $R_1 = CD_3$; $R_2 = Me$
8, $R_1 = R_2 = CD_3$

9, $R_1 = Me$; $R_2 = H$
10, $R_1 = CD_3$; $R_2 = H$
11, $R_1 = CD_3$; $R_2 = Me$
12, $R_1 = R_2 = CD_3$



13, R = H
14, R = Me
15, R = CD_3

The ultraviolet absorption band of grisabine at 287 nm underwent a bathochromic shift to 305 nm, indicative of the presence of phenolic functionality. The presence of two phenolic functions in grisabine was revealed by its reaction with excess diazomethane, which afforded the amorphous *O,O*-dimethylgrisabine (**3**). The composition $C_{39}H_{46}N_2O_6$ was determined by high-resolution mass spectrometry. The NMR spectrum of **3** showed the presence of three resolved methoxyls at δ 3.59, 3.62, and 3.77 and two superimposed methoxyls at δ 3.80; of the 11 aromatic protons of **3**, two were resolved as singlets at δ 6.10 and 6.16 (H-8 and H-8′) and two as singlets at δ 6.56 and 6.57 (H-5 and H-5′).

The corresponding reaction of grisabine with diazomethane-d_2 in dioxane–deuterium oxide yielded the corresponding *O,O*-bistrideuteriomethyl derivative (**4**). A comparison of the NMR spectra of **3** and **4** clearly indicated that the two methoxyls introduced into grisabine in **3** are represented by the signals at δ 3.59 and 3.62. The mass spectra of **3** and **4** show base peaks at *m/e* 206 (**14**) and 209 (**15**), respectively, confirming the presence of a phenolic hydroxyl in each of the head units of grisabine.

The structure and stereochemistry of *O,O*-dimethylgrisabine (**3**) were established chemically by treatment of **3** with sodium in liquid ammonia, which cleanly cleaved the molecule into phenolic and nonphenolic portions. The nonphenolic product was identical with authentic (*S*)-*O*-methylarmepavine (**6**), while the phenolic product was identical with authentic (*R*)-armepavine (**9**).

The location of the phenolic functions of grisabine in the isoquinoline units was shown by sodium–ammonia cleavage of its bistrideuteriomethyl ether **4**, which afforded the fragments (*S*)-7-*O*-trideuteriomethyl-12-*O*-methyl-*N*-methylcoclaurine (**7**) and (*R*)-7-trideuteriomethyl-*N*-methylcoclaurine (**10**). The structure of **10** was confirmed by deuteriomethylation to give (*R*)-*O,O*-bis(trideuteriomethyl)-*N*-methylcoclaurine (**12**), which was identical with an authentic sample. The structure of **7** was established by reaction of **10** with diazomethane to give the ether **11**, which differed from **7** only in the opposite sign of its rotation.

The above observations establish the structure of grisabine as **1**. It is therefore the *SR* diastereomer of the known alkaloid cuspidaline[3] (**1**, *RR*).

Grisabutine (**2**), mp 192–193 °C, formed white needles from methanol, and had the molecular composition $C_{36}H_{40}N_2O_6$, as shown by mass spectrometry. Its mass spectrum showed a fairly weak (15%) molecular ion at *m/e* 598, the base peak appearing at *m/e* 192, as in the case of grisabine. The methyl region of the NMR spectrum of **2** was remarkably simple, consisting only of two superimposed methoxyls at δ 3.71 and two superimposed methylimino groups at δ 2.32.

Treatment of grisabutine with excess diazomethane afforded an *O*-trimethyl derivative which proved to be identical in all respects with *O*-dimethylgrisabine (**3**). The structure determination of **2** consequently required only a proof of the location of the three phenolic hydroxyl groups.

Deuteriomethylation of grisabutine afforded the tristrideuteriomethyl derivative **5**, which was reductively cleaved by sodium in liquid ammonia. The nonphenolic cleavage product was shown to be (*S*)-*O,O*-bis(trideuteriomethyl)-*N*-methylcoclaurine (**8**) by comparison with an authentic sample; the phenolic product was identical with the phenol **10** derived from the grisabine derivative **4**.

Structure **2** is therefore established for grisabutine, which is the *SR* enantiomer of the known alkaloid berbamunine[4] (**2**, *RS*).

Experimental Section

Melting points are uncorrected. NMR spectra were determined in $CDCl_3$ solution (unless otherwise indicated) with tetramethylsilane as internal standard using a Varian A-60 spectrometer; infrared (KBr), ultraviolet (EtOH solution), mass spectra, and optical rotations were determined using Perkin-Elmer Models 137, 202, 270, and 141 instruments, respectively. All preparative chromatography (PLC) was carried out on silica plates using 10:1 $CHCl_3$–MeOH. *Abuta grisebachii* (*Schunke 5498*) was collected in Loreto, Coronel, Portillo, Peru, and identified by B. A. Krukoff. A voucher specimen has been deposited at the New York Botanical Garden and at other institutions.

Isolation of Grisabine (1) and Grisabutine (2) from *Abuta grisebachii*. Six pounds of ground stems of *Abuta grisebachii* was exhaustively extracted with aqueous ammonia–ether (four times with 6 L of ether). The combined ether extracts on evaporation gave 48 g of crude residue. This was extracted with 2 N HCl, the extract was basified with NH_4OH, and the free bases were taken up in $CHCl_3$. The dried bases obtained after evaporation of the $CHCl_3$ (12 g) were subjected to gradient pH countercurrent distribution between chloroform and aqueous acid, starting with pH 6.5 citrate–phosphate buffer and ending with 3 M phosphoric acid. The acidic aqueous layers were basified, reextracted with chloroform, and combined into several fractions (A–G) on the basis of TLC results.

Fraction D (4.4 g) crystallized from MeOH to give colorless needles (2.9 g) of grisabutine (**2**): mp 192–193 °C; $[\alpha]_D$ −50.0° (*c* 0.5, $CHCl_3$); IR 3400 cm^{-1} (OH); UV λ_{max} (ϵ) 224 nm (17 282), 239 (17 670), 287 (10 131), 320 (sh) (1787); λ_{max} (NaOH) (ϵ) 224 nm (17 345), 242 (17 640), 305 (11 084), 343 (sh) (1311); NMR (Me_2SO-d_6) δ 2.32 (s, 6 H, 2 NMe), 3.71 (s, 6 H, 2 OCH_3); mass spectrum *m/e* (rel intensity) 596 (M^+, 15), 404 (M − X, 13), 192 (X, 100), 175 (6); high-resolution mass spectrum *m/e* 596.28509 ($C_{36}H_{40}N_2O_6$ requires *m/e* 596.28863).

Fraction F (1.78 g) on crystallization from MeOH gave white needles of grisabine (**1**, 1.4 g), mp 145–146 °C. Recrystallization from MeOH raised the melting point to 148–149 °C; $[\alpha]_D$ −60.2° (*c* 0.5, $CHCl_3$); IR 3400 cm^{-1} (OH); UV λ_{max} (ϵ) 224 nm (17 875), 237 (18 250), 287 (15 000); λ_{max} (NaOH) (ϵ) 223 nm (18 300), 237 (19 200), 305 (3721); NMR δ 2.43, 2.48 (s, 3 H each, 2 NMe), 3.83 (s, 9 H, 3 OCH_3); mass spectrum *m/e* (rel intensity) 610 (M^+, 4), 418 (M^+ − X, 4), 192 (X, 100), 175 (15); high-resolution mass spectrum *m/e* 610.30206 ($C_{37}H_{42}N_2O_6$ requires 610.30428).

***O,O,O*-Trimethylgrisabutine (3).** To a solution of **2** in methanol–ether was added ethereal diazomethane and the mixture was set aside in the dark overnight. The usual workup gave **3** as an amorphous solid. Further purification was carried out by PLC: $[\alpha]_D$ −10° (*c* 1.0,

$CHCl_3$); NMR δ 2.47, 2.51 (s, 3 H each, 2 NMe), 3.59, 3.62, 3.77, 3.80 (s, 3 H, 3 H, 3 H, and 6 H, 5 OMe), 6.10, 6.16, 6.56, 6.57 (1 H, each), 6.70–7.11 (m, 7 H); mass spectrum *m/e* (rel intensity) 638 (M^+, 20), 432 ($M^+ - X$, 20), 206 (X, 100), 190 (95); high-resolution mass spectrum *m/e* 638.33637 ($C_{39}H_{46}N_2O_6$ requires 638.33558).

***O,O,O*-Tris(trideuteriomethyl)grisabutine (5).** To a cooled solution of excess diazomethane in dioxane (10 mL) and D_2O (1 mL) was added a solution of **2** (50 mg) in dioxane (2 mL) and D_2O (1 mL). After standing for 24 h in the dark, the usual workup afforded **5** as an amorphous solid (45 mg) which was purified by PLC: NMR δ 2.46, 2.51 (s, 3 H each, 2 NMe), 3.80 (s, 6 H, 2 OMe), 6.11, 6.17 (s, 1 H each), 6.58 (s, 2 H), 6.73–7.15 (m, 7 H).

Sodium–Ammonia Cleavage of 3. To liquid ammonia (500 mL) at −78 °C was added alternatively, with stirring, small pieces of sodium and portions of a solution of **3** (320 mg) in dry THF, allowing the color to remain blue prior to each new addition of the alkaloid solution. Finally, more sodium was added until the blue color persisted for 30 min. The ammonia was allowed to evaporate overnight, and the residue was dissolved in water and extracted with $CHCl_3$ to give the nonphenolic fraction (120 mg). The aqueous layer, after saturation with NH_4Cl (pH 8–9), was extracted with $CHCl_3$ (addition of some $NaBH_4$ retarded air oxidation of the phenolic alkaloids) to give the phenolic fraction (130 mg). Both phenolic and nonphenolic fractions were purified by PLC.

From the nonphenolic fraction, **6** was isolated as an oil: $[\alpha]_D$ +83° (c 1.0, MeOH); NMR δ 2.52 (s, 3 H, NMe), 3.56, 3.76, 3.82 (s, 3 H, each, OMe), 6.10 (s, 1 H), 6.59 (s, 1 H), 6.80 (d, 2 H), 7.07 (d, 2 H). The rotation and NMR values were identical with those of (*S*)-*O*-methylarmepavine (**6**) as reported. The oxalate of **6** crystallized from ethanol–ether as white needles, mp 112 °C, $[\alpha]_D$ +99.5° (c 0.05, $CHCl_3$). A mixture melting point of the oxalate with an authentic sample gave no depression.

From the phenolic fraction **9** was obtained as an amorphous solid: $[\alpha]_D$ −81.9° (c 0.5, MeOH); NMR δ 2.54 (s, 3 H, NMe), 3.52, 3.80 (s, 3 H each, 2 OMe), 6.02 (s, 1 H), 6.60 (s, 1 H), 6.66 (d, 2 H), 6.80 (d, 2 H). The rotation and NMR values were identical with those reported for (*R*)-armepavine (**9**). The oxalate was crystalline (EtOH–ether), mp 207–208 °C, $[\alpha]_D$ −84° (c 0.5, MeOH); its mixture melting point with an authentic sample gave no depression.

Sodium–Ammonia Cleavage of 5. The sodium–liquid ammonia cleavage was carried out on **5** (330 mg) exactly as described for **3**, and the products were separated into nonphenolic and phenolic fraction. From the nonphenolic fraction **8** was obtained after PLC purification as an oil (114 mg): NMR δ 2.53 (s, 3 H, NMe), 3.81 (s, 3 H, OMe), 6.01 (s, 1 H), 6.60 (s, 1 H), 6.81 (d, J = 9 Hz, 2 H), 7.08 (d, J = 9 Hz, 2 H). The oxalate of **8** was crystallized from EtOH–ether: mp 128–129 °C $[\alpha]_D$ +98° (c 0.5, $CHCl_3$); mass spectrum *m/e* (rel intensity) 333 (M^+, <1), 332 (1), 209 (100), 124 (13). These values were identical with those reported[1b] for (*S*)-*O,O*-bis(deuteriomethyl)-*N*-methylcoclaurine. A mixture melting point of the oxalate with an authentic sample resulted in no depression.

The phenolic fraction after PLC purification afforded **10** as an oil: NMR δ 2.55 (s, 3 H, NMe), 3.83 (s, 3 H, OMe), 6.01 (s, 1 H), 6.61 (s, 1 H), 6.66 (d, J = 9 Hz, 2 H), 6.80 (d, J = 9 Hz, 2 H). The oxalate crystallized from EtOH–ether: mp 210–212 °C, $[\alpha]_D$ −95.6° (c 0.32, MeOH); mass spectrum *m/e* (rel intensity) 316 (M^+, 12), 285 (80), 209 (100), 194 (10), 191 (15).

Deuteriomethylation of 10. Compound **10** was trideuteriomethylated as described for **2** to give the amorphous **12**, the oxalate of which crystallized from EtOH–ether, mp 130–131 °C, $[\alpha]_D$ −98° (c 0.5, $CHCl_3$). The mixture melting point of **12** oxalate with an authentic sample gave no depression; furthermore, the NMR and IR of base **12** were identical with those of its enantiomer **8** (see above).

***O,O*-Dimethylgrisabine (3).** Treatment of **1** with excess of diazomethane and the usual workup afforded **3** which was identical in all respects with the product obtained from the methylation of grisabutine (**2**).

***O,O*-Bis(trideuteriomethyl)grisabine (4).** About 300 mg of grisabine (**1**) was trideuteriomethylated as described for **2** to give, after PLC purification, the amorphous **4** (300 mg): NMR δ 2.48, 2.52 (s, 3 H each, 2 NMe), 3.78 (s, 3 H, OMe), 3.80 (s, 6 H, 2 OMe), 6.10 (s, 1 H), 6.15 (s, 1 H), 6.56 (s, 2 H), 6.73–7.25 (m, 7 H); mass spectrum *m/e* (rel intensity) 644 (M^+, 15), 626 (5), 435 (18), 420 (6), 209 (100), 193 (25).

Sodium–Ammonia Cleavage of 4. The sodium–ammonia cleavage was carried out on **4** (275 mg) exactly as described for **3** and the products were separated into phenolic and nonphenolic fractions. The nonphenolic fraction, after PLC purification, gave the amorphous **7** (120 mg): NMR δ 2.53 (s, 3 H, NMe), 3.75 (s, 3 H, OMe), 3.83 (s, 3 H, OMe), 6.08 (s, 1 H), 6.60 (s, 1 H), 6.81 (d, J = 9 Hz, 2 H), 7.08 (d, J = 9 Hz, 2 H). The oxalate of **7** crystallized from ethanol–ether: mp 135–136 °C; $[\alpha]_D$ +94° (c 0.80, $CHCl_3$); mass spectrum *m/e* (rel intensity) 330 (M^+, 4), 209 (100), 192 (50), 191 (40).

The phenolic fraction, after PLC purification, gave **10** (70 mg) as a colorless oil, the oxalate of which was crystalline. It was identical in all respects with (*R*)-*O*-(trideuteriomethyl)-*N*-methylcoclaurine obtained as the phenolic product of the Na/NH_3 cleavage of **5**.

Methylation of 10. Phenol **10** was methylated with diazomethane in the usual manner to give **11**, which crystallized as the oxalate, mp 136–137 °C, $[\alpha]_D$ −95° (c 0.10, $CHCl_3$). The NMR values and mass spectral data for **11** were identical with those of **7**, although its rotation was of the opposite sign.

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Registry No.—**1**, 62059-36-7; **2**, 6859-66-1; **3**, 13565-64-5; **4**, 62006-12-6; **5**, 62006-13-7; **6**, 3423-02-7; **7**, 62029-55-4; **7** oxalate, 62029-56-5; **8**, 62029-57-6; **9**, 524-20-9; **10**, 62006-14-8; **10** oxalate, 62006-15-9; **11** oxalate, 62006-17-1; **12**, 57256-00-5.

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Aromatic Hydroxylation of Some Isoquinoline-Type Alkaloids

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Isoquinoline-type alkaloids which undergo selective halogenation can be converted to analogues containing an additional oxygen in the form of a phenolic hydroxyl by the sequence of bromination, metal–halogen interchange, and reaction of the organometallic intermediate with nitrobenzene. Examples are reported using a simple benzyltetrahydroisoquinoline (*dl*-laudanosine, **1**), an aporphine (nuciferine, **8**), and a bisbenzylisoquinoline (tetrandrine, **15**). The method makes possible overall oxidative transformations of a type hitherto not possible, i.e., the synthesis of homomoschatoline (**14**) from nuciferine (**8**), and the synthesis of hernandezine (**19**) from tetrandrine (**15**).

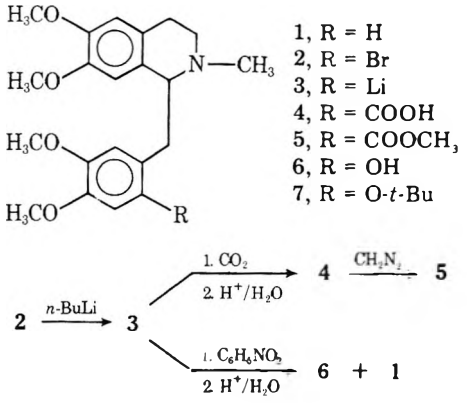
Naturally occurring isoquinoline alkaloids cover a range of structural subtypes, within which there is considerable latitude in the degree of oxygenation of the aromatic rings. A procedure for the introduction of an additional phenolic hydroxyl into a specific position of a known isoquinoline alkaloid would be valuable for several reasons. It would allow not only the preparation of unnatural alkaloid derivatives for pharmacological evaluation, but also the partial synthesis of certain rare natural bases from more readily available ones.

We now report the successful development of such a procedure, based upon the observation of Buck and Köbrich[1,2] that phenol is produced when nitrobenzene is attacked by phenyllithium at low temperatures. To our knowledge, the only synthetic application of this reaction subsequently reported has been the conversion of 5-lithio[3,3]paracyclophane to the corresponding 5-hydroxy derivative.[3] In our work, we have explored the application of the Buck–Köbrich reaction to examples of three different types of isoquinoline alkaloids: the simple benzyltetrahydroisoquinoline laudanosine (**1**), the aporphine nuciferine (**8**), and the bisbenzylisoquinoline tetrandrine (**15**).

Results

In all of the three cases discussed below, hydroxylation was carried out on lithiated alkaloids prepared from the corresponding bromo derivatives, all of which were homogeneous crystalline intermediates. Preliminary attempts to lithiate the parent alkaloids directly were unpromising, since lithium–hydrogen interchange was slow, and O-demethylation to phenolic products was a serious side reaction.

Hydroxylation of Laudanosine (1). Direct bromination of *dl*-laudanosine (**1**) takes place selectively to give the 6′-bromo derivative **2** in good yield,[4] making **2** the most readily

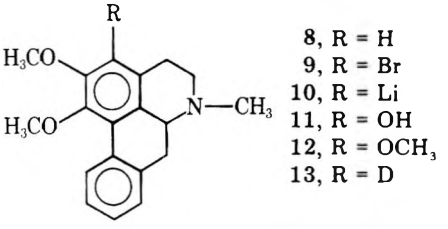


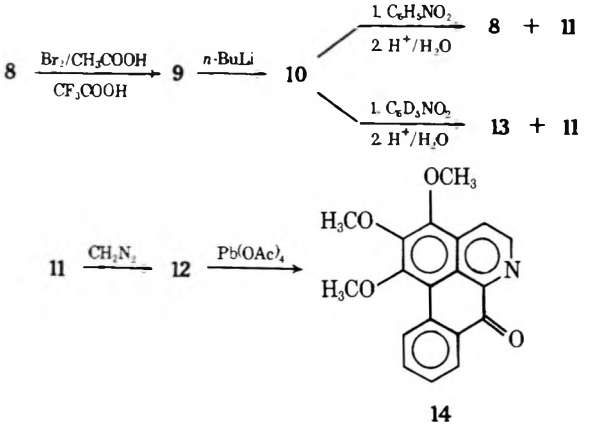
available halo derivative of a simple benzyltetrahydroiso quinoline alkaloid. We have found that bromide **2** undergoes a very clean halogen–lithium interchange when treated with *n*-butyllithium; carbonation of the resulting 6′-lithiolaudanosine (**3**) results in the almost quantitative formation of the crystalline 6′-carboxylaudanosine (**4**), further characterized as its methyl ester **5**.

Reaction of the lithio derivative **3** with excess nitrobenzene at −60 °C afforded, as the major product (65%), 6′-hydroxylaudanosine (**6**), previously known only as a thalicarpine degradation product.[5] The only significant by-product of the reaction (30%) was laudanosine (**1**).

Since simple phenols have been prepared by the reaction of aryllithiums with *tert*-butyl perbenzoate,[6] followed by acid hydrolysis, we also investigated this route to 6′-hydroxylaudanosine. Reaction of lithio derivative **3** with *tert*-butyl perbenzoate, followed by direct acid cleavage of the *tert*-butyl ether **7**, did indeed afford phenol **6**, but only in low yield (13%).

Hydroxylation of Nuciferine (8). Whereas laudanosine is brominated smoothly in an acetic acid–sodium acetate medium,[4] attempts to brominate (*R*)-nuciferine (**8**) under the same conditions afforded a mixture of products as evidenced by TLC. It was suspected that this result was due to a very facile attack of the bromine on the basic nitrogen, leading to a dehydroaporphine, a reaction known to be brought about by iodine.[7] In accord with this supposition, bromination of nuciferine took place cleanly in the presence of the strongly acidic trifluoroacetic acid, giving 3-bromonuciferine (**9**) in high



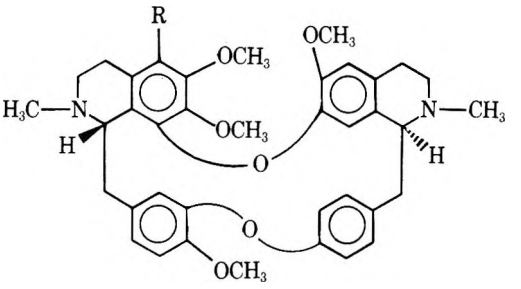


yield (90%). Conversion of bromide **9** to the corresponding lithio derivative **10**, followed by reaction with excess nitrobenzene, afforded 3-hydroxynuciferine (**11**) in about 50% yield, the major by-product being nuciferine.

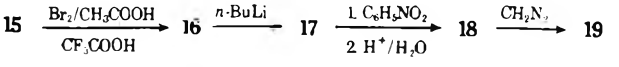
Confirmation of the structure of phenol **11** was obtained not

only from its NMR spectrum (loss of the C-3 nuciferine singlet), but also by further chemical transformations. Thus, diazomethane treatment of 11 afforded 3-methoxynuciferine (12),[8] which on oxidation with lead tetraacetate[9] gave homomoschatoline (14),[10,11] the structure of which has been secured by a total synthesis.[11]

Hydroxylation of Tetrandrine (15). Although the bisbenzylisoquinoline alkaloid tetrandrine (15) contains eight different aromatic sites which are activated by an ether substituent, only one of these sites (C-5) is *doubly* activated by both an ortho and a para ether substituent. In fact, monobromination of tetrandrine in the presence of trifluoroacetic acid afforded, in high yield, the crystalline 5-bromotetrandrine (16). The position of the bromine in 16 was not only consistent with its spectroscopic properties, but was proven chemically by the following reactions. Conversion of 16 to the corresponding lithio derivative 17, followed by treatment with excess nitrobenzene, afforded 5-hydroxytetrandrine (18) in



15, R = H
16, R = Br
17, R = Li
18, R = OH
19, R = OCH_3

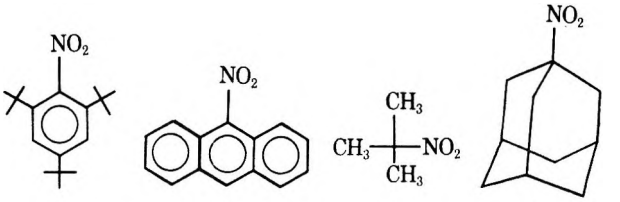


good yield (57%), the major by-product consisting of tetrandrine; diazomethane methylation of 18 gave 5-methoxytetrandrine (19). Comparison with authentic samples showed 18 and 19 to be identical in all respects with the natural alkaloids thalidezine[12] and hernandezine,[13] respectively. The conversion of the antitumor alkaloid tetrandrine to the closely related rare base thalidezine (18) is especially interesting, since it has permitted the preparation of the latter for the first time in quantities sufficient for biological testing.

Discussion

As mentioned in the previous section, the major nonphenolic products of the reaction of excess nitrobenzene with the lithiated alkaloids 3, 10, and 17 are the original alkaloids (1, 8, and 15). It seemed at first that this unwanted side reaction was due simply to protonation of the lithio compounds by traces of moisture, although the protonation reaction could not be suppressed even under the most rigorously anhydrous conditions. It then became evident that the observed products would also be obtained if the lithiated alkaloid were to abstract an ortho (or para) hydrogen from the nitrobenzene at a rate comparable to its attack on the nitro group of the reagent. *o*-Nitrophenyllithium is indeed a known species and is fairly stable at low temperatures.[1,2] Confirmation of this idea was obtained by treatment of 3-lithionuciferine (10) with pentadeuterionitrobenzene. The nuciferine recovered from this reaction was shown by NMR to contain about 75% of 3-deuterionuciferine (13).

Several unsuccessful attempts were made to find a nitro compound which would be superior to nitrobenzene as a hydroxylating agent, 3-lithionuciferine (10) being employed as the test reagent. 2,4,6-Tri-*tert*-butylnitrobenzene (20),[14]



20 21 22 23

which should not be metalated, proved to be very unreactive as an oxidant, only about 5% of phenol 11 being formed after 12 h at room temperature. 9-Nitroanthracene (21), which has only a free para position, gave a fair yield (40%) of phenol 11, but was still not as effective as nitrobenzene. The aliphatic reagents 2-methyl-2-nitropropane (22) and 1-nitroadamantane (23)[15] were totally ineffective, and produced only a trace of phenolic product.

Experimental Section

Melting points are uncorrected. NMR spectra were determined using a Varian A-60 instrument, with tetramethylsilane as internal standard. Infrared spectra (KBr), ultraviolet spectra (EtOH), mass spectra, and optical rotations were determined using Perkin-Elmer instrument Models 137, 202, 270, and 140, respectively.

3-Bromonuciferine (9). To a solution of (−)-nuciferine (2.95 g, 10 mmol) in trifluoroacetic acid (15 mL) and water (10 mL), a solution of bromine in acetic acid (11 mL of 1.1 M solution, 12 mmol) was added dropwise over a period of 5 min, while stirring and warming on a steam bath. A precipitate formed, which quickly redissolved. After the addition of bromine was complete, the solution was further stirred for 45 min, then poured into a mixture of ice and water (150 mL) and slowly basified with concentrated aqueous ammonium hydroxide. Extraction with chloroform (300 mL) and evaporation of the extract gave a brown oil which was passed through a dry silica column (30 g) with chloroform elution. Evaporation of the eluent afforded 3-bromonuciferine as an oil which crystallized upon cooling. The crystals (3.4 g, 90%) were recrystallized from methanol to give fine, pale yellow needles: mp 117–118 °C; $[\alpha]^{28}_D$ −79.7° (c 1.0, chloroform); UV λ_{max} (EtOH) 211 nm (ε 31 100), 288 (sh, 16 100), 276 (18 800); NMR ($CDCl_3$) δ 2.15–3.43 (m, 7 H, aliphatic H), 2.48 (s, 3 H, NCH_3), 3.71 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 7.17–7.51 (m, 3 H, $H_{8,9,10}$), 8.20–8.47 (m, 1 H, H_{11}); mass spectrum *m/e* 375 (M^+).

Anal. Calcd for $C_{19}BrH_{20}NO_2$: C, 60.97; H, 5.39; N, 3.74; O, 8.55. Found: C, 60.98; H, 5.35; N, 3.75; O, 8.58.

Bromotetrandrine (16). To a solution of tetrandrine (207 mg, 0.33 mmol) in trifluoroacetic acid (1 mL) and water(0.5 mL), a solution of bromine in acetic acid (0.35 mL of 1.1 M solution, 0.385 mmol) was added dropwise over a period of 5 min while stirring and warming over a steam bath. The solution was stirred for a further 45 min, then poured into a mixture of ice and water (20 mL) and slowly basified with concentrated ammonium hydroxide. Extraction with chloroform (2 × 50 mL) and evaporation of the extract gave a pale yellow oil which crystallized upon addition of anhydrous ether. The crystals (220 mg, 94%) were recrystallized from methanol–ether mixture (1:1) to give colorless needles of 16: mp 142–144 °C; $[\alpha]^{28}_D$ +218.6° (*c* 1.0, $CHCl_3$); UV (EtOH) λ_{max} 209 nm (ε 79 200), 238 (28 700), 285 (7700); NMR ($CDCl_3$) δ 2.26 (s, 3 H, NCH_3), 2.46–4.47 (m, 14 H, aliphatic H), 2.60 (s, 3 H, NCH_3), 3.20 (s, 3 H, OCH_3), 3.32 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 6.02 (s, 1 H, ArH), 6.12–7.47 (m, 9 H, ArH); mass spectrum (high resolution) M^+ *m/e* 700.20734, 702.20702 (calcd for $C_{38}H_{41}N_2O_6Br$, 700.21583).

General Procedure for Bromine–Lithium Exchange. Reactions were carried out in a dry three-necked flask containing a magnetic stirring bar. Two of the necks were fitted with rubber septums and the third with an argon inlet. The flask was flushed with argon for 5 min while being heated with a Bunsen burner, and then kept under argon until the reaction was completed. Tetrahydrofuran (freshly distilled over lithium aluminum hydride) was introduced, then the flask containing the solvent was cooled in an acetone–dry ice bath. A solution of *n*-butyllithium (2.5 M in hexane) was introduced by a syringe through one of the rubber septums, followed by dropwise addition of the brominated starting material in tetrahydrofuran (freshly distilled over lithium aluminum hydride), again by a syringe through a rubber septum. The mixture was stirred in the acetone–dry ice bath for 45 min before carrying out the subsequent reaction of the lithiated alkaloid.

6′-Carboxylaudanosine (4). Bromolaudanosine (1.03 g, 2.35

mmol) in THF (12 mL) was added to a mixture of *n*-butyllithium (2.9 mL, 7.05 mmol) in hexane and THF (10 mL), and the mixture was allowed to stir for 45 min. The solution was then quickly poured into a dry ice–ether mixture. After evaporation of the solvent, the residue was distributed between 2 N hydrochloric acid and ether. The aqueous layer was washed once with ether, neutralized with sodium bicarbonate, then extracted five times with 100-mL portions of chloroform. After drying (Na_2SO_4), the chloroform extract was concentrated to 50 mL and diluted with anhydrous ether. Heavy white crystals formed on cooling at 0 °C over a period of 48 h. The crystals (905 mg, 95.8%) were recrystallized from benzene–ether to give the pure acid: mp 141–143 °C; UV (EtOH) λ_{max} 206 nm (ϵ 51 700), 250 (sh, 10 000), 283 (8000); ir (KBr) ν 1700 cm^{-1} (m, –COOH); NMR ($CDCl_3$) δ 2.58 (s, 3 H, NCH_3), 2.58–4.45 (m, 7 H, aliphatic H), 3.66 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 6.18 (s, 1 H, ArH), 6.41 (s, 1 H, ArH), 6.67 (s, 1 H, ArH), 7.65 (s, 1 H, ArH). Several attempts at elemental analysis gave erratic results. This compound was then characterized as its methyl ester (**5**).

6′-Carbomethoxylaudanosine (5). A solution of 6′-carboxylaudanosine (100 mg, 0.25 mmol) in methanol (50 mL) was treated twice with excess diazomethane (generated from 1.5 g of *N*-nitrosomethylurea) at room temperature at 24-h intervals. After evaporation of the solvent, the residue was shaken with a mixture of chloroform (50 mL) and water (50 mL). The chloroform layer was separated, dried (Na_2SO_4), and evaporated to a yellow oil, which crystallized upon addition of anhydrous ether. The white crystals (101 mg, 97%) had mp 130–131 °C; UV (EtOH) λ_{max} 207 nm (ϵ 35 500), 221 (sh, 3100), 256 (12 800), 286 (8900); IR (KBr) ν 1730 cm^{-1} (s, C=O); NMR ($CDCl_3$) δ 2.5 (s, 3 H, NCH_3), 2.45–3.7 (m, 7 H, aliphatic H), 3.62 (s, 3 H, OCH_3), 3.66 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 6.19 (s, 1 H, ArH), 6.52 (s, 1 H, ArH), 6.63 (s, 1 H, ArH), 7.52 (s, 1 H, ArH); mass spectrum *m/e* 415 (M^+).

Anal. Calcd for $C_{23}H_{29}NO_6$: C, 66.49; H, 7.04; N, 3.37. Found: C, 66.43; H, 7.11; N, 3.52.

6′-Hydroxylaudanosine (6). A. Using *tert*-Butoxyperbenzoate. 6′-Bromolaudanosine (437 mg, 1 mmol) in THF (7 mL) was added to a solution of *n*-butyllithium (0.5 ml, 1.5 mmol) in hexane and THF (2 mL), then allowed to stir as described in the general procedure. To this mixture kept at the same temperature, a solution of *tert*-butoxyperbenzoate (316 mg, 1.63 mmol) in freshly distilled THF (10 mL) was added dropwise over a period of 15 min. After the addition was complete, the mixture was stirred for a further 3 h before being brought to room temperature, then poured into 3 N hydrochloric acid (50 mL). The mixture was heated on a steam bath until all THF had evaporated, cooled to room temperature, and washed with ether (2 × 50 mL). The aqueous layer was basified with sodium bicarbonate and then extracted with chloroform (3 × 50 mL). Evaporation of the extract gave a brown oil which was subjected to thin layer chromatography, eluting with chloroform–methanol (9:1). The band of R_f 0.7 gave a yellow oil which crystallized upon cooling. Recrystallization of the product (49 mg 13%) gave white needles of **6**: mp 133–134 °C; UV (EtOH) λ_{max} 210 nm (ϵ 29 300), 230 (sh, 13 700), 289 (7800); NMR ($CDCL_3$) δ 2.51 (s, 3 H, NCH_3) 2.51–3.76 (m, 7 H, aliphatic H), 3.64 (s, 3 H, OCH_3), 3.71 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 6.34 (s, 1 H, ArH), 6.39 (s, 1 H, ArH), 6.45 (s, 1 H, ArH), 6.59 (s, 1 H, ArH); mass spectrum *m/e* 373 (M^+).

Anal. Calcd for $C_{21}H_{27}O_5N$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.56; H, 7.29; N, 3.71.

A small sample was converted to its HI salt, mp 183–185 °C (lit.[5] monohydrate, 184–186 °C) and HBr salt, mp 208–210 °C (lit.[16] 209–210 °C).

B. Using Nitrobenzene. A solution of 6′-bromolaudanosine (437 mg, 1 mmol) in THF (12 mL) was added to a solution of *n*-butyllithium (1.2 mL, 3 mmol) in hexane and THF (4 mL) and the mixture was allowed to stir as described in the general procedure. The solution was then immersed in a liquid nitrogen bath and nitrobenzene (1 g, 8.1 mmol) was added quickly. The mixture turned brown when brought up to −60 °C. After stirring at this temperature for 3.5 h the solution was brought to room temperature. A 10% solution of sulfuric acid (20 mL) was added and the mixture was washed with ether (2 × 50 mL). The aqueous layer was basified with concentrated ammonium hydroxide, then extracted with chloroform. Evaporation of the chloroform extract gave a brown oil which was separated by thin layer chromatography eluting with chloroform–methanol (9:1). The band of R_f 0.7 gave a yellow solid (251 mg, 65%) which was recrystallized from ether to give white needles of 6′-hydroxylaudanosine, identical in all respects with the sample obtained previously.

The band of R_f 0.5 afforded a slightly brown solid (107 mg, 30%) which, after recrystallization from petroleum ether, gave white needles, identical in all respects with authentic laudanosine.

3-Hydroxynuciferine (11). A. Using Nitrobenzene. A solution of 3-bromonuciferine (330 mg, 0.88 mmol) in THF (10 mL) was added to a solution of *n*-butyllithium (1.2 mL, 3 mmol) in hexane and THF (3 mL), then the mixture was allowed to stir as described in the general procedure. Addition of nitrobenzene (1 g, 8.1 mmol) followed by workup as described for 6′-hydroxylaudanosine gave the basic fraction which was separated by silica TLC eluting with chloroform–methanol (96:4).

The band of R_f 0.5 gave a yellow oil which crystallized upon addition of anhydrous ether. Recrystallization of the product (135 mg, 50%) from anhydrous ether afforded white needles of 3-hydroxynuciferine: mp 150–152 °C; $[\alpha]^{28}_D$ −83.7 (c 1.0, chloroform); UV (EtOH) λ_{max} 215 nm (ϵ 49 700), 240 (sh, 19 200), 283 (31 100), 292 (sh, 27 000); IR (KBr) ν 3200–3400 cm^{-1} (weak, OH); NMR ($CDCl_3$) δ 2.35–3.53 (m, 3 H, aliphatic H), 2.59 (s, 3 H, NCH_3), 3.77 (s, 3 H, OCH_3), 4.0 (s, 3 H, OCH_3), 5.87 (broad s, 1 H, disappeared on addition of D_2O, OH), 7.22–7.55 (3 H, $H_{8,9,10}$), 8.19–8.40 (m, 1 H, H_{11}); mass spectrum *m/e* 311 (M^+).

Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.49. Found: C, 73.40; H, 6.82; N, 4.48.

The band of R_f 0.6 gave a yellow oil (123 mg, 47%) which, after crystallization from petroleum ether, afforded needles identical in all respects with nuciferine.

The yield of 3-hydroxynuciferine was improved to 53%, along with 26% of nuciferine, in a larger scale reaction (6 mmol of bromonuciferine).

B. Using Pentadeuterionitrobenzene. A similar reaction was carried out using pentadeuterionitrobenzene in place of nitrobenzene. The yields of 3-hydroxynuciferine and nuciferine were comparable to those obtained from the previous reaction. The NMR of the nuciferine, however, showed 75% deuterium incorporation at the 3 position. Its mass spectrum showed M^+ at *m/e* 296 and characteristic peaks corresponding to the combination of nuciferine and 3-deuterionuciferine.

C. Using Other Reagents. Reactions were repeated using reagents **20, 21, 22,** and **23** under these conditions: (1) at −60 °C for 3 h, (2) at −60 °C for 1 h, then at room temperature overnight. Compounds **20, 21,** and **22** gave a trace of **11** and nuciferine (**8**) as the major product, while **23** gave approximately 40% of **11** and more than 50% of nuciferine.

3-Methoxynuciferine (12). A solution of 3-hydroxynuciferine (160 mg) in methanol (30 mL) was treated four times in succession with diazomethane generated from *N*-nitrosomethylurea (1 g) at 24-h intervals. The solvent was evaporated on a steam bath and the residue redissolved in chloroform (50 mL), then washed with 5% sodium hydroxide (50 mL). After drying with sodium sulfate, the solution was evaporated to give a pale yellow oil (120 mg, 72%). Crystallization from hexane afforded pale yellow needles of 3-methoxynuciferine: mp 105–106 °C (lit.[8] *dl* 105–106 °C); $[\alpha]^{28}_D$ −112.149° (*c* 0.214, chloroform); UV (EtOH) λ_{max} 212 nm (ϵ 43 000), 228 (sh, 25 100), 275 (21 400); NMR ($CDCl_3$) δ 2.42–3.48 (m, 7 H, aliphatic H), 2.66 (s, 3 H, NCH_3), 3.87 (s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3), 4.08 (s, 3 H, OCH_3), 7.31–7.81 (m, 3 H, $H_{8,9,10}$), 8.35–8.60 (m, 1 H, H_{11}).

Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.13; N, 4.31. Found: C, 73.82; H, 7.21; N, 4.27.

A small sample was converted to its methiodide, which crystallized from methanol–ether, mp 212–216 °C dec (lit.[8] 214–216 °C).

Homomoschatoline (*O*-Methylmoschatoline, 14). A solution of 3-methoxynuciferine (108 mg, 0.33 mmol) in acetic acid (5 mL) was stirred with lead tetraacetate (492 mg of 90% reagent, 1.0 mmol) at room temperature for 12 h, then poured into a dilute sulfuric acid solution (20 mL) and the mixture was extracted with chloroform until the extract was almost colorless. Evaporation of the extract gave a dark brown oil which was separated by alumina thin layer chromatography eluting with chloroform. The band of R_f 0.7 gave an orange oil (32 mg, 30%) which had an NMR spectrum identical with that of homomoschatoline. Crystallization from methanol gave orange needles, mp 184–187 °C, alone or on admixture with an authentic sample.[11]

Thalidezine (Hydroxytetrandrine, 18). A solution of bromotetrandrine (525 mg, 0.75 mmol) in THF (10 mL) was added to a solution of butyllithium (0.9 ml, 2.25 mmol) in hexane and THF (3 mL), and the mixture was then stirred as described in the general procedure. Treatment with nitrobenzene (720 mg, 6 mmol) and workup as described for 6′-hydroxylaudanosine gave a brown oil which was separated by silica TLC, eluting with chloroform–methanol (95:5, saturated with concentrated ammonium hydroxide). The band of R_f 0.6 gave an oil which crystallized on addition of ether. The crystals (190 mg, 41%) were identical in all respects with tetrandrine. The band of R_f 0.5 gave an oil (270 mg, 57%) which was crystallized from acetone

to give pale yellow needles of thalidezine, mp 155–159 °C and undepressed on admixture with an authentic sample (lit.[12] mp 158–159 °C). These crystals have identical NMR and UV spectra and similar TLC behavior to the authentic sample.

Hernandezine (19). Treatment of thalidezine (110 mg) with diazomethane was carried out as described for 3-methoxynuciferine. Hernandezine (90 mg, 80%) was obtained which was identical in all respects with an authentic sample.[13]

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Cannabinoids. 3.[1] Synthetic Approaches to 9-Ketocannabinoids. Total Synthesis of Nabilone

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The 9-ketocannabinoid, nabilone (**6**), is of clinical interest as one of a new group of totally synthetic cannabinoids that possesses interesting central nervous system properties. Synthetic approaches to **6** from the resorcinol **1** were explored. Three unique approaches to 9-ketocannabinoids are reported (Schemes III, IV, and V) as well as two other approaches (Schemes I and II) that have precedent in the literature. The most efficient synthesis of **6** proceeds through the cis isomer **7** which is isomerized to **6** with $AlCl_3$ in CH_2Cl_2. The optical antipodes, **6a** and **6b**, of nabilone (**6**) can be prepared by two different synthetic routes (Schemes II and III). The most efficient method for the preparation of the optical isomers **6a** and **6b** is from nopinone (**14b**) by the method outlined in Scheme III.

The natural products of marijuana, *Cannabis sativa* L., have been the subject of intensified synthetic endeavors during the past decade.[2a,b] Undoubtedly, some of these efforts were undertaken with the recognition of the therapeutic potentials[3] manifested by this group of interesting compounds. Certainly, our synthetic efforts were motivated by the search for a therapeutically effective drug in the cannabinoid area.

During the course of these studies, our interest focused on a group of compounds containing a keto group at the 9 position of the dibenzo[*b,d*]pyran nucleus.[4] One of these 9-ketocannabinoids, nabilone (**6**), has been selected for clinical evaluation[5a,b] on the basis of its preclinical pharmacology.[5c]

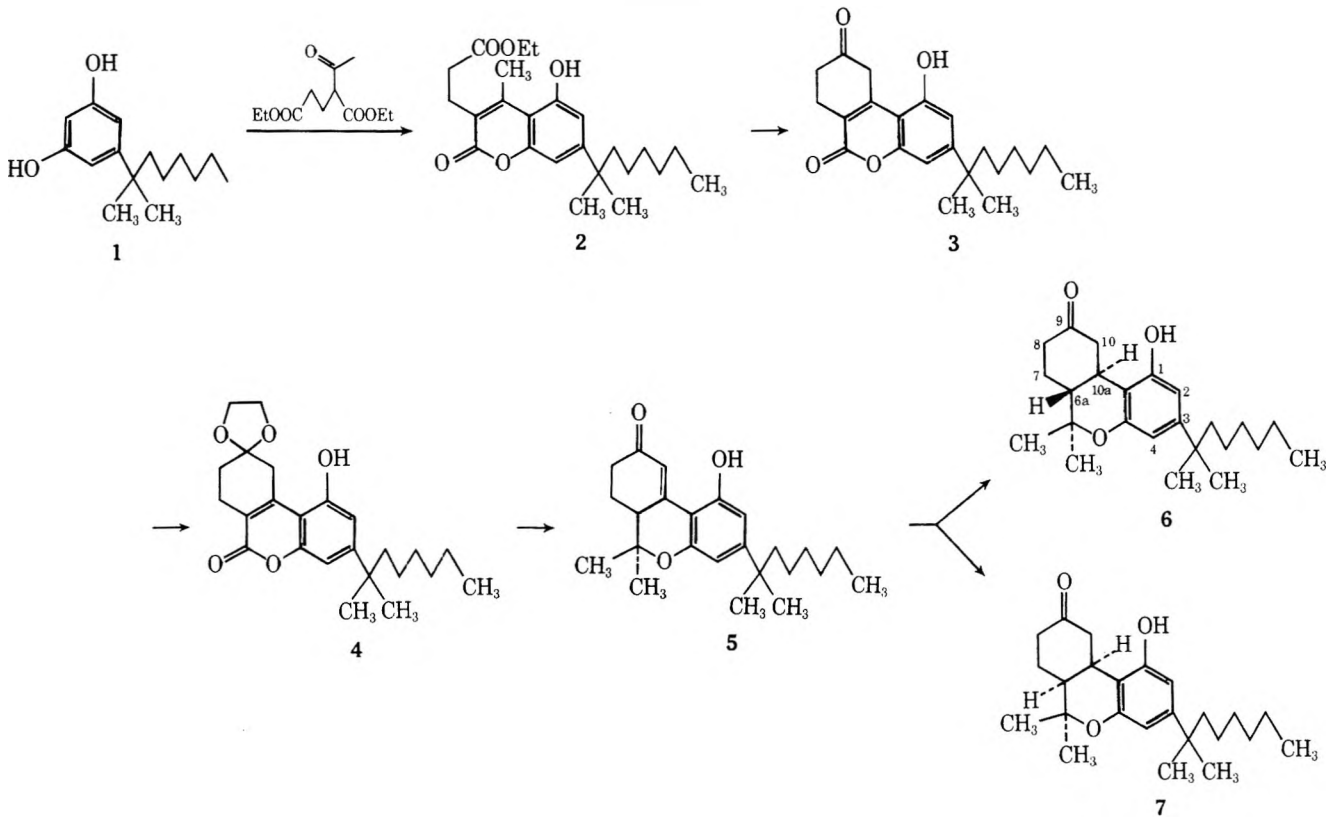
Because the original synthesis (Scheme I) of **6** that we employed was low yielding and cumbersome, we looked for new approaches to the synthesis of 9-ketocannabinoids. This paper describes the results of this search for an efficient synthesis of **6**. Additionally, we report herein the application of a new and shorter synthetic route to the synthesis of the 3-*n*-pentyl analogue (**26**). Previously, **26** has been converted by others[6] into racemic Δ^8- and Δ^9-tetrahydrocannabinol (THC). We also report the preparation of the optical antipodes, **6a** and **6b**, of the parent compound **6** by two different approaches.

Results and Discussion

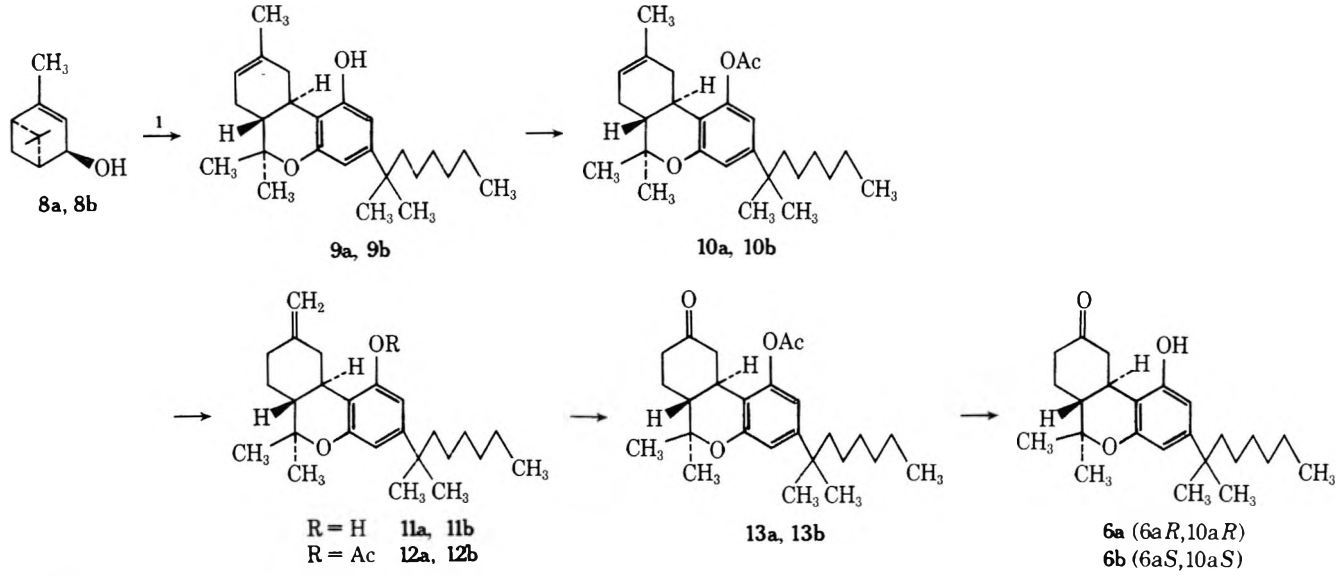
Scheme I outlines our initial approach to the synthesis of **6**. This reaction sequence follows the stepwise approach used by Fahrenholtz et al.[6] for the synthesis of the 3-*n*-pentyl analogues **25** and **26**. The resorcinol **1** was converted into the coumarin **2** by reaction with diethyl 2-acetylglutarate. Cyclization of **2** with NaH in Me_2SO[7] gave the tricyclic ketone **3** in 57% yield. Ketalization to **4** followed by Grignard reaction and strong acid hydrolysis afforded the α,β-unsaturated ketone **5**. Reduction of **5** with Li[8] in liquid NH_3 gave, after separation of the cis isomer **7**, the desired trans isomer **6**. The overall yield from **1** was 24% by this route. The cyclization of **2** to **3** was difficult to perform on a scale larger than 1 mol and never gave greater than 70% yield. Additionally, the chromatographic (and/or crystallization) separation of the trans isomer **6** from the approximately 20% impurity of the cis isomer **7** was difficult. Thus, we sought a better synthetic approach to 9-ketocannabinoids of the type represented by nabilone **6**.

The approach described in Scheme II was chosen primarily because it permitted the use of either (−)- or (+)-α-pinene as

Scheme I



Scheme II[a]



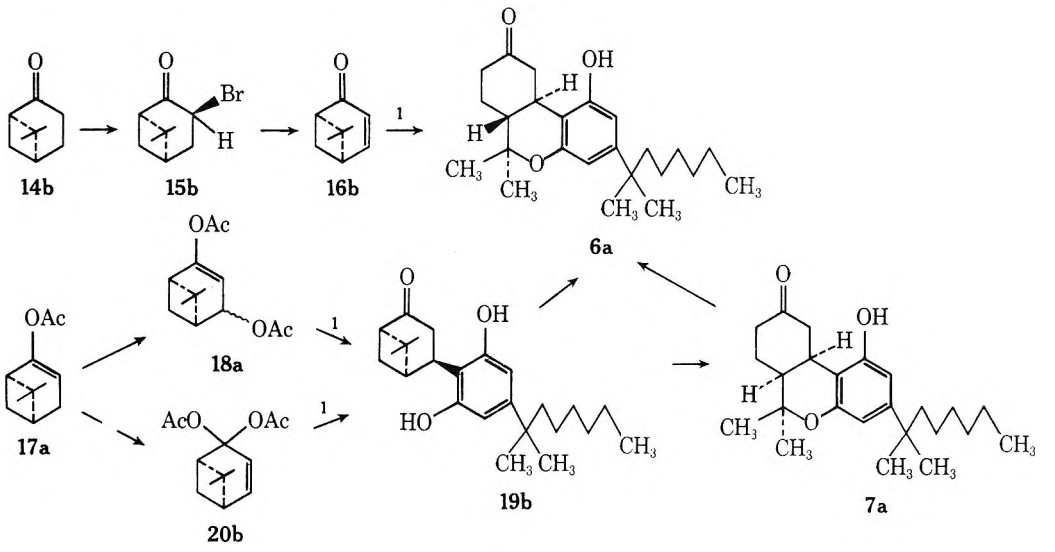
[a] The a and b refer to (−) and (+) optical isomers, respectively.

the starting point. The optically active pinenes could then be converted into the verbenols **8a** and **8b** which would eventually lead to the optically active 9-ketocannabinoids (**6a** and **6b**). Likewise, the choice of the (±)-α-pinene as the starting material would, by this route, give the desired racemate **6**. Fixing the 6a,10a ring juncture trans early in the synthesis avoided the separation of isomers that was a drawback in the first synthesis (Scheme I). Additionally, all of the intended synthetic conversions had a literature precedent in the synthesis[9] of Δ^8-THC and its conversion to the *n*-pentyl ketone **26**.

The appropriate verbenol **8a** or **8b** was converted into the Δ^8 isomers **9a** or **9b** by reaction with the resorcinol **1** in a manner similar to that reported for the synthesis of Δ^8-THC.[9] Acetylation to **10a** or **10b** followed by photolysis, in a manner similar to that published for the preparation of $\Delta^{9,11}$-THC,[10] gave the $\Delta^{9,11}$ isomers **11a** or **11b**. During the photolysis, the 1-acetate group was removed so that it was necessary to reacetylate the $\Delta^{9,11}$ isomers to give **12a** or **12b** which were subsequently ozonized to yield the keto acetates **13a** or **13b**. Hydrolysis of the 1-acetate afforded the desired optically active ketones **6a** or **6b**. From (−)-α-pinene was obtained the 6a*R*,10a*R* isomer **6a**; from (+)-α-pinene, the 6a*S*,10a*S* isomer **6b**. The assignment of absolute stereochemistry rests upon the fact that (−)-verbenol has been converted[9] into (−)-Δ^9-THC whose absolute stereochemistry has been shown[11] to be 6a*R*,10a*R*.

Although this route from verbenol provided optically active

Scheme III[a]



[a] The a and b refer to (−) and (+) optical isomers, respectively.

materials, it suffered from the low-yielding photolysis and ozonolysis steps. Thus, in relation to the synthesis of **6**, it was, in fact, no better than the original synthesis shown in Scheme I. Clearly what was needed was a shorter, more efficient synthesis.

The experience gained from the above synthetic work led us to believe that introduction of the oxygen function earlier in the synthesis might alleviate some problems, especially those associated with the low-yielding photolysis and ozonolysis reactions needed to introduce the 9-keto group by the reactions outlined in Scheme II. Thus, we decided to start with β-pinene and introduce the oxygen function in the first step by ozonolysis. The nopinone (**14b**) obtained by this procedure was converted by bromination to **15b** and dehydrobromination into (+)-apoverbenone (**16b**). Reaction of **16b** with the resorcinol **1** gave the optically active ketone **6a** in 16% yield. Attempts to improve this yield were unsuccessful. Alternatively, nopinone (**14b**) could be converted into the enol acetate **17a** which on treatment with lead tetraacetate in refluxing benzene for 2 h gave the diacetate **20b** in 41% yield. If the reflux time was extended to 18 h, the enol acetate **18a** could be isolated in 39% yield. Either of these acetates, **18a** or **20b**, could be converted in 70% yield into the intermediate norpinanone (**19b**) by the action of *p*-toluenesulfonic acid in chloroform at room temperature.

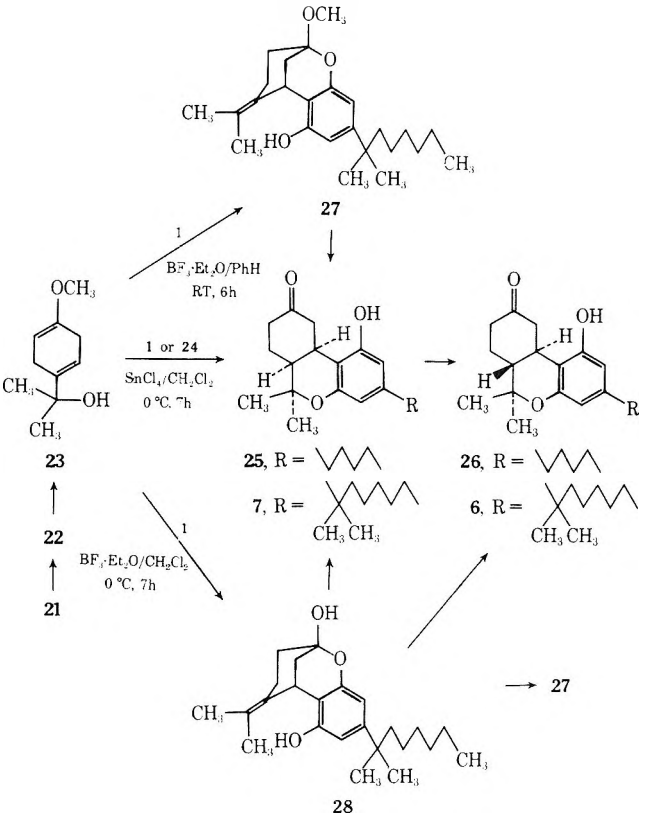
The key intermediate **19b** was then treated with *p*-toluenesulfonic acid in refluxing chloroform to give the optically active cis ketone **7a** in 61% yield. Alternatively, the optically active trans ketone **6a** could be prepared in 82% yield from the treatment of **19b** with stannic chloride in chloroform at room temperature.

Consequently, the synthesis of *cis*- and *trans*-9-ketocannabinoids could be achieved from β-pinene. The lead tetraacetate step (**17a** to **18a** or **20b**) proved to be low yielding and therefore limiting in this approach. Likewise, the direct conversion of **18a** or **20b** gave **6a** in low yield (31%) and contaminated with terpene impurities which were difficult to remove from the desired product. Nevertheless, this synthetic route via the intermediate **19b** provides optically active **6a** in the most convenient method that is presently available.

An optically active terpene (**8a** or **8b**) or terpene-derived moiety (**16b**, **18a**, or **20b**) is condensed with the resorcinol **1** in the approaches outlined in Schemes II and III. This same general conceptual approach provides the basis for most of the efficient syntheses of optically active THC's.[12] For the preparation of racemic 9-ketocannabinoids, such as **6** or **7**, the optically inactive diene **23** is a readily available starting material. It can be prepared from *p*-methoxyacetophenone (**21**) by Grignard addition to provide 2-(4-methoxyphenyl)-2-propanol (**22**), then followed by Birch reduction to the desired diene **23**. The overall yield of **23** from *p*-methoxyacetophenone is 55%.

The reaction of **23** with the resorcinol **1** was studied under a wide variety of acid catalysis conditions (see Scheme IV).

Scheme IV



The products of the reaction showed a surprising dependence on the nature of the acidic catalyst, solvent, temperature, and reaction time. As an example, the ketal **27** was isolated in 37% yield from the reaction of **1** with **23** using 1 mol of BF_3·Et_2O in benzene at room temperature. From a similar reaction using 3 mol of BF_3-Et_2O in CH_2Cl_2 at 0 °C, the hemiketal **28** was

isolated in 42% yield.[13] (Conversion of the hemiketal **28** to ketal **27** was accomplished with oxalic acid in methanol.) The cis ketone **7** was obtained in 65% yield using $SnCl_4$ in CH_2Cl_2, although **28** was observed by TLC to be initially formed and then disappear during the 7-h reaction period. If 1 mol of water was added to the $SnCl_4$ reaction, the yield of **7** dramatically improved to 89%. Conditions were not found under which the trans ketone **6** was the major product, although it was formed in 5–15% yield in the $SnCl_4$ reaction.

The appearance and then disappearance of **28** in the reaction mixture coupled with the observation that either **27** or **28** could be readily converted into **7** on treatment with $SnCl_4$ lead us to the hypothesis that **27** and **28** are intermediates in the formation of **7** from **23**. It follows that the ketal **27** is the initial product of the condensation of **23** and **1**, but is hydrolyzed, especially in the presence of an added mole of water, to the hemiketal **28** which undergoes rearrangement to **7** in the rate-determining step. This suggested mechanism would explain the observed stereoselectivity of the reaction if the ring closure occurs before the hemiketal opening to the ketone.

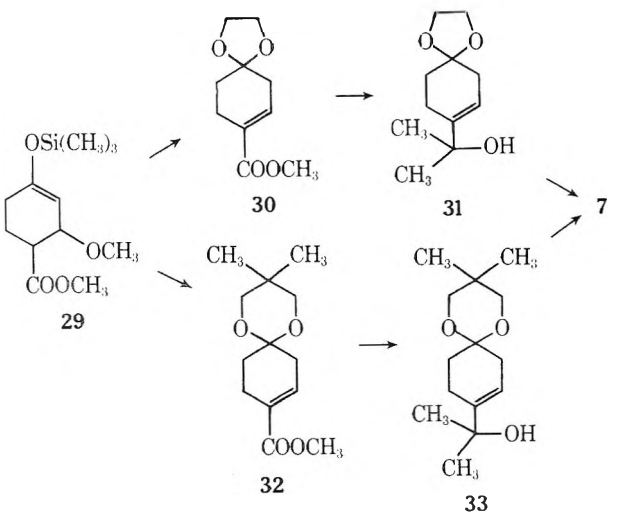
Since our synthetic objective was the trans isomer **6**, it was necessary to either modify reaction conditions to change the stereochemical course of the reaction or find some method to isomerize the 6a,10a cis ring juncture. The isomerization of *cis*-Δ^9-THC to *trans*-Δ^8-THC using BBr_3 in CH_2Cl_2 at low temperature has been reported by Razdan and Zitko.[14] Similar treatment of the cis ketone **7** gave the hemiketal **28** instead of the anticipated trans ketone **6**.

The elusive conditions for isomerization of **7** to **6** were eventually discovered to be $AlCl_3$ in CH_2Cl_2 at 0 °C. Similarly, the cyclic hemiketal **28** can also be converted into **6** using the same $AlCl_3$ isomerization procedure. An overall yield of 80% from diene **23** to trans ketone **6** has been achieved using the two-step approach outlined in Scheme IV. It is our belief that this process proceeds by way of isomerization of the 6a position rather than the 10a position. Work is presently in progress to definitely establish this point. The high yield of this approach (Scheme IV) coupled with the ready availability of **23** from *p*-methoxyacetophenone makes this the most convenient synthesis of **6** that we have discovered.

The generality of this approach to other 3-alkyl-9-keto compounds was demonstrated in the preparation of the 3-*n*-pentyl compounds **25** and **26** by the same procedure using olivetol (**24**). The overall yield of **26** from olivetol was 25%. Since **26** has been previously converted[6] into (±)-Δ^9-THC, this approach (Scheme IV) represents a new synthesis of the optically *inactive* natural products.

Other 'masked ketones" can be used in place of the diene **23**. As examples, the ketals **31** and **33** (Scheme V) are converted by the $SnCl_4$ procedure into **7** in 80% yield. Either of these ketals can be prepared from the ester **29** by way of the intermediate ketal esters **30** and **32**. The ester **29** is available from a Diels–Alder reaction described by Danishefsky and Kitahara.[15]

Scheme V



Experimental Section

Instrumentation. Infrared spectra were obtained using a Perkin-Elmer Model 457 diffraction grating spectrophotometer. A Cary 15 spectrophotometer was used to obtain ultraviolet spectra. Proton magnetic resonance spectra were measured with Varian Associates T-60 and HA-100 spectrometers; chemical shifts are expressed in parts per million (δ) downfield from internal tetramethylsilane. Low-resolution mass spectra were determined on a CEC 21-110 spectrometer at an ionizing voltage of 70 eV. For exact mass determinations a Varian MAT 731 mass spectrometer was used. Optical rotations were determined with a Perkin-Elmer 241 polarimeter. Melting points and boiling points are uncorrected.

7-(1,1-Dimethylheptyl)-5-hydroxy-4-methyl-2-oxo-2*H*-1-benzopyran-3-propionic Acid Ethyl Ester (2). A mixture of 331 g (1.4 mol) of 5-(1,1-dimethylheptylresorcinol (**1**),[1] 322 g (1.4 mol) of diethyl 2-acetylglutarate (Aldrich Chemical Co.), and 214 g (1.4 mol) of $POCl_3$ was stirred at room temperature for 11 days. Ethyl acetate was added, and the solution was washed with 5% $NaHCO_3$ solution and water, dried over Na_2SO_4, filtered, and concentrated to afford 548 g (97% yield) of crude **2** suitable for use in the following reaction. A small sample, purified by column chromatography on Woelm neutral alumina (activity II) using $CHCl_3$ as the eluent, had the following physical and chemical characteristics: mp 78–85 °C; UV (EtOH) λ_{max} 208, 257, and 308 nm (ϵ 16 200, 3900, and 5600); ^{1}H NMR ($CDCl_3$) δ 7.2 (broad s, 1 H, exchanges with D_2O), 6.70, 6.80 (2 d, 2 H, J = 2 Hz, H_6 and H_8), 4.15 (q, 2 H, J = 7 Hz, $-COOCH_2-$), 2.68 (s, 3 H, C-4 CH_3), 1.25 (t, 3 H, J = 7 Hz, $-COOCH_2CH_3$), 1.25 (s, 6 H, *gem*-di-CH_3's), and 0.82 (t, 3 H, ω-CH_3).

Acidification of the $NaHCO_3$ extract gave (5–37% yield) the corresponding carboxylic acid: mp 164–167 °C; ^{1}H NMR ($CDCl_3$–Me_2SO-d_6) δ 10.1 (broad s, 2 H, exchanges with D_2O), 6.75 (m, 2 H), and 2.60 (m, 9 H).

Anal. Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.35; H, 7.80.

3-(1,1-Dimethylheptyl)-7,8,10-dihydro-1-hydroxy-9*H*-dibenzo[*b,d*]pyran-6,9(10*H*)-dione (3). To a suspension of NaH (136 g, 5.66 mol, 272 g of a 50% NaH dispersion in mineral oil, washed several times with *n*-hexane) in 1500 mL of Me_2SO,[11] a solution of 548 g (1.35 mol) of **2** in 1 L of Me_2SO was added dropwise, while maintaining the temperature at 18–20 °C. After standing overnight, the excess NaH was decomposed by dropwise addition of EtOH. The mixture then was poured carefully onto ice and concentrated HCl. The solid that formed was collected and washed with water. The wet filter cake was dissolved in hot methyl ethyl ketone and washed with 5% $NaHCO_3$, saturated NaCl solution, and water. Drying over Na_2SO_4 and evaporating under reduced pressure afforded a light yellow foam. This crude product was triturated with Et_2O, collected, and dried to give 273 g (57% yield) of **3** and a light yellow solid: mp 173–175 °C; UV (EtOH) λ_{max} 204, 258, and 307 nm (ϵ 12 200, 2600, and 3700); ^{1}H NMR ($CDCl_3$–Me_2SO-d_6) δ 6.9 (broad s, 1 H, exchanges with D_2O), 6.70, 6.80 (2 d, 2 H, J = 2 Hz, H_2 and H_4), 1.2 (s, 6 H, *gem*-di-CH_3's), and 0.82 (t, 3 H, ω-CH_3).

Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92; O, 17.95. Found: C, 74.34; H, 7.97; O, 17.95.

3-(1,1-Dimethylheptyl)-7,8-dihydro-1-hydroxyspiro[9*H*-dibenzo[*b,d*]pyran-9-2′-[1,3]dioxalan]-6(10*H*)-one (4). A solution of 310 g (0.87 mol) of **3**, in 1500 mL of benzene[16] containing 53 mL of ethylene glycol and 200 mg of *p*-toluenesulfonic acid, was heated overnight under reflux using a Dean-Stark water separator. After cooling to room temperature, the mixture was poured into 5% $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic extracts were washed with water, dried over Na_2SO_4, and concentrated to give 329 g (95% yield) of **4** as a light yellow solid: mp 55–58 °C; UV (EtOH) λ_{max} 205, 257, and 304 nm (ϵ 11 500, 2700, and 3400); IR ($CHCl_3$) no absorption at 5.75 μ; ^{1}H NMR ($CDCl_3$–Me_2SO-d_6) δ 6.70, 6.80 (2 d, 2 H, J = 2 Hz, H_2 and H_4), 4.05 (s, 4 H, ketal CH_2's), 1.25 (s, 6 H, *gem*-di-CH_3's), and 0.82 (t, 3 H, ω-CH_3).

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05; O, 19.97. Found: C, 71.68; H, 8.08; O, 19.77.

(±)-3-(1,1-Dimethylheptyl)-6,6a,7,8-tetrahydro-1-hydroxy-6,6-dimethyl-9*H*-dibenzo[*b,d*]pyran-9-one (5). A solution of 329 g (0.825 mol) of **4** in 1500 mL of anhydrous Et_2O was added

dropwise to 1780 mL of a 2.8 M CH_3MgBr solution in Et_2O. After overnight reflux the mixture was cooled and poured slowly onto an ice–HCl mixture, the resulting HCl concentration being 6 N. The mixture was then heated on a steam bath, whereupon the Et_2O evaporated and a light yellow precipitate formed. Recrystallization from ethyl acetate gave 195 g (64% yield) of **5** as a yellow solid: mp 194–196 °C; IR (Nujol mull) 6.1 μ (α,β-unsaturated C=O); UV (EtOH) λ_{max} 206, 230, and 323 nm (ϵ 25 600, 13 200, and 23 200); ^1H NMR ($CDCl_3$) δ 10.5 (s, 1 H, exchanges with D_2O), 8.05 (d, 1 H, J = 2 Hz, H_{10}), 6.36, 6.66 (2 d, 2 H, J = 2 Hz, H_2 and H_4), 1.50, 1.17 (2 s, each 3 H, CH_3's at C-6), 1.25 (s, 6 H, *gem*-di-CH_3's), and 0.83 (t, 3 H, ω-CH_3).

Anal. Calcd for $C_{24}H_{34}O_3$: C, 77.80; H, 9.25. Found: C, 77.98; H, 9.00.

(±)-*trans*-(1,1-Dimethylheptyl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9*H*-dibenzo[*b,d*]pyran-9-one (6) and (±)-*cis*-3-(1,1-Dimethylheptyl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9*H*-dibenzo[*b,d*]pyran-9-one (7). A solution of 195 g (0.527 mol) of **5** in 2500 mL of anhydrous THF was added dropwise to a solution of Li metal in 10 L of liquid NH_3 at −78 °C. The reaction vessel was kept under a stream of dry nitrogen to prevent moisture from forming inside the reaction flask. More Li metal was added when the blue color of the reaction mixture dissipated. The end of the addition was determined when the blue color persisted for 10 min, after which solid NH_4Cl was added to decompose the excess Li. The mixture was permitted to warm to room temperature overnight under a N_2 atmosphere; during that time most of the excess NH_3 evaporated. The mixture was acidified with 4 N HCl and extracted with ethyl acetate. The combined organic extracts were washed with water, dried over Na_2SO_4, and concentrated to give 194 g of a yellow solid containing both **6** and **7**. Purification and separation of the isomers were achieved in the following manner: The crude product was recrystallized from EtOAc–*n*-hexane (1:1) to afford 125 g of solid which was chromatographed on 2200 g of Woelm neutral Al_2O_3 (activity II) using EtOAc–benzene (1:1) as an eluent. The combined fractions containing **6** were recrystallized to give 76 g of **6** (39% yield) as a white, crystalline solid: mp 159–160 °C; R_f 0.45 (silica gel; 20% EtOAc–benzene); UV (EtOH) λ_{max} 207, 280 nm (ϵ 47 000, 250); IR ($CHCl_3$) 5.85 μ (C=O); ^1H NMR ($CDCl_3$) δ 7.75 (s, 1 H, exchanges with D_2O), 6.34, 6.36 (2 d, 2 H, J = 2 Hz, H_2 and H_4), 4.15 (d, 1 H, J = 14.3, 3 Hz, H_{10a}), 3.08–0.70 (32 H) especially 1.47, 1.13 (2 s, 3 H each, α and β C-6 CH_3's), 1.21 (s, 6 H, *gem*-di-CH_3's), and 0.83 (t, 3 H, ω-CH_3); mass spectrum *m/e* 372 (M^+).

Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.38; H, 9.74; O, 12.88. Found: C, 77.59; H, 9.68; O, 12.99.

The combined fractions containing **7** were recrystallized to give 5 g (2.5% yield) as a white, crystalline solid: mp 163–165 °C; R_f 0.38 (silica gel; 20% EtOAc–benzene); ^1H NMR ($CDCl_3$) δ 6.98 (s, 1 H, exchanges with D_2O), 6.36 (broad s, 2 H, H_2 and H_4), 1.40, 1.35 (2 s, each 3 H, α and β C-6 CH_3's), 1.20 (s, 6 H, *gem*-di-CH_3's), and 0.83 (t, 3 H, ω-CH_3); mass spectrum *m/e* 372 (M^+).

Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.38; H, 9.74; O, 12.88. Found: C, 77.61; H, 10.00; O, 12.57.

(−)- and (+)-*trans*-Verbenol (8a and 8b). The procedure of Whitman[17] for the conversion of (+)-α-pinene to (+)-*trans*-verbenol was followed.

(−)- or (+)-α-pinene (Aldrich Chemical Co.) was redistilled before use: bp 152–155 °C; $[\alpha]^{25}_D$ −44.6° (c 1, MeOH) and +49.6° (c 0.27, MeOH); ^1H NMR ($CDCl_3$) δ 5.21 (m, 1 H), 2.4–0.80 (15 H), especially 1.67 (q, 3 H, J = 2 Hz), 1.28 (s, 3 H), and 0.83 (s, 3 H).

(−)- or (+)-*trans*-verbenyl acetate had the following physical characteristics: bp 73–75 °C (6 mm); $[\alpha]^{25}_D$ −139° (c 1, MeOH) and +132° (c 0.44, MeOH); ^1H NMR ($CDCl_3$) δ 5.4 (m, 1 H), 2.4–0.80 (17 H), especially 2.03 (s, 3 H), 1.36 (s, 3 H) and 0.93 (s, 3 H).

The optically active *trans*-verbenols, **8a** and **8b**, had the following physical and chemical characteristics: $[\alpha]^{25}_D$ −118° (c 0.96, MeOH) and +112° (c 1, MeOH); ^1H NMR ($CDCl_3$) δ 5.35 (m, 1 H), 4.28 (m, 1 H), 2.50–0.80 (14 H), especially 1.70 (m, 3 H), 1.34 (s, 3 H), and 0.87 (s, 3 H).

(−)-*trans*-3-(1,1-Dimethylheptyl)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[*b,d*]pyran-1-ol (9a). A solution of 48.6 g (0.206 mol) of **1** in 500 mL of CH_2Cl_2 was cooled to −10 °C. To this solution was added 31.3 g (0.206 mol) of **8a** followed by dropwise addition of 28.4 mL (32.7 g, 0.230 mol) of freshly distilled BF_3·Et_2O. The red mixture was stirred for 2 h at −10 °C and then poured into a 5% $NaHCO_3$ solution. The organic layer was separated and washed with water and saturated NaCl solution, dried over Na_2SO_4, and concentrated to afford 72.5 g of a dark, reddish brown gum. Chromatography on 1500 g of silica gel (40% benzene–*n*-hexane) gave a 51% yield of **9a** as a clear resin: $[\alpha]^{25}_D$ −211.8° (c 0.41, MeOH); ^1H NMR ($CDCl_3$) δ 6.21, 6.40 (2 d, 1 H each, J = 2 Hz, H_2 and H_4), 5.42 (m, 1 H, H_8), 5.26 (s, 1 H, exchanges with D_2O), 3.40–0.85 (34 H), especially 1.72 (broad s, 3 H, C-9 CH_3), 1.42 (s, 3 H, 6β-CH_3), 1.37 (s, 6 H, *gem*-di-CH_3's), 1.13 (s, 3 H, 6α-CH_3), and 0.85 (t, 3 H, ω-CH_3).

Anal. Calcd for $C_{25}H_{38}O_2$: C, 81.03; H, 10.34; O, 8.63. Found: C, 80.80; H, 10.10; O, 8.78.

Similarly prepared in 49% yield from **8b** was the (+) isomer, **9b**, which had the following physical and chemical characteristics: $[\alpha]^{25}_D$ +190.9° (c 1, MeOH); ^1H NMR identical with that of **9a**; an exact mass determination gave *m/e* 370.2868 (calcd for $C_{25}H_{38}O_2$, 370.2871).

(+)-*trans*-3-(1,1-Dimethylheptyl)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[*b,d*]pyran-1-ol Acetate (10b). A mixture of 45.6 g (0.123 mol) of **9b**, 456 mL of pyridine, and 456 mL of Ac_2O was stirred under a N_2 atmosphere for 2 h at room temperature. The mixture was then poured onto crushed ice and after warming to room temperature, extracted with Et_2O. The organic extracts were washed (five times) with 1 N HCl solution, water (five times), and saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to give 50.7 g (99% yield) of **10b** as a tan gum which solidified upon standing: $[\alpha]^{25}_D$ +193° (c 1, MeOH); ^1H NMR ($CDCl_3$) δ 6.52, 6.68 (2 d, 1 H each, J = 2 Hz, H_2 and H_4), 5.45 (m, 1 H, H_8), 2.90–0.75 (37 H), especially 2.28 (s, 3 H, acetate CH_3), 1.68 (broad s, 3 H, C-9 CH_3), 1.40 (s, 3 H, 6β-CH_3), 1.23 (s, 6 H, *gem*-di-CH_3's), 1.12 (s, 3 H, 6α-CH_3), and 0.83 (t, 3 H, ω-CH_3); mass spectrum *m/e* 412 (M^+).

Anal. Calcd for $C_{27}H_{40}O_3$: C, 78.60; H, 9.77; O, 11.63. Found: C, 78.88; H, 9.69; O, 11.84.

Similarly prepared from **9a** was the (−) isomer **10a** which had the following physical and chemical characteristics: $[\alpha]^{25}_D$ −186.8° (c 1, MeOH); ^1H NMR ($CDCl_3$) identical with the above spectrum for **10b**.

Anal. Calcd for $C_{27}H_{40}O_3$: C, 78.60; H, 9.77; O, 11.63. Found: C, 78.23; H, 9.52; O, 11.51.

(−)-*trans*-3-(1,1-Dimethylheptyl)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-6*H*-dibenzo[*b,d*]pyran-1-ol (11a). A solution of 1.0 g (2.42 mmol) of **10a** in 200 mL of 5% *p*-xylene–2-propanol was photolyzed (450-W Hanovia, Vycor) for 2.5 h under a helium atmosphere. The organic residue obtained by evaporation under reduced pressure was chromatographed on 20 g of silica gel (impregnated with 25% $AgNO_3$) using 10% EtOAc–benzene as an eluent to afford 0.3 g of **11a** (34% yield) as a yellow gum: $[\alpha]^{25}_D$ −41° (c 0.24, MeOH); ^1H NMR ($CDCl_3$) δ 6.25, 6.40 (2 d, each 1 H, J = 2 Hz, H_2 and H_4), 5.32 (broad s, 1 H, exchanges with D_2O), 4.80 (broad s, 2 H, *exo*-CH_2–), 4.0–0.75 (33 H), especially 1.40 (s, 3 H, 6β-CH_3), 1.18 (s, 6 H, *gem*-di-CH_3's), 1.07 (s, 3 H, 6α-CH_3), and 0.85 (t, 3 H, ω-CH_3); an exact mass determination gave *m/e* 370.2870 (calcd for $C_{25}H_{38}O_2$, 370.2872).

Similarly prepared from **10b** was the (+) isomer **11b** which had the following physical and chemical characteristics: $[\alpha]^{25}_D$ +33.6° (c 1, MeOH); ^1H NMR ($CDCl_3$) identical with the above spectrum for **11a**; an exact mass determination for **11b** gave *m/e* 370.2868 (calcd for $C_{25}H_{38}O_2$, 370.3872).

(−)-*trans*-3-(1,1-Dimethylheptyl)-6a,7,8,9,10,10a-hexahydro-6,6-dimethyl-9-methylene-6*H*-dibenzo[*b,d*]pyran-1-ol Acetate (12a). A mixture of 2.6 g (7.5 mmol) of **11a**, 26 mL of pyridine, and 26 mL of acetic anhydride was stirred at room temperature under N_2 overnight. The mixture was then poured onto ice and extracted with Et_2O. The organic extracts were combined, washed with 1 N HCl (3 × 100 mL) and saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to give 2.8 g (91% yield) of **12a** as a light tan resin: ^1H NMR ($CDCl_3$) δ 6.50, 6.67 (2 d, 1 H each, J = 2 Hz, H_2 and H_4), 4.72 (broad s, 2 H, *exo*-CH_2), 3.40–0.75 (36 H), especially 2.30 (s, 3 H, acetate CH_3), 1.38 (s, 3 H, 6β-CH_3), 1.20 (s, 6 H, *gem*-di-CH_3's), 1.05 (s, 3 H, 6α-CH_3), and 0.83 (t, 3 H, ω-CH_3); mass spectrum *m/e* 412 (M^+).

Anal. Calcd for $C_{27}H_{40}O_3$: C, 78.60; H, 9.77; O, 11.63. Found: C, 78.40; H, 9.81; O, 11.50.

Similarly prepared from **11b** was the (+) isomer **12b** which had the following physical and chemical characteristics: ^1H NMR ($CDCl_3$) identical with the above spectrum for **11a**.

Anal. Calcd for $C_{27}H_{40}O_3$: C, 78.60; H, 9.77; O, 11.63. Found: C, 78.38; H, 9.57; O, 11.92.

(+)-*trans*-3-(1,1-Dimethylheptyl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9*H*-dibenzo[*b,d*]pyran-9-one Acetate (13b). A solution of 1.0 g (2.43 mmol) of **12b** in 100 mL of CH_2Cl_2 was cooled to −78 °C and treated with 1.1 equiv of O_3 from a calibrated ozonizer (Matheson). One minute after the addition of the O_3, 1.7 mL of a 1.52 N solution of $(CH_3)_2S$ in CH_2Cl_2 was added and the mixture permitted to warm to 0 °C. Evaporation of the solvents under reduced pressure gave a crude product which was chro-

matographed on 20 g of silica gel eluted with benzene followed by 1% EtOAc–benzene elution. The desired product, **13b**, was obtained as a light orange resin, 402 mg (41% yield): $[\alpha]^{25}_D$ +55° (*c* 0.89, MeOH); ^{1}H NMR ($CDCl_3$) δ 6.53, 6.71 (2 d, 1 H each, *J* = 2 Hz, H_2 and H_4), 3.5–0.75 (36 H), especially 2.32 (s, 3 H, acetate CH_3), 1.48 (s, 3 H, 6β-CH_3), 1.22 (s, 6 H, *gem*-di-CH_3's), 1.12 (s, 3 H, 6α-CH_3), and 0.85 (t, 3 H, ω-CH_3); mass spectrum *m/e* 414 (M^+).

Anal. Calcd for $C_{26}H_{38}O_4$: C, 75.32; H, 9.24; O, 15.44. Found: C, 75.11; H, 8.98; O, 15.34.

Similarly prepared from **12a** was the (−) isomer **13a** which had the following physical characteristics: $[\alpha]^{25}_D$ −48° (*c* 1.7, MeOH); ^{1}H NMR ($CDCl_3$) identical with the above spectrum for **13b**; an exact mass determination for **13a** gave *m/e* 414.2771 (calcd for $C_{26}H_{38}O_4$, 414.2770).

(+)-*trans*-3-(1,1-Dimethylheptyl)-6a,7,8,9,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9*H*-dibenzo[*b,d*]pyran-9-one (6b). To a solution of 3.56 g (8.6 mmol) of **13b** in 100 mL of MeOH was added, dropwise with stirring at room temperature, a solution of 10.0 g of K_2CO_3 in 50 mL of H_2O. After stirring for an additional 1 h, the mixture was concentrated, diluted with water, and extracted with EtOAc. The combined organic extracts were washed with 1 N HCl, water, and saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to give 3 g of a light yellow glass. Chromatography on 100 g of Woelm neutral alumina (activity II) with Et_2O as the eluent gave 2.65 g (83% yield) of **6b** as a clear glass: $[\alpha]^{25}_D$ +54.9° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) identical with that of the (±) racemate **6**; an exact mass determination gave *m/e* 372.2663 (calcd for $C_{24}H_{36}O_3$, 372.2664).

Similarly prepared from **13a** was the (−) isomer **6a** which had the following physical characteristics: $[\alpha]^{25}_D$ −55.7° (c 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) identical with that of the (±) racemate **6**; mass spectrum *m/e* 372 (M^+).

Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.38; H, 9.74; O, 12.88. Found: C, 77.60; H, 9.50; O, 13.24.

(+)-Apoverbenone (16b) was prepared according to the literature[18] procedure from (−)-β-pinene (Aldrich Chemical Co.) which was converted into nopinone **14b** followed by bromination to **15b** and dehydrobromination to **16b**: bp 52–55 °C (4 mm); ^{1}H NMR ($CDCl_3$) δ 7.55 (q, 1 H, *J* = 9 Hz), 5.95 (d, 1 H, *J* = 9 Hz), 3.35–2.35 (m, 3 H), 2.15 (d, 1 H, *J* = 9 Hz), 1.55 (s, 3 H), and 1.10 (s, 3 H).

Preparation of 6a from 16b. To a solution of **16b** (1.6 g, 12 mmol) and **1** (2.8 g, 12 mmol) in 50 mL of CH_2Cl_2 at 0 °C was added 1.6 g (12 mmol) of anhydrous $AlCl_3$. After stirring for 3 days at room temperature, the reaction mixture was poured onto ice and extracted with Et_2O. The organic extracts were combined and washed with 2 N HCl, water, and 5% $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated to afford 4.5 g of crude product. Chromatography on Woelm silica gel (activity II) with benzene as the eluent gave 720 mg (16% yield) of **6a**: $[\alpha]^{20}_D$ −40.2° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) identical with that of **6**; mass spectrum *m/e* 372 (M^+).

(−)-Nopinone enol acetate (17a) was prepared according to the literature[19] procedure: $[\alpha]^{20}_D$ −37.3° (*c* 1, $CHCl_3$) [lit. $[\alpha]^{20}_D$ −18.6° ($CHCl_3$)]. We believe that the literature rotation value is in error by a factor of 2.

(−)-6,6-Dimethyl-2,4-diacetoxy-2-norpinene (18a). To a solution of 18.0 g (0.1 mol) of **17a** in 250 mL of dry benzene under a N_2 atmosphere was added 48.8 g (0.11 mol) of $Pb(OAc)_4$ (previously dried in vacuo over P_2O_5/KOH). The mixture was refluxed for 18 h, then cooled and filtered. The filtrate was washed with 10% $NaHCO_3$ and water, dried over Na_2SO_4, filtered, and concentrated to afford 23.5 g of a clear liquid. Distillation gave 9.3 g (39% yield) of **18a**: bp 115–118 °C (5 mm); $[\alpha]^{20}_D$ −89.7° (c 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.25 (m, 2 H), 2.4 (m, 4 H), 2.1 (s, 3 H), 2.0 (s, 3 H), 1.35 (s, 3 H), and 1.0 (s, 3 H); IR ($CHCl_3$) 1730 and 1763 cm^{-1} (C=O); mass spectrum *m/e* 196 ($M^+ - CH_2$=C=O).

Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.72; H, 7.43.

Using the above procedure with a reflux time of 2 h gave 9.8 g (41% yield) of (+)-6,6-dimethyl-2,2-diacetoxy-3-norpinene (**20b**): bp 102–103 °C (5 mm); $[\alpha]^{20}_D$ + 33.2° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.4 (m, 2 H), 3.15 (m, 1 H), 2.3 (m, 3 H), 2.1 (s, 6 H), 1.4 (s, 3 H), and 1.1 (s, 3 H); mass spectrum *m/e* 196 (M^+ − 42); IR ($CHCl_3$) 1750 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61; $COCH_3$, 36.12. Found: C, 65.77; H, 7.32; $COCH_3$, 36.56.

(+)-4-[4-(1,1-Dimethylheptyl)-2,6-dihydroxyphenyl]-6,6-dimethyl-2-norpinanone (19b). A mixture of 1.19 g (5 mmol) of either **18a** or **20b**, 1.18 g (5 mmol) of **1**, and 0.95 g (5 mmol) of *p*-TSA–H_2O in 50 mL of $CHCl_3$ was permitted to stand at room temperature for 4 h. Ether was added and the organic extracts were washed with 10% $NaHCO_3$ and water, dried over Na_2SO_4, and concentrated to give a semicrystalline residue. The residue was triturated with 25 mL of *n*-hexane and filtered to provide 1.30 g (70% yield) of **19b** as a white, crystalline solid: mp 171–174 °C; $[\alpha]^{20}_D$ +55.8° (c 1, $CHCl_3$); IR (KBr) 1668 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$–Me_2SO-d_6) δ 8.05 (s, 2 H, exchanges with D_2O), 6.35 (s. 2 H), 4.05 (t, 1 H), 3.65 (m, 1 H), 2.45 (m, 5 H), 1.35 (s, 3 H), 1.15 (m, 19 H), and 0.95 (s, 3 H); mass spectrum *m/e* 372 (M^+).

Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.38; H, 9.74. Found: C, 77.59; H, 9.83.

(−)-*cis*-3-(1,1-Dimethylheptyl-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9*H*-dibenzo[*b,d*]pyran-9-one (7a). A solution of 372 mg (1 mmol) of **19b** and 190 mg (1 mmol) of *p*-TSA–H_2O in 25 mL of $CHCl_3$ was refluxed for 24 h. After cooling to room temperature the mixture was extracted with Et_2O. The organic extracts were washed with 10% $NaHCO_3$ solution and water, dried over Na_2SO_4, and concentrated to give 380 mg of a white foam. Purification by chromatography (Woelm activity II silica gel; 5% Et_2O–benzene) afforded 228 mg (61% yield) of **7a** as a white, crystalline solid: mp 139.5–141 °C; $[\alpha]^{20}_D$ −50.0° (c 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) identical with the spectrum obtained from the (±) racemate **7**; an exact mass determination gave *m/e* 372.2665 (calcd for $C_{24}H_{36}O_3$, 372.2664).

Also obtained from the above reaction mixture after chromatography was 114 mg (31% yield) of **6a**.

Conversion of 19b into 6a. To a solution of 372 mg (1 mmol) of **19b** in 25 mL of $CHCl_3$ was added 1.0 mL of $SnCl_4$. The resulting mixture was stirred at room temperature for 16 h and then poured onto ice and extracted with Et_2O. The organic extracts were combined, washed with 2 N HCl solution, water, and 5% $NaHCO_3$ solution, dried over Na_2SO_4, filtered, and concentrated to afford 378 mg of a foam. Chromatography (Woelm activity II, silica gel; benzene) yielded 305 mg (82% yield) of **6a**, $[\alpha]^{20}_D$ −52.3° (*c* 1, $CHCl_3$), and 55 mg (14% yield) of **7a**, $[\alpha]^{20}_D$ −50° (c 1, $CHCl_3$). ^{1}H NMR and other spectral data were identical with those obtained for the racemates **6** or **7**, respectively; an exact mass determination for **6a** gave *m/e* 372.2667 (calcd for $C_{24}H_{36}O_3$, 372.2664).

Conversion of 7a into 6a. A mixture of 77 mg (0.2 mmol) of **7a**, 5 mL of CH_2Cl_2, and 77 mg of $AlCl_3$ was stirred at room temperature for 4 h. The mixture was poured onto ice and extracted with Et_2O. The organic extracts were washed with 2 N HCl solution, water, and 10% $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated to yield 75 mg of an oil.

Purification by preparative TLC (silica gel; 80% benzene–20% ethyl acetate) gave 54 mg (70% yield) of **6a** as an oil, $[\alpha]^{20}_D$ −53.8° (*c* 1, $CHCl_3$).

Conversion of 18a or 20b into 6a. To a solution of 2.38 g (10 mmol) of either **18a** or **20b** and 2.76 g (10 mmol) of **1** in 50 mL of CH_2Cl_2 at 0 °C was added 10.2 g (12 mL, 0.1 mol) of BF_3-Et_2O. After stirring for 1 h at 0 °C, the mixture was allowed to warm to room temperature overnight, poured onto ice, and extracted with Et_2O. The organic extracts were washed with 10% $NaHCO_3$ solution, dried over Na_2SO_4, filtered, and concentrated to give 4.1 g of a brown oil. Column chromatography (Woelm activity II silica gel; benzene) afforded 1.06 g (31% yield) of **6a** as a colorless oil, $[\alpha]^{20}_D$ −47.5° (*c* 1, $CHCl_3$) (90% optical purity).

2-(4-Methoxyphenyl)-2-propanol (22). A solution of 128 g (0.85 mol) of 4-methoxyacetophenone (**21**) (Aldrich Chemical Co.) in 200 mL of dry Et_2O was added dropwise to a solution of 1 mol of CH_3MgBr in Et_2O. The reaction mixture was heated under reflux for 3 h and cooled to 0–5 °C, and then 85 mL of H_2O was added carefully dropwise. The organic layer was decanted from the solid phase, washed with water and saturated NaCl solution, dried over K_2CO_3, and concentrated to give 132 g (94% yield) of **22**[20] which was sufficiently pure for use in the next reaction: ^{1}H NMR ($CDCl_3$) δ 7.09 (q, 4 H, aromatics), 3.77 (s, 3 H, OCH_3), 1.99 (s, 1 H, exchanges with D_2O), and 1.53 (s, 6 H).

2-(4-Methoxy-1,4-cyclohexadienyl)-2-propanol (23). The procedure of Birch[21] was modified as follows. A solution of 130 g (0.78 mol) of **22** in 260 mL of anhydrous EtOH was added carefully to 1300 mL of liquid NH_3. Lithium metal (26 g, 3.9 g-atoms) was added in small pieces until the blue color persisted in the reaction mixture. Then, 200 g (3.8 mol) of NH_4Cl and 500 mL of toluene were added. After the NH_3 had evaporated, 600 mL of H_2O was added. The organic layer was separated, washed with H_2O and saturated NaCl solution, dried over K_2CO_3, and concentrated to give an oil. Crystallization from 125 mL of *n*-hexane at 0 °C gave 76.5 g (59% yield) of **23**[21,22] as a white, crystalline solid: mp 33–35 °C; ^{1}H NMR ($CDCl_3$) δ 5.70, 4.67 (2 broad s, 1 H each, H_2 and H_5), 3.52 (s, 3 H, OCH_3), 2.84 (broad s, 4 H, $-CH_2$'s at C-3 and C-6), 1.78 (s, 1 H, exchanges with D_2O), and 1.33 (s, 6 H, *gem*-di-CH_3's).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59; O, 19.02. Found: C, 71.31; H, 9.65; O, 18.72.

Preparation of 7 from 23. A solution of 11.8 g (50 mmol) of 1 and 10.0 g (60 mmol) of **23** in 200 mL of CH_2Cl_2 was cooled to −10 °C. To this solution was added, in one portion, 0.9 mL (50 mmol) of H_2O and then 13 mL (111 mmol) of $SnCl_4$ was added dropwise over a 30-min period. After stirring for 7 h at 0 °C H_2O was added and the organic layer was separated and washed with 1 N NaOH (twice) and water, dried over $MgSO_4$, and concentrated to give a white solid. Recrystallization from *n*-hexane gave 16.6 g (89% yield) of **7** which was shown by GC analysis to contain 12% of **6**: spectral data were identical with those obtained from **7** prepared from **5**; mp 163–165 °C.

Isomerization of 7 to 6. To a solution of 30 g (0.081 mol) of **7** in 300 mL of CH_2Cl_2 at 0 °C was added 37.5 g (0.28 mol) of $AlCl_3$. The mixture was stirred at 0 °C for 4 h and then poured into ice water. The organic layer was separated, washed two times with water, dried over $MgSO_4$, filtered, and concentrated to give a solid residue. Recrystallization from methylcyclopentane (225 mL) gave 27.7 g (92% yield) of 6.

(±)-*cis*-3-*n*-Pentyl-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9*H*-dibenzo[*b,d*]pyran-9-one (25). A. From Olivetol (24) and 23. The same procedure was used as for the preparation of **7** from **23**. From 1.8 g (10 mmol) of **24** there was obtained 0.38 g (12% yield) of **25** which was shown by TLC to contain some of the trans isomer, **26**: mp 148–152 °C (lit.[6] 149.5–150.5 °C); ^1H NMR ($CDCl_3$) δ 7.28 (s, 1 H, exchanges with D_2O), 6.20 (s, 2 H, H_2 and H_4), 3.7–0.7 (25 H), especially 1.40, 1.33 (2 s, 3 H each, $C_{6\beta}CH_3$ and $C_{6\alpha}CH_3$), 0.87 (t, 3 H, ω-CH_3).

B. From 24 and 31. The same procedure was used as for the preparation of **7** from **31**. From 1.8 g (10 mmol) of **24** there was obtained 0.5 g (16% yield) of **25** which was shown by TLC to contain only a trace of the trans isomer **26**, mp 152–154 °C.

(±)-*trans*-3-*n*-Pentyl-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9*H*-dibenzo[*b,d*]pyran-9-one (26). To a solution of 400 mg (1.27 mmol) of **25** in 20 mL of CH_2Cl_2 was added 0.6 g of $AlCl_3$. The mixture was stirred for 3 h and then poured into water. The organic layer was separated, washed with water, dried over $MgSO_4$, filtered, and concentrated to give a solid residue. This solid was triturated with hot *n*-hexane and collected by filtration to afford 220 mg (55% yield) of **26**: mp 146–150 °C (lit.[6] mp 148–150 °C for the lower melting polymorph); ^1H NMR ($CDCl_3$) δ 7.74 (broad s, 1 H, exchanges with D_2O), 6.26 (s, 2 H, H_2 and H_4), 4.13 (d, 1 H, $H_{10\alpha}$), 3.3–0.7 (24 H), especially 1.45, 1.10 (2 s, 3 H each, $C_{6\beta}$ and $C_{6\alpha}CH_3$'s), and 0.87 (t, 3 H, ω-CH_3).

(±)-9-(1,1-Dimethylheptyl)-3,4,5,6-tetrahydro-5-isopropylidene-2-methoxy-2,6-methano-2*H*-1-benzoxocin-7-ol (27). To a solution of 4.72 g (20 mmol) of 1 and 4.0 g (24 mmol) of **23** in 100 mL of benzene was added 2 mL of $BF_3{\cdot}Et_2O$. After stirring for 6 h, water was added, and the organic layer was separated, washed with 1 N NaOH and water, dried over $MgSO_4$, and concentrated to give an off-white solid. Recrystallization from *n*-hexane gave 2.8 g (37% yield) of **27** as a white, crystalline solid: mp 131–133 °C; R_f 0.85 (silica gel; 20% EtOAc–benzene); ^1H NMR ($CDCl_3$) δ 6.30, 6.51 (2 d, 1 H each, J = 2 Hz, H_8 and H_{10}), 4.58 (s, 1 H, exchanges with D_2O), 4.33 (broad s, 1 H, H_6), 3.45 (s, 3 H, $-OCH_3$), 2.80–0.70 (31 H) especially 1.96, 1.70 (2 s, 3 H each, isopropylidene CH_3's), 1.20 (s, 6 H, *gem*-di-CH_3's), and 0.83 (t, 3 H, ω-CH_3); mass spectrum m/e 386 (M^+).

Anal. Calcd for $C_{25}H_{38}O_3$: C, 77.68; H, 9.91. Found: C, 77.49; H, 9.71.

(±)-9-(1,1-Dimethylheptyl)-3,4,5,6-tetrahydro-5-isopropylidene-2,6-methano-2*H*-1-benzoxocine-2,7-diol (28). To a solution of 4.72 g (20 mmol) of 1 and 4.0 g (24 mmol) of **23** in 150 mL of CH_2Cl_2 at −5 °C was added 6.0 mL (72 mmol) of $BF_3{\cdot}Et_2O$. After stirring for 7 h at 0 °C, water was added. The organic layer was separated and washed with H_2O and 1 N NaOH, dried over $MgSO_4$, and concentrated to give an off-white solid. Crystallization from 25 mL of *n*-hexane gave 3.1 g (42% yield) of **28** as a white, crystalline solid: mp 155–156 °C; R_f 0.65 (silica gel; 20% EtOAc–benzene); ^1H NMR ($CDCl_3$) δ 6.23, 6.42 (2 d, 1 H each, J = 2 Hz, H_8 and H_{10}), 4.58, 2.87 (2 s, 1 H each, exchange with D_2O), 4.28 (broad s, 1 H, H_6), 2.80–0.70 (31 H), especially 1.93, 1.67 (2 s, 3 H each, isopropylidene CH_3's), 1.18 (s, 6 H, *gem*-di-CH_3), and 0.83 (t, 3 H, ω-CH_3); mass spectrum m/e 372 (M^+).

Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.38; H, 9.74. Found: C, 77.33; H, 9.55.

Conversion of 28 to 27. A solution of 1 g (2.7 mmol) of **28** and 0.1 g of oxalic acid in 50 mL of CH_3OH was heated under reflux for 5 h. After evaporation of the MeOH, the organic residue was dissolved in CH_2Cl_2, washed with water, dried over $MgSO_4$, filtered, and concentrated to give a solid residue. The residue was triturated with *n*-hexane and collected to give 0.85 g (82% yield) of **27**, identical with that obtained from **23**.

Preparation of 7 from 27. To a solution of 1 g (2.6 mmol) of **27** and 0.05 mL of H_2O[23] was added 0.6 mL of $SnCl_4$. After 2 h the reaction mixture was poured into H_2O. The organic layer was separated, washed with 1 N HCl solution and water, dried over $MgSO_4$, filtered, and concentrated to give 0.90 g (93% yield) of **7**, identical with that obtained from **5**.

Preparation of 7 from 28. To a solution of 1 g (2.7 mmol) of **28** in 20 mL of CH_2Cl_2 was added 1.5 mL of $SnCl_4$. The resulting mixture was stirred at 0–5 °C for 4 h and then poured onto ice. The organic layer was separated, washed with 1 N HCl, NaOH solution, and water, dried over $MgSO_4$, filtered, and concentrated to give a solid residue. The residue was triturated with *n*-hexane and filtered to give 0.78 g (78% yield) of **7** identical with that obtained from **5**.

Preparation of 6 from 28. A mixture of 1 g (2.7 mmol) of **28**, 20 mL of CH_2Cl_2, and 1 g (7.5 mmol) of $AlCl_3$ was stirred at 0 °C for 2 h. The mixture was then poured onto ice and the organic layer was separated, washed with water, dried over $MgSO_4$, filtered, and concentrated to give a solid residue. The residue was triturated with *n*-hexane and filtered to afford 0.82 g (82% yield) of **6** identical with that prepared from 5.

1,4-Dioxaspiro[4.5]dec-7-ene-8-carboxylic acid methyl ester (30) was prepared according to the procedure of Danishefsky and Kitahara:[15] mp 41–42 °C (lit.[15] mp 40–41 °C); ^1H NMR ($CDCl_3$) δ 6.9 (m, 1 H, CH=C), 3.9 (s, 4 H, OCH_2CH_2O), 3.7 (s, 3 H, $COOCH_3$). 2.4 (m, 4 H), and 1.8 (m, 2 H).

α,α-Dimethyl-1,4-dioxaspiro[4.5]dec-7-ene-8-methanol (31). A solution of 11 g (55 mmol) of **30** in 100 mL of toluene was added dropwise to a solution of CH_3MgBr (110 mmol) in Et_2O at 15 °C. After stirring for 2 h, the reaction mixture was cooled to 5 °C and then added to 100 mL of an ice-cold 1.3 M NH_4Cl solution. The organic phase was separated, washed with water, dried over $MgSO_4$, filtered, and concentrated to give 6.6 g (60% yield) of **31** as an oil: ^1H NMR ($CDCl_3$) δ 5.6 (m, 1 H, CH=C), 3.9 (s, 4 H, OCH_2CH_2O, 2.6 (s, 1 H, exchanges with D_2O), 2.3 (m, 4 H), 1.8 (m, 2 H), and 1.3 [s, 6 H, $C(CH_3)_2$]; mass spectrum m/e 198 (M^+).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15; O, 24.21. Found: C, 66.68; H, 9.05; O, 24.30.

3,3-Dimethyl-1,5-dioxaspiro[5.5]undec-8-ene-9-carboxylic Acid Methyl Ester (32). Using the same procedure as for the preparation of **30** except to replace ethylene glycol with 2,2-dimethyl-1,3-propanediol gave **32** (10.6 g, 80% yield): mp 60 °C; ^1H NMR ($CDCl_3$) δ 6.8 (m, 1 H, CH=C), 3.7 (s, 3 H, $COOCH_3$), 3.5 (s, 4 H, OCH_2CCH_2O), 2.5 (m, 4 H), 2.1 (m, 2 H), and 1.0 [s, 6 H, $C(CH_3)_2$]; mass spectrum m/e 241 (M^+).

Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.89; H, 8.18.

α,α,3,3-Tetramethyl-1,5-dioxaspiro[5.5]undec-8-ene-9-methanol (33). Using the same Grignard procedure as for the preparation of **31** gave **33** (50% yield): mp 114 °C; ^1H NMR ($CDCl_3$) δ 5.6 (m, 1 H, CH=C), 3.5 (s, 4 H, OCH_2CCH_2O), 2.1–2.5 (m, 7 H, 1 H exchanges with D_2O), 1.3 [s, 6 H, $C(CH_3)_2OH$], 1.0 [2 s, 3 H each, C–$C(CH_3)_2$].

Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07; O, 19.97. Found: C, 70.17; H, 10.11; O, 20.07.

Preparation of 7 from 31. To a solution of 2.12 g (9 mmol) of 1 and 2.18 g (10.1 mmol) of **31** at −10 °C was added 3.6 mL (31 mmol) of $SnCl_4$ over a 5-min period. The reaction mixture was stirred for an additional 4 h at 0 °C and then poured onto ice water. The organic layer was separated, washed with water, 1 N NaOH solution, and water, dried over $MgSO_4$, and concentrated to afford a white solid. Recrystallization from 20 mL of *n*-hexane gave 2.66 g (80% yield) of **7** containing only a 1% impurity of **6** by GC.

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Registry No.—**1**, 56469-10-4; **2**, 56469-11-5; **3**, 56469-12-6; **4**, 56469-13-7; **5**, 56469-14-8; **6**, 51022-71-0; **6a**, 61617-09-2; **6b**, 61664-39-9; **7**, 56469-15-9; **7a**, 61664-40-2; **8a**, 19890-02-9; **8a** acetate, 19890-04-1; **8b**, 22339-08-8; **8b** acetate, 39863-91-7; **9a**, 61597-27-1; **9b**, 61597-28-2; **10a**, 61597-29-3; **10b**, 61597-30-6; **11a**, 61597-31-7; **11b**, 61604-70-4; **12a**, 61597-32-8; **12b**, 61597-33-9; **13a**, 61617-10-5; **13b**, 61617-11-6; **16b**, 35408-03-8; **17a**, 28239-05-6; **18a**, 61597-34-0; **19b**, 61597-35-1; **20b**, 61597-36-2; **21**, 100-06-1; **22**, 7428-99-1; **23**, 61597-37-3; **24**, 500-66-3; **25**, 16964-51-5; **26**, 16964-48-0; **27**, 61597-38-4; **28**, 61597-39-5; **30**, 54584-38-2; **31**, 61597-40-8; **32**, 61597-41-9; **33**, 61597-42-0; diethyl 2-acetylglutarate, 1501-06-0; 7-(1,1-dimethylheptyl)-5-hydroxy-4-methyl-2-oxo-2*H*-1-benzopyran-3-propionic acid, 61597-43-1; ethylene glycol, 107-21-1; (−)-α-pinene, 7785-26-4; (+)-α-pinene, 7785-70-8; Ac_2O, 108-24-7; 2,2-dimethyl-1,3-propanediol, 126-30-7.

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Studies on Vitamin D (Calciferol) and Its Analogues. 12. Structural and Synthetic Studies of 5,6-*trans*-Vitamin D_3 and the Stereoisomers of 10,19-Dihydrovitamin D_3 Including Dihydrotachysterol$_3$[1,2]

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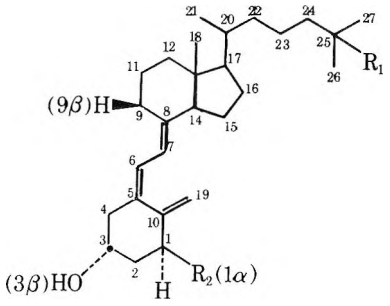
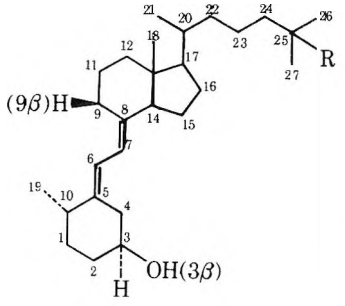
Catalytic hydrogenation of 5,6-*trans*-vitamin D_3 (**3a**, 5*E*-D_3) afforded the previously unknown C_{10} epimer of dihydrotachysterol$_3$ (**2a**, DHT_3 or 10*S*-b), 10*R*,19-dihydro-5*E*-vitamin D_3 (10*R*-b). Reaction of **3a** with 9-borabicyclo[3.3.1]nonane (9-BBN) produced the 9-BBN/**3a** adduct, which upon treatment with acetic acid produced low yields of equal amounts of **2a** and its C_{10} epimer 10*R*-b. When the 9-BBN/**3a** adduct was oxidized with basic hydrogen peroxide, good yields of the 19-hydroxy counterparts of 10*S*-b and 10*R*-b, **7a** and **7b**, respectively, were produced. The 9-BBN/**1a** adduct, produced similarly by treating vitamin D_3 (**1a**) with 9-BBN, reacted with acetic acid to afford 10*S*,19- (10*S*-a) and 10*R*,19-dihydrovitamin D_3 (10*R*-a), which differ from 10*S*-b and 10*R*-b, respectively, in their Δ^5-double bond configurations. Basic hydrogen peroxide treatment of the 9-BBN/**1a** adduct gave good yields of the 19-hydroxy derivatives of 10*S*-a and 10*R*-a, **8a** and **8b**, respectively. The stereoisomeric 10*S*-a, 10*R*-a, 10*S*-b (**2a**), and 10*R*-b vitamin D analogues are also labeled DHV_3-II, DHV_3-III, DHT_3, and DHV_3-IV, respectively, in this study. The stereochemistries and conformations of the A ring of the five analogues (5*E*-D_3, 10*S*-a, 10*R*-a, 10*S*-b, and 10*R*-b) have been studied by two ^1H NMR methods: correlation of the observed coupling constants with the limiting values for the two conformers (coupling constant method) and computer analysis of the 300-MHz tris(dipivalomethanato)europium(III) [Eu(dpm)$_3$] shifted spectra (the lanthanide induced shift or LIS method). The reduction products of vitamin D_3 (**1a**) are clearly identifiable by both methods as the 10*S*-a and 10*R*-a isomers. By contrast the LIS method only partially serves to distinguish the stereochemistries assigned to the reduction products of 5*E*-D_3 (**3a**). The LIS method distinguishes DHT_3 as the 10*S*-b isomer but its epimer is equally well assigned by this method to the 10*S*-b or 10*R*-b diastereomers. Coupling constants do not help in the latter case either. Thus NMR methods must be used with a great deal of care especially when only one epimer of a fluxional molecule is available for study. Both epimers were fortunately available in this study. The A ring of these steroids is dynamically equilibrated between two chair conformers and both methods were in good agreement as regards their A-ring chair population ratios. The 10*S*-a and 10*R*-a isomers were strongly biased in single (~95%) but opposite chair conformers with the C_{10} methyl group axial in both cases. The clinically useful analogue 10*S*-b (DHT_3) also exists principally (~90%) as only one conformer (C_{10} methyl and C_3 hydroxyl equatorial), while its epimer 10*R*-b exists as an approximately equimolar mixture of two A-ring chairlike conformers. Lastly, 5*E*-D_3 is biased (~70%) in favor of the chair possessing the equatorial hydroxyl.

In order to evaluate further the structural requirements necessary for optimal or minimal vitamin D activity and thus obtain more information concerning its mode of action, we have directed our attention toward the synthesis and biological evaluation of analogues of vitamin D_3 (**1a**) and its principal metabolites, 25-hydroxyvitamin D_3 (**1b**) and 1α,25-dihydroxyvitamin D_3 (**1c**).[4] The latter, **1c**, is considered to be the active functional form of vitamin D_3. Among the most

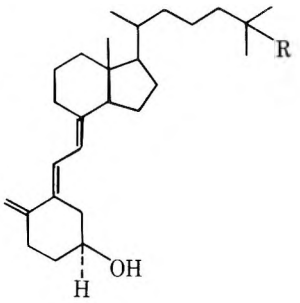


1a, $R_1 = R_2 = H$
b, $R_1 = OH$; $R_2 = H$
c, $R_1 = R_2 = OH$

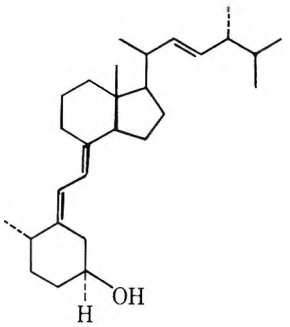
interesting vitamin D analogues are dihydrotachysterol$_3$ (**2a**, DHT_3)[5] and 5,6-*trans*-vitamin D_3 (**3a**, 5*E*-D_3).[6] Both substances are being used clinically and in fact dihydrotachysterol$_2$ (**4**, DHT_2)[7] was marketed as early as 1934 under the trade name A.T.10 by E. Merck (Darmstadt) as an antitetany agent.[8] The biological activity of DHT_3 (**2a**) and 5*E*-D_3 (**3a**)



2a, R = H
b, R = OH



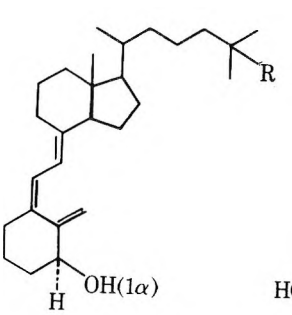
3a, R = H
b, R = OH



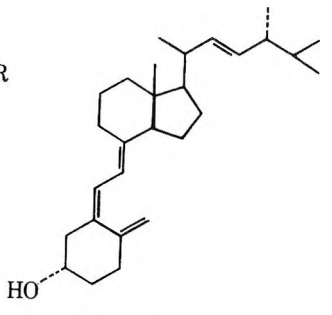
4

in anephric animals has been attributed to the presence of a pseudo-1α-OH group.[9,10] The 3β-OH of **2a** and **3a** are spatially oriented in a topology similar to the key 1α-OH group of the natural hormone **1c**. It is suggested that the 3β-OH in **2a** and **3a** can mimic the function of the 1α-OH group of **1c**. The unusual importance of the 1α-OH group to the function of vitamin D was recently emphasized by the observation of high biological potency for 3-deoxy-1α-hydroxyvitamin D_3 (**5a**),[11] which lacks both the 3β- and 25-OH groups of **1c**. It also appears that **5a** as well **2a** and **3a** are 25-hydroxylated to **5b**,[12] **2b**,[13] and **3b**,[14] respectively, prior to their elicitation of a biological response (intestinal calcium absorption). In order for analogues to retain significant biological properties, it seems evident that a hydroxyl located in a position corresponding topologically to the 3β positior of **1a** is less important and that the $C_{10(19)}$ bond can be located in an unnatural position as in **2** and **3**.

The preparation of DHT_2 (**4**)[7] appears to have been first described by von Werder as a minor component of the sodium–propanol reduction of vitamin D_2 (**6**). This reduction involves not only the saturation of the 10,19 double bond of



5a, R = H
b, R = OH



6

6 but also the *Z* to *E* isomerization of its Δ^5 double bond. The nature of this reduction is such that there remains stereochemical ambiguity in the configuration at C_{10} as well as in the Δ^5 and Δ^7 double bonds. There are thus eight diastereomeric possibilities (shown in Figure 1 for the vitamin D_3 series) for the stereochemistry of **4**. The 10,19-dihydro products resulting from the catalytic hydrogenation of **6** were labeled dihydrovitamin D_2-II (DHV_2-II, major) and dihydrovitamin D_2-IV (DHV_2-IV, minor) by Schubert.[15] The major isomer DHV_2-II appears to differ from DHT_2 only in the configuration of the Δ^5 double bond.[7c] The minor isomer DHV_2-IV is considered by von Werder to differ from DHT_2 only in the configuration at C_{10}.[16,17] However, Westerhof and Keverling-Buisman consider perhaps more logically that DHV_2-II and DHV_2-IV are merely C_{10} configurational isomers.[17,18] Additional substances, DT 66 and dihydrovitamin D_2-III,[15,18] both possessing the UV triplet centered near 250 nm characteristic of DHT_2, DHV_2-II, and DHV_2-IV, have also been described.

In the vitamin D_3 side chain series, only DHT_3 (**2a**) and DHV_3-II (the major catalytic hydrogenation product of **1a**)[5] appear to have been described. It was of some interest that DHT_3, which possesses the natural vitamin D_3 side chain, proved to be significantly more active than DHT_2.[5,19] In a recent preliminary communication, we suggested on the basis of ^{1}H NMR studies that the configuration of DHT_3 at C_{10} is *S* (the 10*S*-b isomer shown in Figure 1).[20] It became apparent that investigations of the other 10,19-dihydrovitamin D_3s (DHV_3s) would provide more rigorous evidence for the configuration assigned to DHT_3 and that these DHV_3s would also be of interest in their own right from a biological standpoint. In Figure 1, we have categorized the eight DHV_3s according to their diene geometry (a, 5*Z*,7*E*; b, 5*E*,7*E*; c, 5*Z*,7*Z*; d, 5*E*,7*Z*) and their C_{10} configuration (10*S* or 10*R*). DHT_3 and DHV_3-II are the 10*S*-b and 10*S*-a stereoisomers, respectively. In our studies, we have *labeled* DHV_3-III and DHV_3-IV as the 10*R*-a and 10*R*-b isomers, respectively.[17]

Our interest in the stereoisomeric DHV_3s (Figure 1) also stems from our recently proposed structure-function model.[10] From ^{1}H NMR studies, we determined that the A ring of **1c** is partitioned between a ~55/45 equilibrium mixture of chairlike conformers favoring the chair with the 1α-OH group equatorially oriented.[20,21] Our model elaborates on the thesis that only one of the two A-ring chair conformations of **1c** binds optimally to its receptor protein. One way to test this hypothesis is through the study of a series of 1α-hydroxylated (or pseudo-1α-hydroxylated) analogues whose A rings are biased in one conformation or the other. Such a series includes DHT_3 (**2a**), its hitherto unreported C_{10} epimer DHV_3-IV, and 5*E*-D_3 (**3a**). In this paper, we report on the detailed stereochemical and A-ring conformational analysis of these (10*S*-b, 10*R*-b, and 5*E*-D_3) and related stereoisomers (10*S*-a and 10*R*-a). Synthetic studies of these five substances and related derivatives are also described.

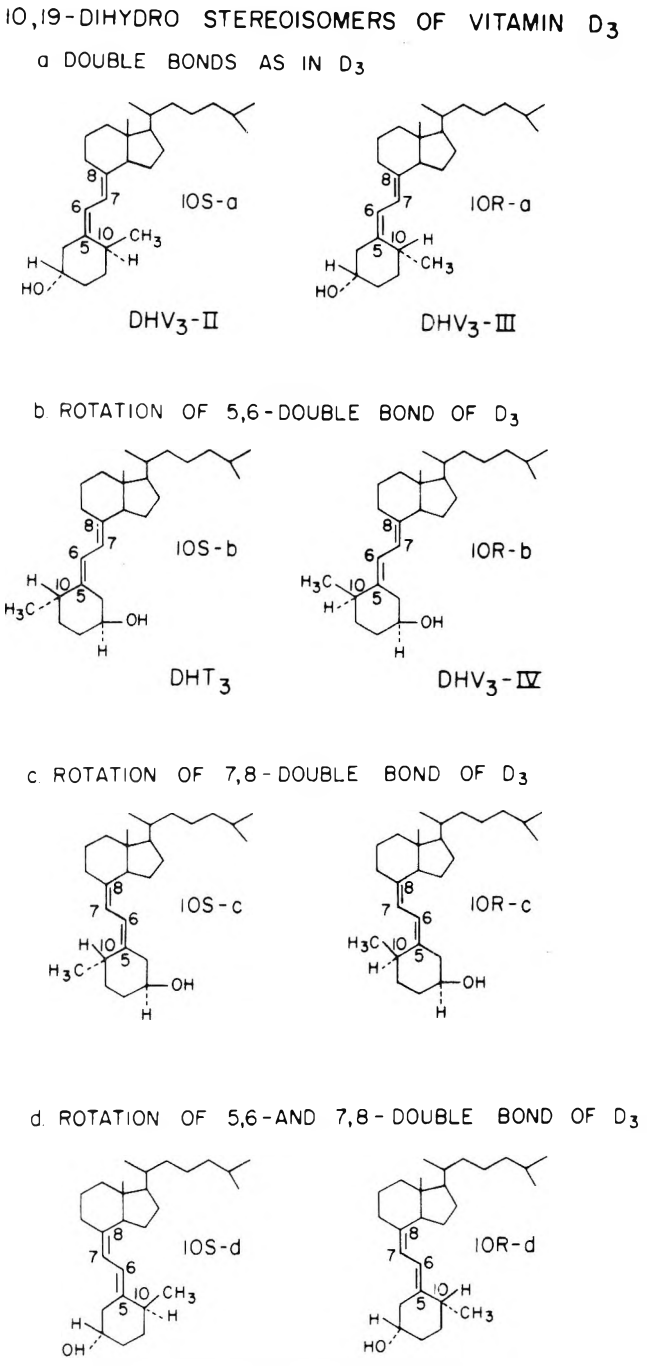
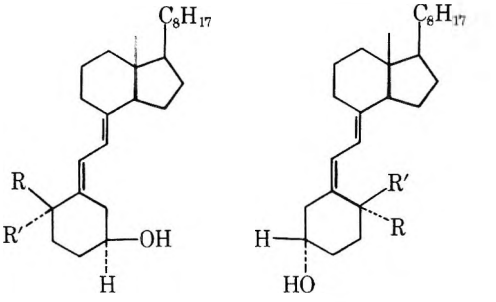


Figure 1. The eight possible stereoisomeric 10,19-dihydrovitamin D_3s (DHV_3s) categorized according to configurational permutations about C_5 (*Z* or *E*), C_7 (*Z* or *E*) and C_{10} (*R* or *S*) after reduction of the 10,19 double bond of vitamin D_3 (**1a**): a, 5*Z*,7*E*; b, 5*E*,7*E*; c, 5*Z*,7*Z*; d, 5*E*,7*Z*. See footnote 17 for an important comment corcerning the DHV_3-III and DHV_3-IV labels.

Results

Catalytic hydrogenation (ethanol, 5% rhodium on carbon) of the analogue 5*E*-D_3 (**3a**), prepared in ~60% purified yield by iodine-catalyzed isomerization of vitamin D_3 (**1a**),[6,22] afforded the 10*R*-b isomer (DHV_3-IV) in 28% yield along with trace amounts of the 10*S*-b isomer (DHT_3, **2a**).[23] The latter was characterized by TLC and UV spectroscopy, but it was not isolated in pure form. Hydroboration (9-borabicyclo[3.3.1]nonane, 9-BBN)[24] of **3a** followed by acetic acid treatment afforded a ~1:1 mixture of the 10*S*-b and 10*R*-b isomers isolated pure in ~6% yields each. The hydroboration step appears to occur in high yield as determined by UV analysis.[25] When the **3a**/9-BBN adduct was reacted with basic hydrogen peroxide, a 64% yield of a 60/40 mixture of **7a** and **7b**, the 19-OH counterpart of the 10*S*-b and 10*R*-b isomers, respectively, was obtained. When the parent vitamin D_3 (**1a**)



7a, R′ = CH_2OH; R = H **8a**, R′ = CH_2OH; R = H
b, R = CH_2OH; R′ = H **b**, R = CH_2OH; R′ = H

was subjected to 9-BBN,[24] an organoborane intermediate again appeared to be formed (by UV analysis) in high yield. Acetic acid decomposition of the **1a**/9-BBN adduct afforded a 31% yield of a mixture of the 10*S*-a (DHV_3-II) and 10*R*-a (DHV_3-III) isomers.[25] Treatment of the borane adduct with basic hydrogen peroxide afforded a 70% yield of a mixture of their 19-hydroxy counterparts, **8a** and **8b**, respectively.

In all cases, separation of stereoisomers was achieved by chromatography over silica gel and the homogeneity of each stereoisomer could be ascertained by ^1H NMR spectroscopy or better by analytical thin layer chromatography. There was no evidence to indicate that the hydroboration reactions led to isomerization of either the Δ^5 or Δ^7 double bond. Only two isomers could be isolated from each of the four hydroboration sequences (acetic acid or peroxide treatment of the 9-BBN adducts of **3a** or **1a**). All the 10,19-dihydrovitamins and their 19-hydroxy counterparts studied exhibited a characteristic ultraviolet triplet (λ_{max} 240, 250, 260 nm) as well as appropriate mass spectral and infrared data. It should be noted that the conjugated diene is nearly planar as attested to by the ultraviolet (λ_{max} 250 nm; calculated by Woodward's rules, 245 nm) and NMR ($J_{6,7} \sim 11.2$ Hz)[21] spectra. It is logical that all of the DHVs reported be assigned the 7*E* rather than the 7*Z* geometry (Figure 1). Molecular models imply that the diene component of the putative 7*Z* isomers (c and d isomers of Figure 1) should be nonplanar as a result of steric congestion between the C_6 and the C_{14} protons. In line with the conformational analysis results described below, the thin layer chromatography R_f value for the C_{10} epimeric pairs of stereoisomers was always larger for the isomers whose A ring was partitioned by a larger extent toward the chair possessing an axial 3β-hydroxyl (see below).

The conformations of the A rings of 5*E*-D_3 (**3a**) and the four 10,19-dihydrovitamin (10*S*-a, 10*R*-a, 10*S*-b, and 10*R*-b, Figure 1) isomers were studied by the two ^1H NMR methods described earlier.[21a] They include correlation of the observed averaged coupling constants with the limiting values for the two chair forms of D_3, and computer analysis of the 300-MHz tris(dipivalomethanato)europium(III) [Eu(dpm)$_3$] shifted spectra. The 300-MHz high-resolution ^1H NMR spectra are given in Figure 2 for the five analogues; a typical lanthanide induced shift (LIS) titration curve, as exemplified by that for the clinically important 10*S*-b (DHT_3, **2a**) stereoisomer, is shown in Figure 3; and finally, the NMR spectral parameters for the five substances including the observed and calculated LIS geometric shifts[26] are given in Table I. The ^1H NMR spectral parameters of the four 19-hydroxy forms (**7** and **8**) are summarized in the Experimental Section.

Discussion

The 9-BBN/HOAc reductions in each case (**1a** or **3a**) gave only two products. Therefore a complete and exhaustive

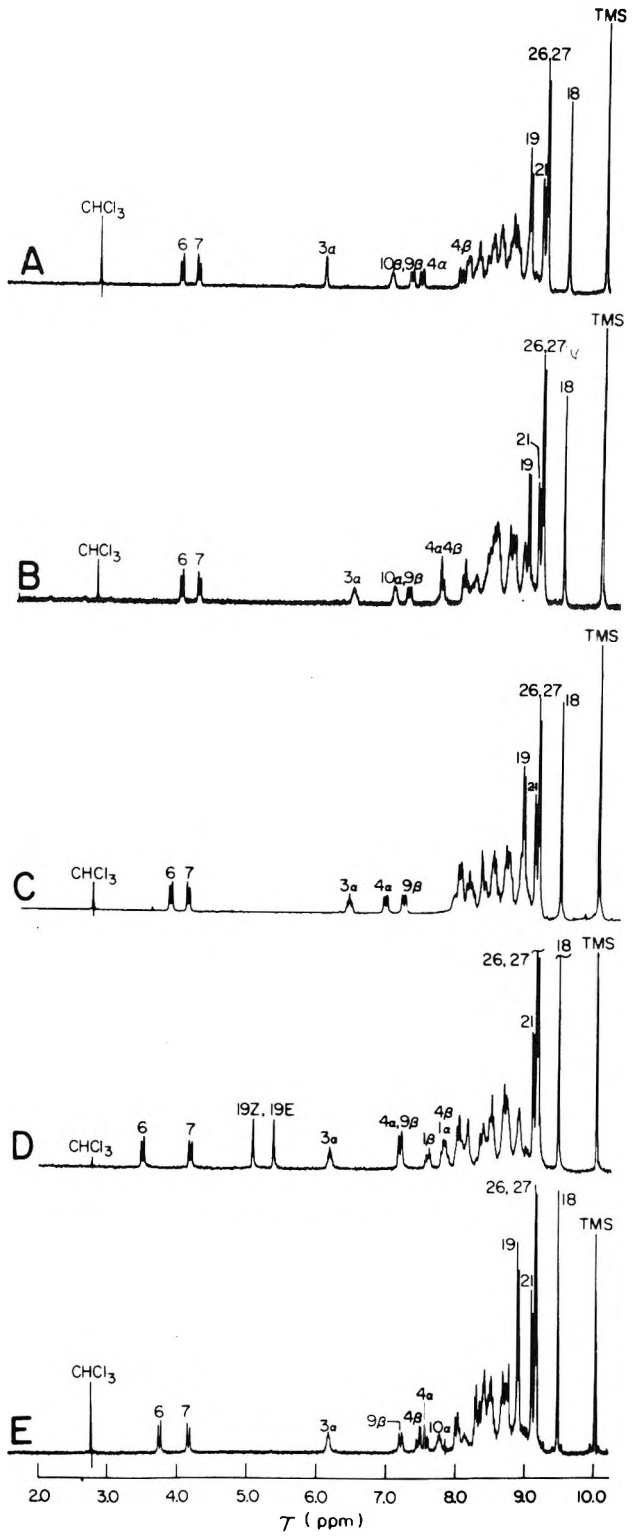


Figure 2. ^1H NMR spectra at 300 MHz of (A) 10*S*-a (DHV_3-II), (B) 10*R*-a (DHV_3-III), (C) 10*S*-b (DHT_3, **2a**), (D) 5*E*-D_3 (**3a**), and (E) 10*R*-b (DHV_3-IV) in deuteriochloroform solvent. Tetramethylsilane and chloroform ($CHCl_3$) (2180 Hz apart) appear as internal standards. See Figure 3 for the lanthanide induced shift spectra for DHT_3. The observable chemical shifts and coupling constants are given in Table I.

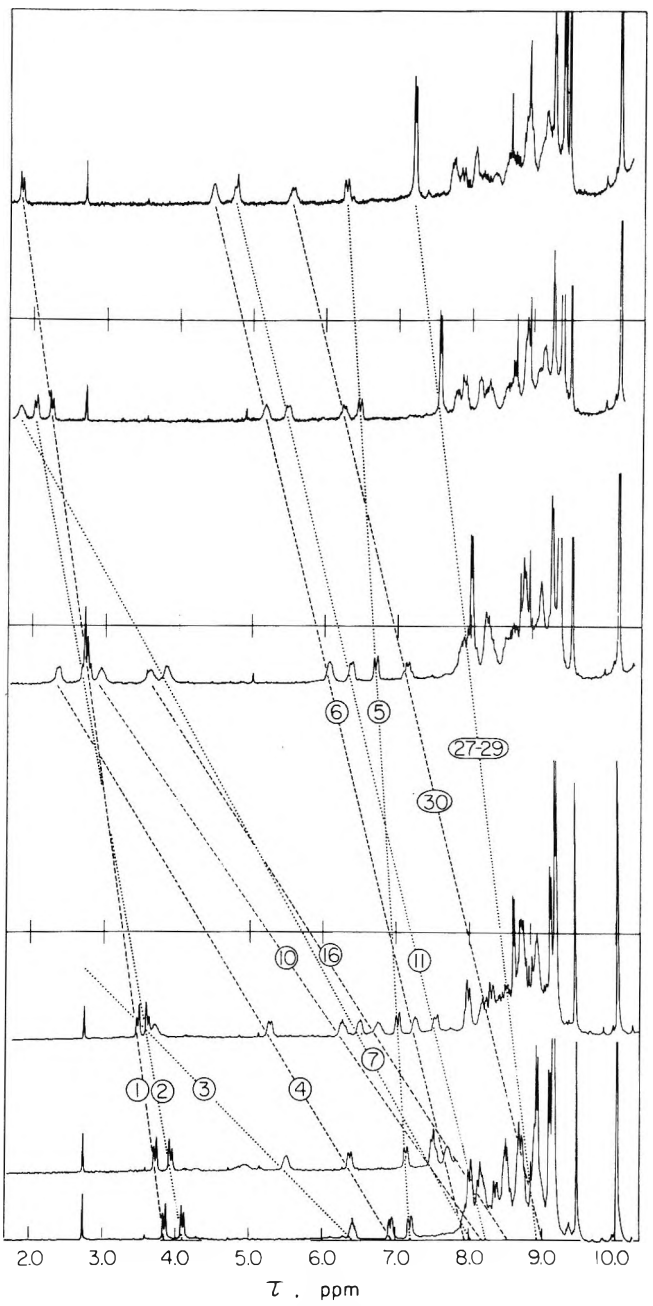


Figure 3. A titration of dihydrotachysterol$_3$ (10*S*-b, **2a**) with tris-(dipivalomethanato)europium(III) [Eu(dpm)$_3$]. The titration of DHT_3 was carried out by adding small increments of solid Eu(dpm)$_3$ to DHT_3 in deuteriochloroform until a near equimolar mixture of steroid and shift reagent was obtained. ^1H NMR spectra (300 MHz) were recorded immediately after each incremental addition of Eu(dpm)$_3$. The vertical scale represents increasing amounts of shift reagent and the dotted lines denote those shifts, which, among others, could be unambiguously followed. The numbers refer to those resonances followed listed in increasing field. The geometric shifts (observed and calculated) are tabulated in Table I. The unshifted spectrum is given in Figure 2C.

analysis of the structures requires that we test the four possible permutations of two compounds with two spectra. When this is done, the spectra can be assigned to compounds as detailed in Table II at the 99.5% confidence[26b] level for the 5*E* series and at the 99.9% confidence[26b] level for the 5*Z* series.

Reduction of **1a** gave two products having spectra A and B (Figure 2). When spectrum A is analyzed, assuming structure 10*R*-a (DHV_3-II), a 9.0% residual for fit of LIS data obtains. Conversely, a 2.75% residual results assuming the 10*S*-a (DHV_3-II) stereochemistry. Likewise when spectrum B is analyzed based on 10*S*-a vs. 10*R*-a stereochemistries residuals of 7.1 and 4.7% result. Assignment of stereochemistries to spectra can now be made using the *R*-ratio test of Hamilton.[26b] Although the above cases are clear cut, the assignment to spectra C and E present a more difficult problem. If LIS titration C is fit to the 10*R*-b configuration, a residual of 4.2% is obtained as against a residual of 2.2% for the 10*S*-b configuration. However, both configurations (10*S*-b and 10*R*-b) fit

Table I. Summary of NMR Results[a]

Line	Assignment[b]	Chemical Shift, τ	Fine Structure (Hz)	Geom. Obs.	Shift Cal.[c]
A. 10S-a					
1	H-6	3.93	d(11.2)	100	100
2	H-7	4.18	d(11.2)	57	66
3	H-3α	5.98	q(~3)[e]	397	399
4	H-10α	6.93	br m	96	106
5	H-9β	7.22	d(12.0)	22	37
6	H-4α	7.36	d(14.3)	128	127
7	H-4β	7.91	d(14.3)	243	244
8	H-2β	8.14[d]	--	227	222
9	H-2α	8.21[d]	--	135	141
10	H-1β	8.40[d]	--	230	228
11	H-1α	8.60[d]	--	101	106
12-31	others	7.9-9.2	--	--	--
32-34	CH_3-19	8.90	d(7.0)	68	64
35-37	CH_3-21	9.08	d(6.0)	--	--
38-43	$(CH_3)_2$-26,27	9.13	d(6.6)	--	--
44-46	CH_3-18	9.46	s	16	15[f]
B. 10R-a					
1	H-6	3.97	d(11)	59	59
2	H-7	4.23	d(11)	48	45
3	H-3α	6.43	m	579	579
4	H-10α	7.03	br m	86	90
5	H-9β	7.22	d(12)	5	4
6	H-4α	7.66	dd(13.0, 4.0)	320	322
7	H-4β	7.72	dd(13.0, 10.5)	387	403
8	H-2α	8.17[d]	--	346	329
9	H-1β	8.42[d]	--	115	122
10	H-1α	8.47[d]	--	144	140
11	H-2β	8.50[d]	--	386	369
12-31	others	7.9-9.2	--	--	--
32-34	CH_3-19	8.94	d(7)	102	130
35-37	CH_3-21	9.08	d(6)	--	--
38-43	$(CH_3)_2$-26,27	9.13	d(7)	--	--
44-46	CH_3-18	9.46	s	7	-8[f]
C. 10S-b					
1	H-6	3.82	d(11.2)	106	94
2	H-7	4.07	d(11.2)	124	126
3	H-3α	6.39	dddd(10.0,10.0,4.1,4.1)	665	661
4	H-4α	6.92	d(12.2)	407	397
5	H-9β	7.18	d(12.0)	44	42
6	H-10β	7.91	br d (~12)[g]	165	176
7	H-2α	8.01[d]	--	369	376
8	H-4β	8.12	dd(~10.0,~12.2)	464	464
9	H-1β	8.21[d]	m	164	167
10	H-2β	8.51[d]	--	432	435
11	H-1α	9.00[d]	br ddd(~12,~12,~12)[g]	163	154
12-31	others	7.9-9.3	--	--	--
32-34	CH_3-19	8.91	d(6.5)	82	84
35-37	CH_3-21	9.08	d(6.3)	--	--
38-43	$(CH_3)_2$-26,27	9.13	d(6.5)	--	--
44-46	CH_3-18	9.45	s	10	19[f]
D. 5E-D_3					
1	H-6	3.48	d(11.2)	85	80
2	H-7	4.16	d(11.2)	102	100
3	H-19Z	5.05	br	78	87
4	H-19E	5.35	br	72	83
5	H-3α	6.14	dddd(8.5,8.5,4.1,4.1)	582	578
6	H-4α	7.16	br d(13.8)[g]	314	316
7	H-9β	7.16	d(12.0)[g]	39	34
8	H-1β	7.56	ddd(14.0,~5.0,~5.0)	161	167
9	H-4β	7.79	dd(13.8,8.5)	404	395
10	H-1α	7.83	br d(14)	139	127
11	H-2α	8.06[d]	--	300	302
12	H-2β	8.42[d]	--	363	367
13-32	other	7.9-9.3	--	--	--
33-35	CH_3-21	9.08	d(6.2)	--	--
36-41	$(CH_3)_2$-26,27	9.13	d(6.7)	--	--
42-44	CH_3-18	9.43	s	4	9
E. 10R-b					
1	H-6	3.76	d(11.2)	125	121
2	H-7	4.17	d(11.2)	179	157
3	H-3α	6.18	ddd(7.0,~4.4,~4.4)	693	683
4	H-9β	7.21	d(12.0)	51	59
5	H-4β	7.47	dd(13.5,7.0)	468	443
6	H-4α	7.58	dd(13.5,3.5)	301	312
7	H-10α	7.77	pseudo-sextet(~6-7)	157	140
8	H-1α	8.33[d]	--	151	146
9	H-2α	8.33[d]	--	293	284
10	H-2β	8.46[d]	--	397	395
11	H-1β	8.61[d]	--	257	270
12-31	others	7.9-9.3	--	--	--
32-34	CH_3-19	8.88	d(6.9)	101	138
35-37	CH_3-21	9.08	d(6.2)	--	--
38-43	$(CH_3)_2$-26,27	9.13	d(6.6)	--	--
44-46	CH_3-18	9.46	s	-11	15[f]

[a] Varian HR300, 24°, in $DCCl_3$ with $HCCl_3$ and TMS standards. [b] The numbering scheme is defined in 1 and 2. [c] The 'PSEUDO' optimized structures gave the following: 10S-a, Eu-O = 2.55(2) Å, Eu-O-C = 105(3)°, Eu-O-C-$H_{3\alpha}$ torsion angle 1(2)°, % axial 3β-OH conformer 94(3) with a residual error, R, of 2.75% based on all data for protons whose geometric shifts are calculated; 10R-a, Eu-O = 2.89(9) Å, Eu-O-C = 114(3)°, Eu-O-C-$H_{3\alpha}$ torsion angle 6(6)°, % axial 3β-OH conformer 8(5) with R = 4.66%; 10S-b, Eu-O = 2.94(6) Å, Eu-O-C = 123(2)°, Eu-O-C-$H_{3\alpha}$ torsion angle -14(3)°, % axial 3β-OH conformer 11(2) with R = 2.21%; 5E-D_3: Eu-O = 2.87(6) Å, Eu-O-C = 118(2)°, Eu-O-C-$H_{3\alpha}$ torsion angle ~9(3)°, % axial 3β-OH conformer 24(3) with R = 2.56%; 10R-b: Eu-O = 2.77(14) Å, Eu-O-C = 117(5)°, Eu-O-C-$H_{3\alpha}$ torsion angle -18(7)°, % axial 3β-OH conformer 58(6) with R = 5.76%. [d] Extrapolated from LIS spectra (not directly observable). [e] H-3α appears as a pseudo-quintet at 60 MHz with an average J ~ 3 Hz while at 300 MHz, the resonance was broad with $W_{\frac{1}{2}}$ ~ 4.2 Hz. [f] Uncertainty in the CH_3-18 coordinate due to perturbation of seco-B ring conformation by CH_3-19 gives rise to a large error in calculated shifts, but does not effect the determined A ring conformers and assignments. [g] From LIS spectra at high resolution.

Table II. Conformational Population Ratios for the A Ring

	Coupling constant[a,b]	LIS[a,c]
A. 10S-a isomer (DHV_3-II)	100 (6), ax	94 (3), ax
B. 10R-a isomer (DHV_3-III)	6 (6), ax	8 (5), ax
C. 10S-b isomer (DHT_3, **2a**)	88 (6), eq	89 (2), eq
D. 5,6-*trans*-D_3(5E-D_3, **3a**)	69 (5), eq	76 (3), eq
E. 10R-b isomer (DHV_3-IV)	50 (5), eq	42 (6), eq

[a] The expression $J_{3\alpha,4\beta} = \lambda J_{ee} + (1 - \lambda)J_{aa}$ where λ is the mole fraction of the conformer with the A-ring hydroxyl axial (ax) or equatorial (eq) and the values of $J_{ee} \sim 3$ Hz and $J_{aa} \sim 11$ Hz taken from the work of Anet (see ref 27). The conformational population percentage refers to the orientation of the hydroxyl group (ax or eq) as calculated by either method. [b] The values in parentheses are standard errors computed by assuming linear propagation of errors with a standard error of 0.5 Hz in J_{ee} and J_{aa}, and 0.1 Hz in $J_{3\alpha,4\beta}$. [c] The values in parentheses are standard deviations from the LIS calculated PSEUDO least-squares fit (see Table I and ref 21a).

the LIS titration E to the same 5.6% residual. Clearly spectrum C is representative of the 10S-b stereochemistry and further the coupling constant parameter ($J_{3\alpha,4\beta} \sim 10.1$ Hz) is consistent only with this assignment. By elimination the 10R-b configuration is assigned to spectrum E. Thus if we only had isolated 10R-b, structure analysis would not have been possible by our ^1H NMR methods. The importance of examining both epimers in studies of this kind cannot be overemphasized.

Figure 4 gives a graphical description of the two chair conformations available to 5E-D_3 and to each of the four dihydrovitamin D_3 stereoisomers. The population ratios determined by the LIS studies are in good agreement with those estimated from correlating the observed coupling constants (Table II). For the latter, the values of Anet[27] for cyclohexanol ($J_{aa} \sim 11$ Hz and $J_{ee} \sim J_{ea} \approx 3$ Hz) were used.

Of special interest is the observation that both the 10S-a and 10R-a stereoisomers exist in conformations which place the methyl groups almost exclusively axial. As Schubert[15] originally hypothesized for DHV_2-II, a side chain analogue of the 10S-a isomer, this observation for both the 10S-a and 10R-a stereoisomers can be attributed to the steric repulsion between the C_{19} and C_7 protons when the C_{19} methyl is equatorially oriented. Thus, the 10S-a isomer, which possesses a trans relationship between the C_{19} methyl and 3β-OH, has its OH group oriented almost entirely axially, just the opposite of what would have been predicted from simple cyclohexane models.[28] The C_{19} methyl and 3β-OH of the 10R-a isomer are cis to one another, which orients its 3β-OH almost completely equatorially.

The unusual significance of the A-ring hydroxyl (3β- or pseudo-1α-OH) of 10S-b (**2a**, DHT_3), whose C_{10} configuration is definitively established to be S in this paper, and 5E-D_3 (**3a**) was emphasized earlier in this report. These previously known substances, **2a** and **3a**, along with the new 10R-b (DHV_3-IV) isomer reported herein constitute a series which exhibits decreasing equatorial 3β-OH (pseudo-1α-OH) character. They contain ~90, ~70, and ~50%, respectively, of the equatorial 3β conformer (Figure 4, Table II).

In preliminary in vivo (chicks) intestinal calcium transport assays,[19] the biological activities have been observed to follow the order 5E-$D_3 \gtrsim$ 10S-b > 10R-b while the 10S-a and 10R-a isomers exhibited no activity at all. The interpretation of the biological activity results is complicated because the 10S-b isomer (DHT_3) and 5E-D_3, and presumably the 10R-b isomer (DHV_3-IV), are known to be metabolized (25-hydroxylated)

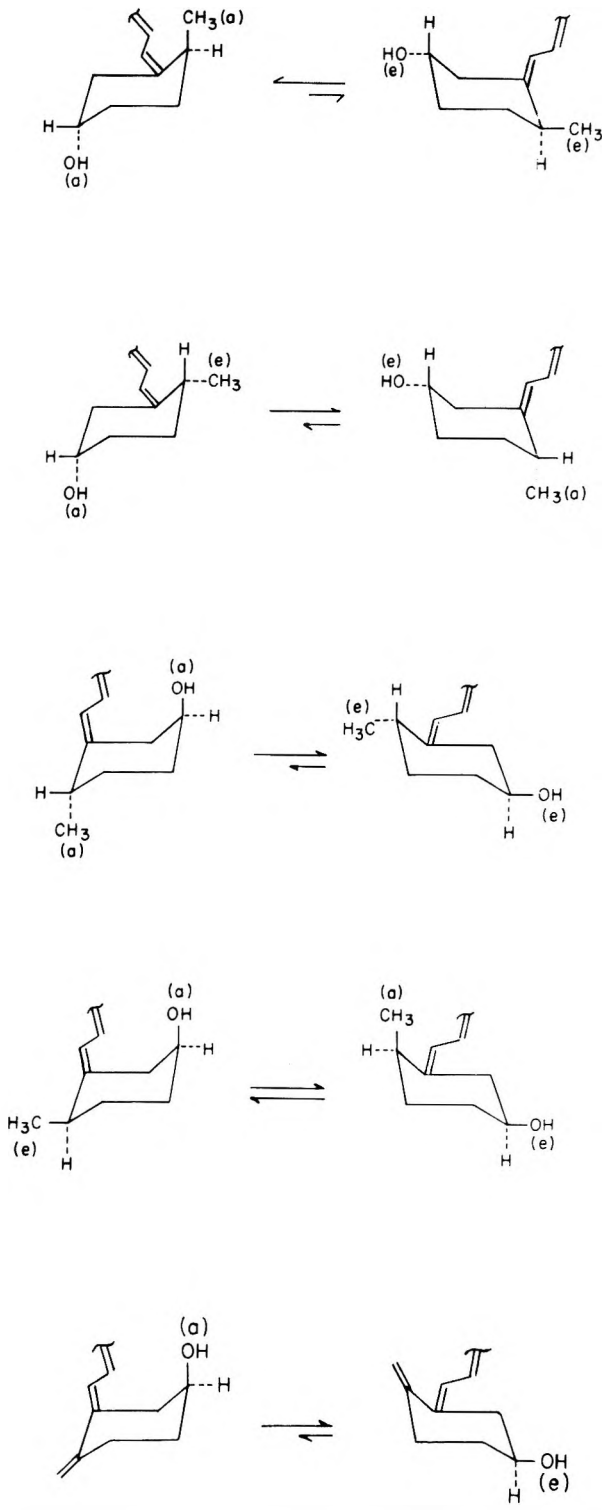


Figure 4. Representations (top to bottom) of the dynamically equilibrating pairs of chair conformers available to the A ring of 10*S*-a (DHV_3-II), 10*R*-a (DHV_3-III), 10*S*-b (DHT_3, **2a**), 10*R*-b (DHV_3-IV), and 5*E*-D_3 (**3a**). See Table II for a comparison of the A-ring population ratios as determined by the two ^1H NMR methods (coupling constants and LIS).

prior to eliciting their physiological action at the intestine.[13,14] Thus the biological activity order observed for 5*E*-D_3, 10*S*-b, and 10*R*-b reflects rates of metabolism (and transport) as well.[29] It would be more meaningful to compare analogues already possessing the 25-hydroxyl group. Further studies from this laboratory are being directed toward the synthesis of these 25-OH counterparts by the methods described in this report and a detailed study of their biological activities.

Experimental Section

General. Ultraviolet spectra (UV, ethanol) were taken on a Beckman DBGT spectrophotometer; ^1H nuclear magnetic resonance spectra (NMR, deuteriochloroform with tetramethylsilane at τ 10.00) were taken on a Varian HR300 spectrometer unless otherwise indicated; mass spectra were taken on a Finnigan 1015C mass spectrometer at 70 eV (parent and base peaks and peaks with >10% intensity at m/e >100 are given); infrared spectra (IR, carbon tetrachloride) were taken on a Perkin-Elmer 621 spectrophotometer; melting points (uncorrected) were taken on a Thomas-Hoover capillary apparatus. Dry tetrahydrofuran (THF) refers to solvent freshly distilled from lithium aluminum hydride; lbpe refers to redistilled reagent 30–60 °C low-boiling petroleum ether; 9-BBN is a 0.5 M solution of 9-borabicyclo[3.3.1]nonane in THF (Aldrich Chemical Co.). Silica gel for column chromatography was Baker Analyzed reagent (60–200 mesh). Silica gel G (EM reagents, type 60) was used for thin layer chromatography (TLC, 0.25 mm analytical plates).

Crystalline vitamin D_3 was purchased from Aldrich Chemical Co. or obtained as a gift from Philips-Duphar (Weesp, the Netherlands). The latter firm also provided the sample of dihydrotachysterol$_3$ used in our initial NMR studies. Tris(dipivalomethanato)europium(III) [Eu(dpm)$_3$] was used directly as purchased from Ventron, Inc. Tris(dipivalomethanoto)lanthanum(III) [La(dpm)$_3$] was synthesized by the method of Eisentraut and Sievers[30] as modified by Selbin et al.[31] (in vacuo mp 237–245 °C, lit.[30] 238–248 °C).

Preparation of 5*E*-Vitamin D_3 (5*E*-D_3, 5,6-*trans*-Vitamin D_3, 3a). A solution of iodine (5.7 mL of a stock solution containing 0.22 mg iodine/mL lbpe) was added to lbpe (500 mL). Vitamin D_3 (**1a**, 503 mg, 1.31 mmol) was added to the above dilute iodine solution and the mixture was allowed to stand for 1 h at ambient temperature. The reaction was quenched by vigorous shaking with 1% aqueous sodium bisulfite (100 mL). The separated organic layer was washed with water (2 × 100 mL) and then dried (Na_2SO_4). After filtering and concentrating under vacuum, the resulting residue was chromatographed on a dry column of silica gel (60 × 2.5 cm column; isopropyl ether; 11-mL fractions); fractions 2–7 contained 5*E*-D_3 [**3a**, 317 mg (63%), white foam]; fractions 8–13 consisted of starting material (**1a**), contaminated by a small amount of 5*E*-D_3 (164 mg, 33%). The 5*E*-vitamin D_3 was sufficiently pure for subsequent reactions: TLC (isopropyl ether, R_f 0.50) and NMR (see Table I and Figure 2) indicated that the material was homogeneous.

Catalytic Hydrogenation of 3a. Preparation of 10*R*(19)-Dihydro-5*E*-vitamin D_3 (10*R*-b or DHV_3-IV). A stirred suspension of 5% rhodium on carbon (29 mg) in ethanol (23 mL) containing 5*E*-D_3 (**3a**, 227 mg, 0.59 mmol) was allowed to absorb 1.08 molar equiv of hydrogen (25 min) at ambient temperature and pressure. Removal of catalyst and solvent afforded a residue which was chromatographed (silica gel, 20 g, linear gradient between 0–20% ether/lbpe, 10-mL fractions). Fractions 32–38 were combined and concentrated to afford TLC and NMR homogeneous 10*R*-b (DHV_3-IV) in 28% yield (63 mg). The product was identical with that described below. Later fractions of the chromatography afforded material exhibiting a UV spectrum and TLC R_f value identical with those of an authentic specimen of DHT_3 (10*S*-b, **2a**). The DHT_3, however, was present in very small amounts and it could not be isolated pure.

Hydroboration of Vitamin D_3 (1a) and 5*E*-D_3 (3a). A solution of 9-BBN (32 mL, 16 mmol) in THF was added dropwise (syringe) to crystalline **1a** (2.00 g, 5.21 mmol) (nitrogen atmosphere, room temperature, magnetic stirring) whereupon immediate hydrogen evolution was observed to occur. After 1.5 h, the resulting clear solution was quenched (methanol, 5 mL) and then allowed to stand for 15 min. UV analysis indicated that the 10(19)-boron adduct was formed in essentially quantitative yield (solution A).

The 10(19)-boron adduct of 5*E*-D_3 (**3a**) in THF after methanol quench was prepared in an exactly analogous manner (solution B). Again UV analysis indicated that the boron intermediate had been formed nearly quantitatively.

Preparation of 19-Hydroxy-10*S*(19)- (19-OH-10*S*-b, 19-OHDHT$_3$, 7a) and 19-Hydroxy-10*R*(19)-dihydro-5*E*-vitamin D_3 (19-OH-10*R*-b, 19-OHDHV$_3$-IV, 7b). Solution B (9-BBN in THF, 14 mL, 7 mmol; **3a**, 530 mg, 1.38 mmol/4 mL of THF; 5 mL of methanol) was cooled (ice) and then aqueous NaOH (6 M, 2 mL) and 30% H_2O_2 (4 mL, dropwise) were added sequentially. The ice bath was removed and then the mixture was heated (55 °C, 1 h). The cooled mixture was transferred to a separatory funnel, diluted with saturated aqueous K_2CO_3 (50 mL), and then extracted with ether (2 × 50 mL). The combined ether extract was dried (Na_2SO_4) and then concentrated (vacuum) to afford a white, foamy residue. Chromatography of the residue on silica gel (ether) afforded a pure mixture of **7a** and

7b (353 mg, 64%) in a 60/40 ratio (determined by NMR). Careful chromatography (silica gel, 2.5 × 65 cm column, ether–lbpe, 10-mL fractions) of the prepurified mixture afforded fractions containing completely homogeneous **7a** or **7b.**

7a (19-OH-10*S*-b, 19-OHDHT$_3$): noncrystalline, white foam, 91 mg; TLC, ethyl acetate, R_f 0.54; NMR τ 3.72 and 4.10 ($H_{6,7}$, AB q, $J \sim 11$ Hz), 6.15 and 6.37 (2 H_{19}, AB q; A, dd, $J \sim 10, 7.5$ Hz; B, dd, $J \sim 10, 6$ Hz), 6.21 ($H_{3\alpha}$, m), 7.20 ($H_{4\alpha}$, dd, $J \sim 12, 4$ Hz), 7.23 ($H_{9\beta}$, d, $J \sim 12$ Hz), 7.72 ($H_{10\alpha}$, m), 7.78 ($H_{4\beta}$, d, $J \sim 13.8$ Hz), 9.08 (C_{21} CH_3, d, $J \sim 6$ Hz), 9.13 ($C_{26,27}$ 2 CH_3, d, $J \sim 7$ Hz), 9.45 (C_{18} CH_3, s); UV λ_{max} 242.5 nm (ϵ 28 800), 251 (32 800), 261 (22 000); IR ν_{max} 3360 cm^{-1}; mass spectrum *m/e* (rel intensity) 402 (M, 5.8), 384 (M − H_2O, 1.4), 109 (18), 105 (12), 43 (base).

7b (19-OH-10*R*-b, 19-OHDHV$_3$-IV): noncrystalline, white foam, 52 mg; TLC, ethyl acetate, R_f 0.51; NMR τ 3.66 and 4.12 ($H_{6,7}$, AB q, $J \sim 11$ Hz), 6.23 and 6.43 (2 H_{19}, AB q; A, $J \sim 10, 10$ Hz; B, $J \sim 10, 6$ Hz), 6.33 ($H_{3\alpha}$, m) 7.15 ($H_{4\alpha}$, d, $J \sim 11$ Hz), 7.21 ($H_{9\beta}$, d, $J \sim 11$ Hz), 7.66 ($H_{10\beta}$, m), 9.08 ($C_{21}CH_3$, d, $J \sim 6.5$ Hz), 9.13 ($C_{26,27}$ 2 CH_3, d, $J \sim 6.5$ Hz), 9.45 (C_{18} CH_3, s); UV λ_{max} 242.5 nm (ϵ 32 800), 251 (37 000), 260.5 (25 000); IR ν_{max} 3380 cm^{-1}; mass spectrum *m/e* (rel intensity) 402 (M, 4.7), 384 (M − H_2O, 0.2), 107 (12), 105 (11), 43 (base).

Preparation of 10*S*,19- (10*S*-b, DHT$_3$, 2a) and 10*R*,19-Dihydro-5*E*-vitamin D$_3$ (10*R*-b, DHV$_3$-IV) by Hydroboration. Solution B (9-BBN in THF, 20 mL, 10 mmol; **3a**, 946 mg, 2.46 mmol/5 mL of THF; 5 mL of methanol) was concentrated under vacuum. Freshly distilled acetic acid (15 mL) and acetic anhydride (5 mL) were added to the residue and the mixture refluxed (2 h, nitrogen). The cooled mixture was poured into water (50 mL) and then extracted with ether. The ether layer was washed repeatedly with saturated aqueous $NaHCO_3$ (until the acetic acid was removed) and then water. After dyring and concentrating the organic layer, a light green solid residue remained which was taken up in lbpe (25 mL). The resulting white precipitate was removed by filtration. The filtrate was concentrated and then the lbpe precipitation procedure was repeated until no precipitate was observable upon dissolving the residue in lbpe. The soluble residue was chromatographed (silica gel, lbpe and 5% ether–lbpe) and fractions containing products (mainly as acetates; UV, TLC) were pooled and concentrated. The residue was saponified (5% KOH/methanol, 25 mL, and THF, 9 mL; overnight, nitrogen) and then worked up conventionally with water and ether. The ether solution was dried and concentrated to afford the product mixture residue. Careful chromatography (silica gel, 2.5 × 64 cm, 250-mL portions of 0, 2.5, 5, 7.5% ether–lbpe and 750 mL of 10% ether–lbpe, 15-mL fractions) of the residue afforded excellent separation of the stereoisomers.

Fractions 67–77 were combined and concentrated to yield 10*R*-b (DHV$_3$-IV): clear, colorless oil, 60 mg (6.3%); TLC, isopropyl ether, R_f 0.52; NMR, see Figure 2E and Table I; UV λ_{max} 241.5 nm (ϵ 25 600), 250 (28 800), 259 (19 900); IR ν_{max} 3360 cm^{-1}; mass spectrum *m/e* (rel intensity) 386 (M, 22), 273 (12), 255 (10), 147 (12), 135 (14), 121 (19), 119 (13), 109 (11), 107 (17), 105 (13), 43 (base).

Fractions 80–90 upon similar treatment afforded 10*S*-b (DHT$_3$, **2a**): colorless solid, 64 mg (6.7%); TLC, isopropyl ether, R_f 0.47; NMR, see Figure 2C and Table I; UV λ_{max} 241.5 nm (ϵ 25 900), 250 (29 800), and 259 (20 400); IR ν_{max} 3360 cm^{-1}; mass spectrum *m/e* (rel intensity) 386 (M, 11), 147 (11), 135 (16), 121 (13), 119 (13), 109 (10), 107 (22), 105 (14), 43 (base). Comparison of the sample to an authentic specimen obtained from Philips-Duphar proved that they were identical.

Preparation of 19-Hydroxy-10*S*(19)- (19-OH-10*S*-a, 19-OHDHV$_3$-II, 8a) and 19-Hydroxy-10*R*(19)-dihydrovitamin D$_3$ (19-OH-10*R*-a, 19-OHDHV$_3$-III, 8b). Solution A (9-BBN in THF, 10.4 mL, 5.2 mmol; **1a** 500 mg, 1.3 mmol; 5 mL of methanol) was ice cooled and then 6 M aqueous NaOH (1.1 mL) and 30% H_2O_2 (2.2 mL, dropwise) were added sequentially. The stirred mixture was heated for 1 h (55 °C), cooled, diluted with saturated aqueous K_2CO_3 (25 mL), and then extracted with ether. The ether extract was dried (Na_2SO_4), filtered, and then concentrated. The residue was taken up in ether (50 mL) and then the solution cooled (freezer) to precipitate most of the cyclooctanediol. The cold mixture was filtered and then the filtrate was concentrated to afford a white foam which was chromatographed (silica gel, 2.5 × 60 cm; 250 mL each of 75, 85, and 95% ether–lbpe followed by 500 mL of ether, 15-mL fractions).

Combination and concentration of fractions 19–29 afforded pure **8a** (19-OH-10*S*-a, 19-OHDHV$_3$-II): white foam, 230 mg (44%); TLC, ethyl acetate, R_f 0.59; NMR τ 3.64 and 4.12 ($H_{6,7}$, AB q, $J \sim 11$ Hz), 5.94 ($H_{3\alpha}$, m), 6.29 and 6.38 (2 H_{19}, AB q; A, dd, $J \sim 10.3, 9.2$ Hz; B, dd, $J \sim 10.3, 7.0$ Hz), 6.87 ($H_{10\beta}$, m), 7.21 ($H_{9\beta}$, d, $J \sim 12.0$ Hz), 7.43 ($H_{4\beta}$, br, d, $J \sim 14.5$ Hz), 7.82 ($H_{4\alpha}$, d, $J \sim 14.5$ Hz), 9.09 (C_{21} CH_3, d, $J \sim 6$ Hz), 9.13 ($C_{26,27}$ 2 CH_3, d, $J \sim 7$ Hz), 9.48 (C_{18} CH_3, s); UV, λ_{max} 243 nm (ϵ 32 500), 251.5 (36 900), 261 (24 700); IR ν_{max} 3340 cm^{-1}; mass spectrum *m/e* rel intensity) 402 (M, 8), 121 (10), 119 (10), 109 (30), 107 (12), 105 (16), 43 (base).

Fractions 31–49 afforded 60 mg of pure **8b** (19-OH-10*R*-a, 19-OHDHV$_3$-III). Fractions 50–90 were combined and concentrated to a small volume and left in the cold overnight to allow precipitation of additional cyclooctanediol. The decanted liquid phase was concentrated and then rechromatographed (silica gel, 2.5 × 64 cm; 1000 mL of ether, 15-mL fractions). Combination and concentration afforded additional (74 mg) pure product: white foam, 134 mg (25.6%); TLC, ethyl acetate, R_f 0.43; NMR τ 3.72 and 4.20 ($H_{6,7}$, AB q, $J_{AB} \sim 12$ Hz), 6.39 ($H_{3\alpha}$, m), 6.34 and 6.39 (2 H_{19}, AB q; A, dd, $J \sim 11.5, 9.0$ Hz; B, dd, $J \sim 11.5, 7.8$ Hz), 6.99 ($H_{10\alpha}$, m), 7.21 ($H_{9\beta}$, d, $J \sim 12$ Hz), 7.58 ($H_{4\alpha}$, dd, $J \sim 13.0, 4$ Hz), 7.81 ($H_{4\beta}$, dd, $J \sim 13.0, 10.5$ Hz), 9.08 (C_{21} CH_3, d, $J \sim 6$ Hz), 9.12 ($C_{26,27}$ 2 CH_3, d, $J \sim 7$ Hz), 9.45 (C_{18} CH_3, s); UV λ_{max} 243 nm (ϵ 27 800), 251 (32 200), 261 (21 400); IR ν_{max} 3350 cm^{-1}; mass spectrum *m/e* (rel intensity) 402 (M, 1.9), 127 (11), 109 (21), 108 (14), 107 (18), 57 (base), 43 (69).

Preparation of 10*S*,19- (10*S*-a, DHV$_3$-II) and 10*R*,19-Dihydrovitamin D$_3$ (10*R*-a, DHV$_3$-III) by Hydroboration. After solution A (9-BBN in THF, 32 mL, 16 mmol; **1a**, 2.00 g, 5.2 mmol; 5 mL of methanol) was concentrated under vacuum, acetic acid (60 mL) and acetic anhydride (20 mL) were added to the residue and then the mixture was heated (~135 °C, 2 h, nitrogen). The cooled mixture was poured into water (200 mL) and then extracted with ether. The ether phase was backwashed repeatedly with saturated aqueous $NaHCO_3$ (until the acetic acid was removed) and then water. After drying (Na_2SO_4) and concentrating the ether solution, the resulting semisolid residue was taken up in lbpe (100 mL). The colorless, insoluble material was removed by filtration and washed with additional lbpe. The filtrate and washings were combined, dried (Na_2SO_4), and concentrated to yield a viscous residue which was chromatographed (silica gel, 2.5 × 63 cm; ~1000 mL of 0–10% ether–lbpe) to yield after pooling and concentrating appropriate fractions (by UV, TLC) a colorless residue consisting of acetates of the desired products. After saponification (5% KOH/methanol, 300 mL; overnight, ambient temperature, nitrogen) and conventional workup, a residue consisting mainly of the desired alcohol mixture was obtained. The residue was chromatographed (dry silica gel column, 2.5 × 64 cm, isopropyl ether, 15-mL fractions) to afford a pure mixture of the 10*S*-a and 10*R*-a stereoisomers (629 mg, 31.3%). Rechromatography (dry silica gel column, 2.0 × 170 cm, isopropyl ether, 10-mL fractions) of the product mixture effected good separation.

Fractions 7–14 were pooled and concentrated to afford pure 10*S*-a (DHV$_3$-II): oil, 322 mg (16%); TLC, isopropyl ether, R_f 0.43; NMR, see Figure 2A and Table I; UV λ_{max} 241.5 nm (ϵ 26 800), 250 (30 800), 259.5 (21 000); IR ν_{max} 3360 cm^{-1}; mass spectrum *m/e* (rel intensity) 386 (m, 12), 121 (21), 109 (10), 105 (18), 43 (base).

Fractions 15–17 were found to contain 56 mg (3%) of a mixture of the 10*S*-a and 10*R*-a isomers.

Fractions 18–28 upon similar treatment afforded pure 10*R*-a (DHV$_3$-III): oil, 202 mg (10%); TLC, isopropyl ether, R_f 0.32; NMR, see Figure 2B and Table I; UV λ_{max} 241.5 nm (ϵ 28 100), 250 (32 400), 259 (21 700); IR ν_{max} 3340 cm^{-1}; mass spectrum *m/e* (rel intensity) 386 (M, 5), 121 (8), 110 (11), 43 (12).

Shift Reagent Titration. Titration of 10*S*-a (DHV$_3$-II), 10*R*-a (DHV$_3$-III), 10*S*-b (DHT$_3$, **2a**), 5*E*-D$_3$ (**3a**), and 10*R*-b (DHV$_3$-IV) was carried out by adding ~3–5-mg increments of solid Eu(dpm)$_3$ to the NMR sample tubes containing ~20 mg of vitamin/0.5 mL of deuteriochloroform. NMR spectra were recorded immediately after each incremental addition of Eu(dpm)$_3$.

Diamagnetic Correction. In order to test the possibility of complexation shifts and whether the Eu(dpm)$_3$ magnetic probe influences the conformational equilibria of the A ring, La (DPM)$_3$, a diamagnetic analogue of Eu(dpm)$_3$, was introduced (0.3 molar equiv) to each of the vitamin samples (ca. 20 mg in 0.5 mL of $CDCl_3$). No detectable differences were noted for observable coupling constants. Very slight diamagnetic shifts were noted only for the $H_{3\alpha}$ and $H_{4\alpha}$, $H_{4\beta}$ resonances, and therefore no corrections to the data were made prior to the LIS calculation.

Computational Procedures. The program PSEUDO, described elsewhere,[21a,32] was used in the interactive mode for all calculations. Parameters varied were the Eu–O distance, the Eu–O–C angle, the Eu–O–C–$H_{3\alpha}$ torsion angle, and the conformational populations. The values obtained are listed in footnote c of Table I.

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Health Service and the Intramural Fund of the University of California, Riverside, provided the financial support for this study.[2] A.R. acknowledges the Institutional Biomedical Support Fund of the Public Health Service for a predoctoral fellowship. M.L.H. thanks the Graduate Division, University of California, Riverside, for a predoctoral fellowship.

Registry No.—**1a,** 67-97-0; **1a** BBN adduct, 62077-03-6; **2a,** 57885-34-4; **3a,** 22350-41-0; **3a** BBN adduct, 62077-04-7; **7a,** 62077-05-8; **7b,** 62107-42-0; **8a,** 62077-06-9; **8b,** 62107-43-1; DHV_3-II, 62107-44-2; DHV_3-III, 62107-45-3; DHV_3-IV, 22481-38-5; 9-BBN, 280-64-8.

Supplementary Material Available. Tables giving the atom coordinates and geometric shifts used in the LIS calculations as well as the computer optimized parameters (11 pages). Ordering information is given on any current masthead page.

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(3) (a) Department of Chemistry; (b) Department of Biochemistry and recipient of a USPHS Career Development Award (AM-13654).
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(23) No previous studies concerning the reduction of 5*E*-D_3 appear to have been reported. Raney nickel W-2 was the catalyst employed by the earlier workers (ref 5, 15, 16, 18) for the reduction of vitamins D_3 (**1a**) and D_2 (**6**). Attempted reduction of 5*E*-D_3 with this nickel catalyst also produced 10*R*-b, but the yields were lower and the purification was substantially more difficult as a result of contaminating overreduction products and starting material. We observed the formation of 10*S*-a (DHV_3-II), as previously reported (ref 5), upon catalytic reduction of **1a** with the Raney nickel catalyst as well as with the rhodium catalyst. We did not observe formation of detectable amounts of a second stereoisomer (i.e., 10*R*-a). Similar results were obtained when vitamin D_2 (**6**) was reduced employing these catalysts.
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Organoboranes. 20. The Facile Allylboration of Representative Carbonyl Compounds with *B*-Allyl Derivatives of 9-Borabicyclo[3.3.1]nonane[1]

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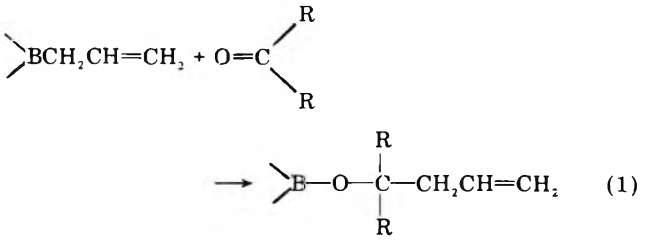
The reaction of *B*-allyl derivatives of 9-borabicyclo[3.3.1]nonane with representative organic compounds containing carbonyl groups occurs cleanly in the common organometallic manner with the allyl undergoing transfer to the carbonyl carbon and the boron moiety to the carbonyl oxygen. This process evidently proceeds with total rearrangement of the allyl moiety; thus, the *B*-crotyl derivative yields α-methallyl products exclusively. Aldehydes and ketones react in a 1:1 stoichiometry, while acid chlorides, esters, and *N,N*-dimethylamides react with 2 equiv of the allylborane; acid anhydrides utilize 4 equiv. Simple protonolysis of the borinic esters thus formed, conveniently accomplished via transesterification with ethanolamine, affords excellent yields of the corresponding homoallylic alcohols. In many instances, this allylboration reaction competes favorably with the familiar Grignard allylations; however, for the higher *B*-allyl homologues, many of which are easily prepared via hydroboration, the hydroboration–allylboration sequence offers significant advantages.

The chemistry of unsaturated organoboranes often differs markedly from that of their saturated analogues. Both vinyl- and allylboranes react readily with many substrates toward which trialkylboranes are inert.[2] Over the past decade Mikhailov and his co-workers have extensively examined the chemistry of the simple triallylboranes.[3-5] They have reported that such allylboranes add smoothly to various carbonyl derivatives in the usual organometallic fashion, transferring an allyl group to the carbonyl carbon with boron going to the oxygen (eq 1). Such allylborations of aldehydes and ketones



(1)

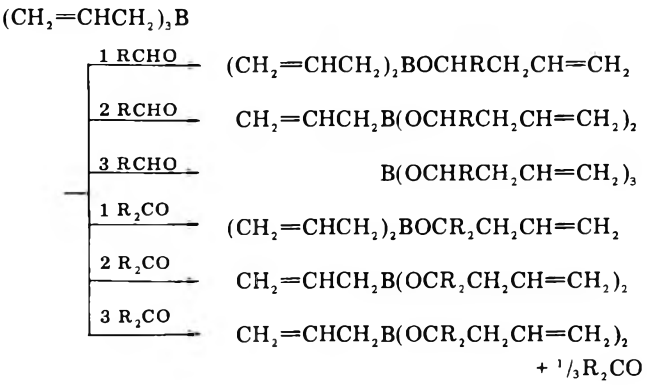
proceed simply, utilizing all three allyl groups in the former case, but only two allyl moieties in the latter. Hydrolysis of the borate ester products affords the corresponding homoallylic alcohols. The allylborations of other carbonyl derivatives, such as nitriles and quinones, are not as straightforward, being accompanied by subsequent reactions of the initial products.[3,4]

Recent studies have shown that the *B*-alkyl derivatives of 9-borabicyclo[3.3.1]nonane (9-BBN) possess unique advantages over simple trialkylboranes in many synthetic applications.[6,7] Consequently, we undertook to study the chemistry of the *B*-allyl derivatives of 9-BBN. We recently reported simple preparations and described some of the basic chemistry of these derivatives.[8] In the present article, we report the results of our investigation into the reactions of the *B*-allyl derivatives of 9-BBN with carbonyl compounds.

Results and Discussion

Allylboration of Aldehydes and Ketones. It was initially reported that treatment of aldehydes with triallylborane leads to mixtures of products containing cyclohexadiene.[9] Mikhailov has established that these early reports are incorrect. Triallylborane reacts with aldehydes to form esters of diallylborinic, allylboronic, or boric acids, depending on the stoichiometry of the reactants. Similarly, ketones afford esters of either diallylborinic or allylboronic acids. The third allyl moiety fails to react with ketones, presumably a result of the severe steric crowding around boron atom (Scheme I).[4] These

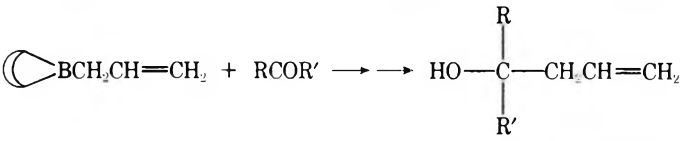
Scheme I



borate esters are easily hydrolyzed. Consequently, the allylboration sequence provides a synthetically useful alternative to the familiar Grignard synthesis of homoallylic alcohols. The allylboration reaction appears to possess synthetically valuable characteristics, and Mikhailov has provided several examples of such applications. However, not much is known about the full range of applicability and possible limitations of this reaction. The ready availability of *B*-allyl derivatives of 9-BBN suggested an examination of their utility in such allylborations. Preliminary results revealed some significant advantages of these reagents. Accordingly, a detailed study of the full scope and possible limitations of the reaction of *B*-allyl derivatives of 9-BBN with representative organic compounds containing carbonyl groups was undertaken.

Analysis of the homoallylic alcohols is considerably easier than analysis of their borinate ester precursors. Therefore, effort was devoted in the initial stages of this study to achieve a simple protonolysis procedure to convert the initial borinate ester product into the corresponding alcohol. In his original work, Mikhailov used triethanolamine to protonolyze the borate esters produced in his allylborations. When this reagent is used with the borinate esters of 9-BBN, the protonolysis is readily achieved, but the homoallylic alcohol is difficult to extract from the thick, sticky, air-sensitive, boron-containing by-product. Hydrolysis may also be effected readily with aqueous sodium hydroxide. Unfortunately, it is again difficult to extract the homoallylic alcohol free of boron-containing materials. Fortunately, ethanolamine solved the problem. Treatment of a pentane solution of a borinate ester of 9-BBN with 1 equiv of ethanolamine results in the rapid formation of a fluffy, white precipitate. VPC analysis of the supernatant liquid reveals a quantitative yield of the corresponding alcohol with no traces of boron-containing materials. The white pre-

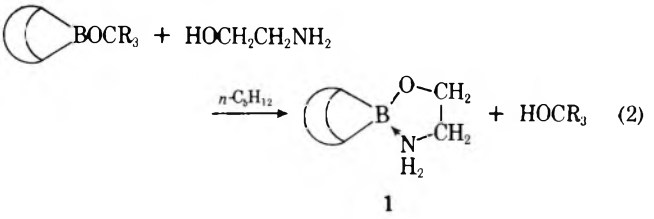
Table I. Allylboration of Aldehydes and Ketones with *B*-Allyl-9-BBN[26]



R	R′	Product n^{20}D	% yield (GLC)[a]	Registry no.
n-C_5	H	1.4409	92	35192-73-5
t-Bu	H	1.4379	97	19550-89-1
Ph	H	1.5322	96	936-58-3
CH_3CH=CH	H	1.4535	91	5638-26-6
Me	Me	1.4271	99	624-97-5
Me	*t*-Bu	1.4467	101	1185-08-6
Me	Ph	1.5271	101	4743-74-2
Ph	Ph	1.5875	100	4165-79-1
i-Pr	*i*-Pr	1.4567	98	36971-15-0
t-Bu	*n*-Pr	1.4551	97	61967-23-5
t-Bu	*i*-Pr	1.4591	74[b]	61967-24-6
t-Bu	Ph	1.5178	82[c]	38400-74-7
t-Bu	*t*-Bu	1.4663	<25[d]	754-56-3
Cyclopentanone		1.4676	102	36399-21-0
Cyclohexanone		1.4772	100	1123-34-8
Cycloheptanone		1.4855	94	49564-90-1
4-*tert*-Butylcyclohexanone		1.4756	100[e]	42437-24-1 (cis) 42437-23-0 (trans)
Norcamphor		1.4955	100[f]	61967-25-7 (endo) 61967-26-8 (exo)
Bicyclo[3.3.1]nonan-9-one		41.5–42[g]	85	61967-27-9
H_2C=CH	Me	1.4478	94	5903-40-2
CH_3CH=CH	Me	1.4578	96	919-98-2
$(CH_3)_2C$=CH	Me	1.4616	94	926-20-5

[a] Unless otherwise stated, the reaction mixtures were allowed to stir for 2 h at 25°C before workup even though the allylborations were generally complete in a few minutes. [b] Stirred for 1 week at 25 °C. [c] Stirred for 4 h at 25 °C. [d] Stirred for 5 days in refluxing *n*-octane. [e] 54.8:45.2 axial:equatorial alcohol. [f] 95.8:4.2 endo:exo alcohol. Anal. Calcd for $C_{10}H_{16}O$ (152.238): C, 78.90; H, 10.59. Found: C, 79.05; H, 10.87. *m/e* M⁺ calcd for $^{12}C_{10}{}^{1}H_{16}{}^{16}O$: 152.1201. Found: 152.1210. ^{13}C NMR (C_3D_6O) δ 135.3 (d), 117.4 (t), 78.5 (s), 47.3 (t), 47.1 (d), 45.2 (t), 32.8 (t), 37.6 (d), 28.9 (t), 22.5 (t). [g] Melting point.

cipitate is virtually insoluble in pentane, stable to air, and readily removed by simple filtration or centrifugation–decantation. This solid, mp 202–203.5 °C (with decomposition), was isolated and characterized by spectroscopy and elemental analyses as the ethanolamine ester of 9-BBN (1) (eq 2).[10]



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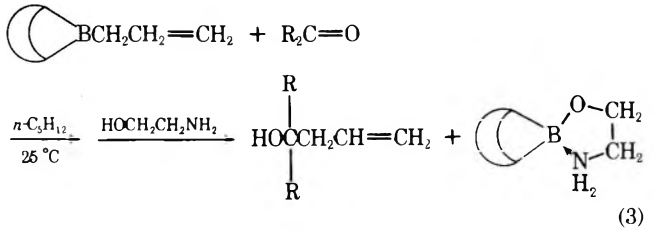
The stoichiometry of the allylborations of aldehydes and ketones with *B*-allyl-9-BBN is 1:1. No secondary addition reactions, such as those which sometimes accompany Grignard allylations,[11] were detected under our conditions. Representative aldehydes and ketones were allylborated with *B*-allyl-9-BBN. The results (Table I) reveal the significant characteristics of this reaction (eq 3). First, the reaction is extremely



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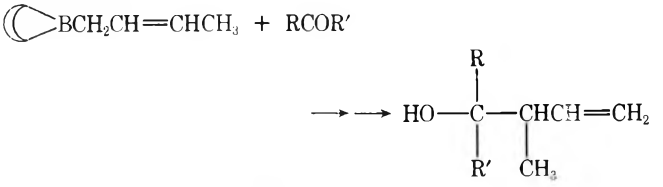
clean. After transesterification with ethanolamine, the only material left in solution is the homoallylic alcohol. In nearly every case studied, the yield of homoallylic alcohol is essentially quantitative. The allylboration of aldehydes and unhindered ketones is usually a very rapid process, being complete in a matter of minutes at room temperature. However, as the steric crowding around the carbonyl group becomes greater, the reaction rate decreases. For example, moderately hindered ketones such as diisopropyl ketone or *tert*-butyl *n*-propyl ketone react readily, but the reaction with pivaloylphenone is only 82% complete in 4 h. In the case of *tert*-butyl isopropyl ketone, the allyboration is only 74% complete after 1 week at room temperature, while di-*tert*-butyl ketone affords less than 25% of the expected product even after 5 days in refluxing *n*-octane. The steric sensitivity of these allylborations is in sharp contrast with the corresponding allylations utilizing Grignard reagents.[12] Even di-*tert*-butyl ketone is completely allylated by allylmagnesium bromide within 6 h in refluxing ether.

Unlike simple trialkylboranes, which add in a 1,4 manner to α,β-unsaturated carbonyl compounds,[13] allylboranes add exclusively in a 1,2 fashion to these substrates.[4] The *B*-allyl derivatives of 9-BBN behave similarly; in all cases, only the products arising from 1,2-addition were detected. It should be noted that allyl Grignard reagents also add exclusively in a 1,2 manner to carbonyl derivatives containing conjugated double bonds.[12]

The allylboration of 4-*tert*-butylcyclohexanone with *B*-allyl-9-BBN produces a 54.8:45.2 mixture of the axial and equatorial homoallylic alcohols. This product distribution is almost identical with that realized in the allylation of this ketone with allylmagnesium bromide in refluxing ether.[14] Similarly, the allylboration of norcamphor afforded a mixture of homoallylic alcohols with an endo:exo alcohol ratio of

Table II. Allylboration of Aldehydes and Ketones with *B*-Crotyl-9-BBN[26]



R	R′	Product n^{20}D	% yield (GLC)[a]	Registry no.
H	H	1.4272	88	4516-90-9
n-C_5	H	1.4436	89[b]	52922-27-7 (threo) 52922-22-2 (erythro)
Ph	H	1.5251	87	25201-44-9
Me	Me	1.4358	100	19781-52-3
Ph	Me	1.5250	97	61967-11-1
Ph	Ph	51–52[c]	96	61967-12-2

[a] Reaction mixture allowed to stir for 2 h at 25 °C before workup, even though the allylboration was generally complete in a few minutes. [b] Threo:erythro = 60:40. [c] Melting point.

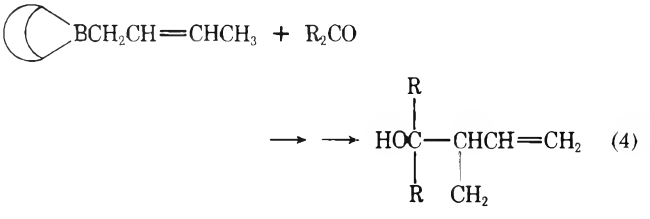
Table III. Allylboration of Acetone with *B*-Allyl-9-BBN Derivatives[26]

B-Allyl-9-BBN derivative	Product	n^{20}D	% yield (GLC)[a]
Allyl	2-Methyl-4-penten-2-ol	1.4271	99
2-Methylallyl	2,4-Dimethyl-4-penten-2-ol	1.4384	95
Crotyl	2,3-Dimethyl-4-penten-2-ol	1.4385	100
3,3-Dimethylallyl	2,3,3-Trimethyl-4-penten-2-ol	1.4490	93
3,3-Dimethyl-1-isopropylallyl	2,3,3,6-Tetramethyl-4-hepten-2-ol	1.4520	85[b]
2-Cyclohexen-1-yl	2-(2-Cyclohexenyl)-2-propanol	1.4833	86

[a] Reaction mixture allowed to stir for 2 h at 25 °C before workup, even though the allylboration was generally complete in a few minutes. [b] Largely the trans isomer.

95.8:4.2. Allylation of norcamphor with ethereal allylmagnesium bromide at reflux produced the same mixture of homoallylic alcohols (endo:exo 99:1).

Allylborations with the parent compound, *B*-allyl-9-BBN, cannot detect one very important feature of this reaction: the complete allylic rearrangement of the allyl moiety during the allylation.[4] However, the *B*-crotyl derivative shows this nicely (eq 4). No evidence was obtained through GLC, ^{13}C NMR, or



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^{1}H NMR examination of any unrearranged products (Table II). Two products were detected in the allylborations of aldehydes with *B*-crotyl-9-BBN; however, these proved to be diastereomers, not positional isomers. One interesting difference between the 9-BBN and the parent borane derivatives

Table IV. In Situ Hydroboration–Allyboration Sequence with Acetone[26]

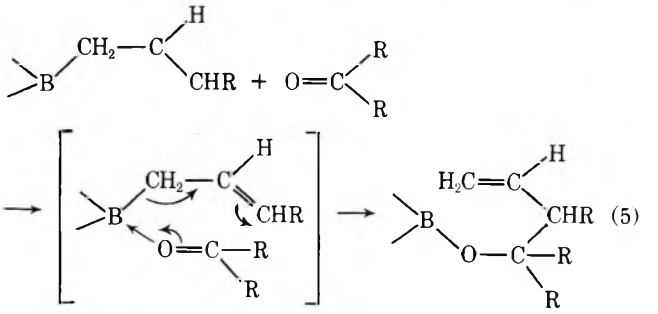
Diene[a]	Product	% yield (GLC)[b]
1,3-Cyclohexadiene	2-(2-Cyclohexenyl)-2-propanol	68
3-Methyl-1,2-butadiene	2,3,3-Trimethyl-4-penten-2-ol	80
2,5-Dimethyl-2,4-hexadiene	2,3,3,6-Tetramethyl-4-hepten-2-ol	80

[a] Diene was hydroborated with 9-BBN (1:1 stoichiometry) for 24 h at 25 °C in pentane; then 1 equiv of acetone was added, and the mixture allowed to stir for 2 h at 25 °C before workup.

was observed. *B*-Crotyl-9-BBN reacts with monomeric formaldehyde to give only the rearranged alcohol, 2-methyl-3-buten-1-ol, after protonolysis. On the other hand, Mikhailov has reported that treatment of tricrotylborane with monomeric formaldehyde gives only 15% of this alcohol accompanied by 85% of the unrearranged alcohol.[17]

Several other *B*-allyl derivatives of 9-BBN were treated with 1 equiv of acetone. Unsymmetrical allylboranes gave only the rearranged homoallylic alcohol (Table III). In several of these cases, the allylboranes can be prepared directly via hydroboration of the appropriate allene or conjugated diene. In order to demonstrate the synthetic utility of this hydroboration–allylboration sequence, these allylboranes were prepared with 9-BBN and the appropriate diene and then treated in situ with acetone. The results (Table IV) show that the desired homoallylic alcohols are produced in good yield. Consequently, the allylboration sequence offers a very simple method for preparing relatively complex homoallylic alcohols.

The formation of rearranged homoallylic alcohols from unsymmetrical allylboranes has been accounted for by Mikhailov in terms of a six-centered transition state mechanism (eq 5).[4] The possibility of the six-centered mechanism, along



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with the enhanced Lewis acidity of the allylboranes, may account for their ability to add easily to carbonyl derivatives, whereas normal trialkylboranes do not.[18]

The allylboration sequence offers certain advantages over the more familiar Grignard route for the preparation of homoallylic alcohols. First, certain functional groups are better tolerated by the allylboration reaction. For example, the presence of halide substituents in the substrate should offer no difficulties, since the allylboration can be carried out in carbon tetrachloride or chloroform without difficulty. In addition, as pointed out later, the reactions with unhindered aldehydes and ketones are far faster than those with esters and amides. The former groups are readily allylborated in the presence of the latter. Secondly, the intermediate boronic ester is not strongly basic, as are the intermediates in the lithium or magnesium allylations. Thirdly, the workup conditions are extremely mild. Acidic hydrolysis agents are not required, and there are no problems with gels, emulsions, or extractions from

Table V. Allylboration of Carbonyl Derivatives with *B*-Allyl- and *B*-Crotyl-9-BBN

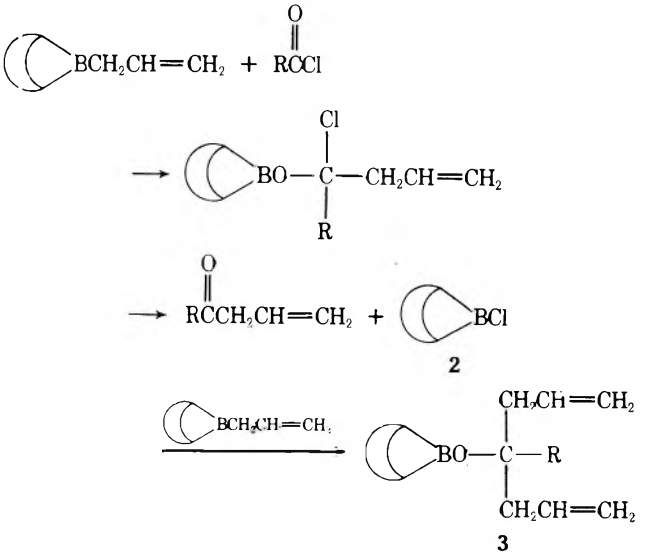
B-R-9-BBN, R	Substrate	Stoichiometry[a]	Product[b]	% yield (GLC)[c]
Allyl	Acetyl chloride	2:1	A	95
	Benzoyl chloride	2:1	B	89
	Acetic anhydride	4:1	A	95
	Benzoic anhydride	4:1	B	82
	Ethyl acetate	2:1	A	90
	Ethyl benzoate	2:1	B	50[d]
	N,N-Dimethylacetamide	2:1	A	50–57
	N,N-Dimethylbenzamide	2:1	B	91[e]
	B-Acetoxy-9-BBN	2:1	A	84
Crotyl	Acetyl chloride	2:1	C	93
	Acetic anhydride	4:1	C	97

[a] Allylborane to substrate. [b] A = 4-methyl-1,6-heptadien-4-ol, $n^{20}D$ 1.4518; B = 4-phenyl-1,6-heptadien-4-ol, $n^{20}D$ 1.5290; C = 3,4,5-trimethyl-1,6-heptadien-4-ol (mixture of diastereomers), $n^{20}D$ 1.4594. [c] Unless noted otherwise, the reaction mixture was stirred for 2 h at 25 °C before workup, even though the allylboration was generally complete in a few minutes. [d] After 50 h in refluxing *n*-hexane. [e] After 3 h at 25 °C.

aqueous hydrolysis media. Finally, the greater sensitivity to the steric environment should make possible more selective reactions.

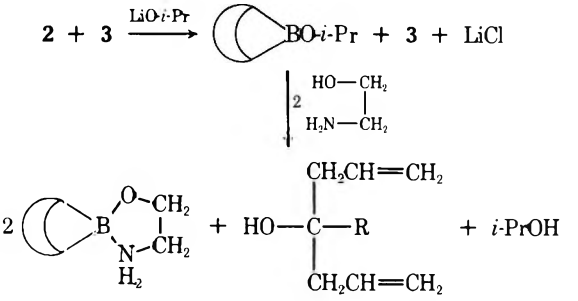
Allylboration of Acid Chlorides. *B*-Allyl-9-BBN reacts vigorously with acid chlorides. The stoichiometry of the reaction is two allylboranes to one acid chloride. The products of this reaction are 1 equiv each of *B*-chloro-9-BBN (**2**) and the 9-BBN borinic ester of the alkyldiallylcarbinol (**3**) (Scheme II).

Scheme II

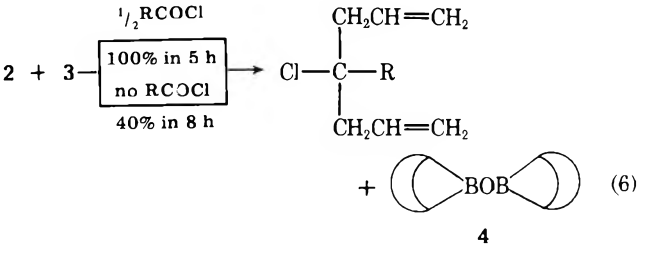


The presence of the chloroborane (**2**) necessitates a slight modification of the usual protonolysis procedure (eq 2). If 2 equiv of ethanolamine is added to the mixture of **2** and **3**, the protonolysis is incomplete, and the boron-containing products form a sticky gel. This is probably due to the formation of hydrogen chloride from the protonolysis of the chloroborane (**2**). To circumvent this difficulty, it is only necessary to add 1 equiv of lithium isopropoxide before adding the 2 equiv of ethanolamine. The lithium isopropoxide, chosen because it is soluble in hexane, reacts with the chloroborane forming lithium chloride and the isopropyl ester of 9-BBN borinic acid. The 2 equiv of ethanolamine then transesterifies both borinic esters liberating the alkyldiallylcarbinol and 2-propanol (Scheme III) (Table V).

Scheme III

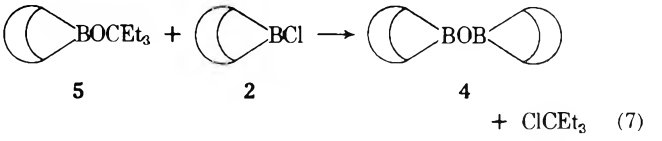


If the mixture of products from Scheme II is not worked up immediately after the reaction is complete, or if excess acid chloride is used, an interesting side reaction occurs (eq 6). It



should be emphasized that this side reaction can be entirely avoided by short reaction times and use of the exact stoichiometry.

Since the side reaction occurs only after long reaction times, it is probably due to a reaction between the products of the allylboration reaction (**2** and **3**). This was confirmed by the formation of triethylcarbinyl chloride from the reaction of **2** and **5** (eq 7). This reaction appears to be catalyzed by the acid

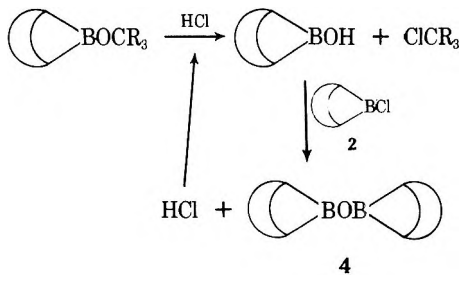


chloride, for when **2** and **5** are mixed, no reaction occurs even after 30 h. However, when 1 equiv of acetyl chloride is added, the formation of the tertiary chloride is complete in a few hours. Analyses by infrared and ^1H NMR show that the acetyl chloride is not consumed to any significant extent during the reaction. Furthermore, the chloride formation is only observed when the borinate ester is tertiary. When similar experiments were carried out with the *n*-butyl or *sec*-butyl esters of 9-BBN borinic acid, no *n*-butyl chloride or *sec*-butyl chloride were detected even after 15 days.

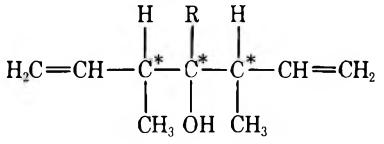
Although we did not carry out a detailed study of the tertiary chloride formation, it is probably produced by the cleavage of the borinate ester with hydrogen chloride formed by trace hydrolysis of the acid chloride or chloroborane. Lappert and Gerrard have shown that tertiary and benzylic borinate esters undergo carbon–oxygen cleavage with hydrogen halides, whereas secondary and primary borinate esters do not react under anhydrous conditions.[20] In the present case, such a cleavage can be a chain process (Scheme IV).

B-Crotyl-9-BBN reacts with acid chlorides in the same fashion as the parent *B*-allyl derivative. As noted earlier for aldehydes and ketones, complete allylic rearrangement of the crotyl moieties occur in the reaction with the acid chloride. GLC analyses of the products after protonolysis revealed a

Scheme IV



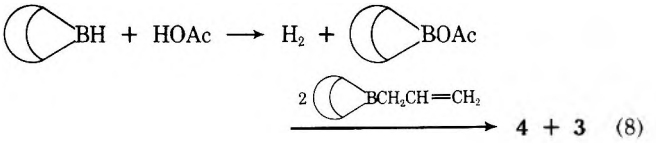
mixture. Fortunately, it was possible to isolate separately two of the major components by preparative GLC. ^{1}H NMR showed them to be diastereomers due to the juxtaposition of three asymmetric centers (**6**), not positional isomers.



Some preliminary attempts were made to stop the allylboration following the addition of but one allyl group. Unfortunately, these attempts failed. Even with reaction at low temperature with a 1:1 stoichiometry, only the diallylated product was observed.

Allylboration of Acid Anhydrides. *B*-Allyl-9-BBN reacts vigorously with acid anhydrides. The stoichiometry of the reaction is four allylboranes to one anhydride. The products, determined by ^{11}B NMR, ^{1}H NMR, and GLC, are 1 equiv of oxybis-9-BBN (**4**) and 2 equiv of the 9-BBN borinic ester of the alkyldiallylcarbinol (**3**). A possible reaction path leading to these products is outlined in Scheme V. Transesterification with 4 equiv of ethanolamine results in the formation of high yields of the corresponding alkyldiallylcarbinols (Table V). *B*-Crotyl-9-BBN reacts similarly; here again the addition occurs with complete allylic rearrangement of the crotyl moieties.

One step in our reaction mechanism (Scheme V) involves the allylboration of *B*-acetoxy-9-BBN (**7**). We tested this proposal by preparing this material (**7**) by an independent route, and then treated it with *B*-allyl-9-BBN in a 1:2 stoichiometry. The products anticipated were formed rapidly (eq 8). Attempts to stop the addition to acid anhydrides at the monoaddition stage were unsuccessful.



Allylboration of Carboxylic Acid Esters. *B*-Allyl-9-BBN reacts much more slowly with carboxylic acid esters than with the carbonyl derivatives discussed earlier. The stoichiometry is two allylboranes per ester. The products are 1 equiv each of the alkyldiallylcarbinyl ester of 9-BBN borinic acid (**3**) and the *B*-alkoxy-9-BBN ester (**8**) (Scheme VI). The usual transesterification with 2 equiv of ethanolamine affords good yields of the corresponding alcohols. The allylboration reaction is quite sluggish for aromatic carboxylic esters. For example, the allylboration of ethyl benzoate is incomplete even after 6 days at room temperature. In refluxing hexane, the reaction is 50% complete in 50 h. At higher temperatures, in *n*-nonane at reflux, the allylborane is consumed in 3 h. Unfortunately, side reactions occur, and the yield of the homoallylic alcohol, following transesterification, is only 28%. Attempts to stop the allylboration at the monoaddition stage were not successful.

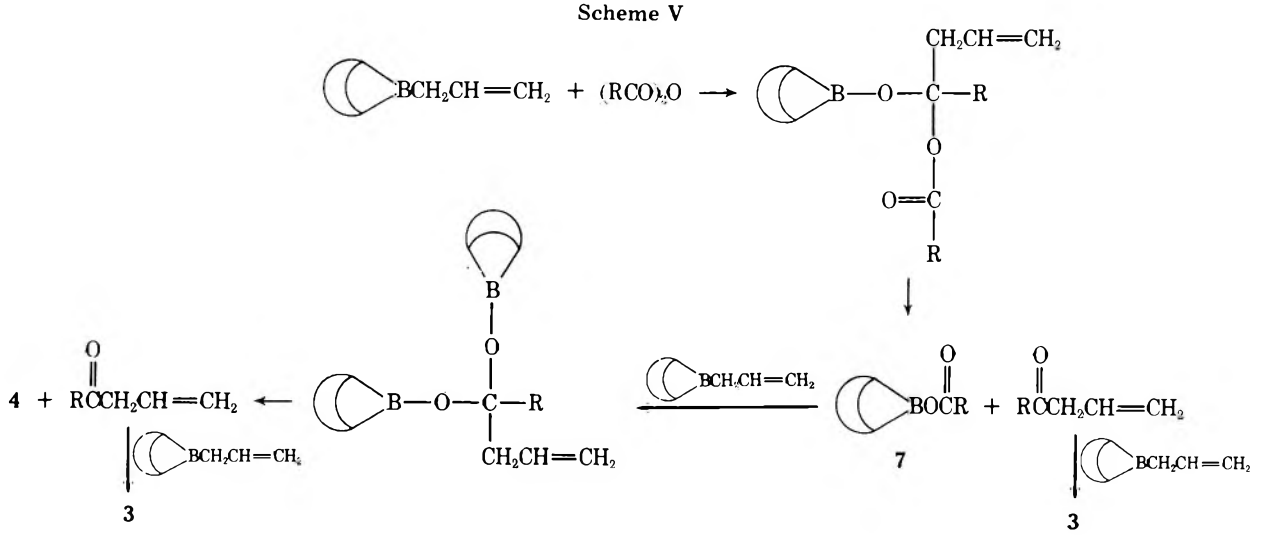
Allylboration of *N,N*-Dimethylamides. *B*-Allyl-9-BBN reacts slowly with *N,N*-dimethylbenzamide in a 2:1 stoichiometry. The products, as identified by ^{11}B NMR, ^{1}H NMR, and GLC, are 1 equiv each of *B*-*N,N*-dimethylamino-9-BBN (**9**) and the diallylphenylcarbinyl ester of 9-BBN borinic acid (Scheme VII). Transesterification wth ethanolamine produces the corresponding homoallylic alcohol and dimethylamine.

In contrast to the straightforward allylboration of *N,N*-dimethylbenzamide, the reaction with *N,N*-dimethylacetamide is complex. The stoichiometry appears to be two allylboranes to one amide. Analysis of the reaction mixture by ^{1}H NMR shows evidence of several competing reactions. The exact nature of these reactions, as well as the identities of all of the products, is not known at present. Transesterification of the reaction mixture affords only a 50% yield of the expected diallylmethylcarbinol.

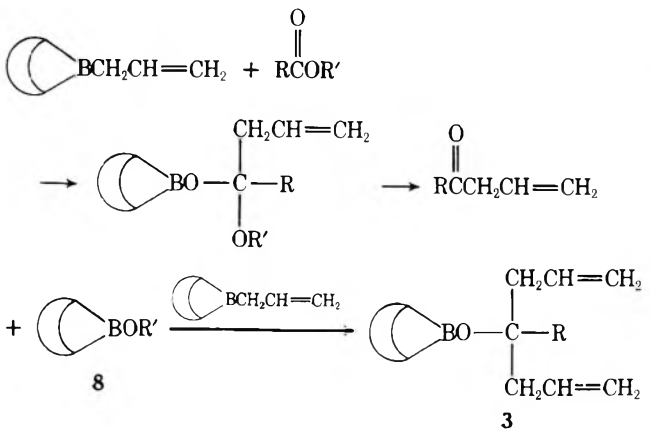
Summary

The allylborations of carbonyl compounds with *B*-allyl derivatives of 9-BBN, followed by transesterification with ethanolamine, provides a simple, convenient method for the synthesis of homoallylic alcohols. Unsymmetrical allylboranes show complete allylic rearrangement of the allyl moiety during addition. The tolerance of the allylboration reaction to certain functional groups, as well as its very mild reaction and workup conditions, make it competitive with the more familiar Gri-

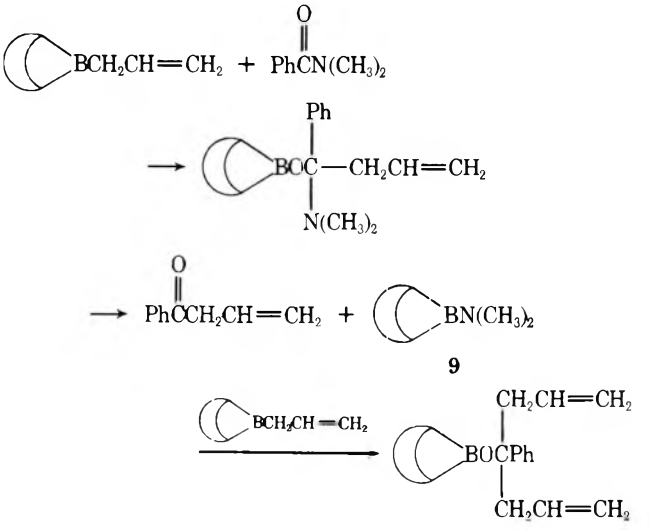
Scheme V



Scheme VI



Scheme VII



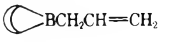
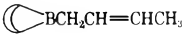
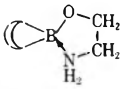
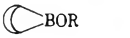
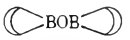
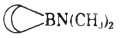
gnard allylations. Since many *B*-allyl derivatives of 9-BBN may be readily prepared via hydroboration of the appropriate allenes or conjugated dienes, the in situ hydroboration–allylboration sequence provides a simple, one-pot synthesis of many complex homoallylic alcohols.

Experimental Section

General Comments. The techniques described in Chapter 9 of ref 7 were used extensively. All glassware was dried at 140 °C for at least 4 h, assembled hot, and allowed to cool under a purge of prepurified nitrogen. The reaction flasks were fitted with side arms capped with rubber septa and were flamed out under a nitrogen purge immediately before use. All reactions were carried out under a static pressure of prepurified nitrogen. The transfers of liquids and solutions of organometallics were done either with oven-dried, nitrogen-purged hypodermic syringes fitted with stainless steel needles or by the double-ended needle technique.[7] All reactions were stirred magnetically using oven-dried, Teflon-coated stirring bars.

Materials. The solvents, allylboranes, and other organoboron derivatives used as standard samples for identification purposes were prepared as described previously.[8] Most of the aldehydes and ketones used in this study were commercial materials. All were purified by distillation, recrystallization and vacuum drying, or preparative GLC prior to use. The bicyclo[3.3.1]nonan-9-one was prepared as previously described.[21] Acetyl chloride, *N,N*-dimethylacetamide, ethyl acetate, and benzoyl chloride were distilled under nitrogen from calcium hydride. Acetic anhydride and ethyl benzoate were distilled under nitrogen from phosphorus pentoxide. The *N,N*-dimethylbenzamide was recrystallized from pentane. Benzoic anhydride, triethanolamine, and ethanolamine were used without purification. The simple *B*-alkoxy-9-BBN derivatives were prepared by treatment of 1 equiv of 9-BBN with 1 equiv of the corresponding alcohol (dried over 4 Å molecular sieves). Lithium isopropoxide in hexane was prepared by the addition of the calculated quantity of 2-propanol (dried over 3 Å molecular sieves) to a standardized solution of *n*-butyllithium in hexane.

Table VI. ^{11}B NMR Resonances of Pertinent 9-BBN Derivatives

Compd	^{11}B resonance, δ
	−85.6
	−86.0
	−5.7
	−82
	−56 to −52
	−55
	−16.4
	−47.7

Analyses. ^{11}B NMR spectra were recorded on a Varian XL-100-15 spectrometer (32.1 MHz) using a Nicolet 1080 data system. The spectra were recorded in the CW mode using ^{1}H, ^{2}H internal, or ^{19}F external locks; all chemical shifts are relative to $BF_3{\cdot}OEt_2$ (δ 0) with the chemical shifts downfield from $BF_3{\cdot}OEt_2$ assigned as negative (Table VI). ^{1}H NMR spectra were recorded on Varian T-60 (60 MHz) or Perkin-Elmer R-32 (90 MHz) machines, while ^{13}C NMR spectra were obtained on a Varian CFT-20 (20 MHz FT) spectrometer. Both the ^{1}H and ^{13}C NMR chemical shifts are relative to tetramethylsilane (δ 0).

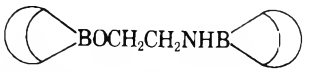
GLC analyses were generally carried out on a Hewlett-Packard 5752B chromatograph fitted with a Disc integrator using 6 ft × 0.25 in. stainless steel columns filled with 10% loaded packing on AW DMCS 60/80 Chromosorb W. Apiezon L and SE-30 were used for the analyses of the organoboranes, while Carbowax 20M, XE-60, SE-30, and DC-710 were used for the analyses of most of the homoallylic alcohols. The isomeric alcohols from the allylboration of 4-*tert*-butylcyclohexanone were analyzed on either DEGS or QF-1 columns, while the diastereomeric α-methallyl products were analyzed on DEGS or Carbowax 1540. The GLC analyses for the endo and exo norbornyl derivatives were carried out on a Perkin-Elmer 226 capillary chromatograph fitted with a 150 ft × 0.01 in. Golay column coated with DEGS. Quantitation of all GLC analyses was done by the internal standard method using appropriate normal hydrocarbons (usually *n*-octane or *n*-decane) as standards. Preparative GLC was carried out on a modified Wilkins A-100 instrument using 5 ft × 0.5 in. columns filled with 10–20% loaded packing on AW DMCS 60/80 Chromosorb W. The following liquid phases were used: SE-30, XE-60, DC-710, and DEGS.

Mass spectra were obtained from Hitachi Perkin-Elmer RMU6-D (low resolution) or CEC 21-110 (high resolution) spectrometers. Exact mass determinations were done by peak matching technique using PFK standard.

In general the homoallylic alcohols products were identified either by comparison of their GLC retention times (on at least two columns of differing polarities) with those of commercial samples or samples prepared by the Grignard allylation of the corresponding ketone, or by isolation and characterization through their infrared, ^{1}H NMR, ^{13}C NMR, and mass spectra. The identification of the isomeric alcohols from the allylboration of 4-*tert*-butylcyclohexanone, as well as the threo and erythro products from the crotylboration of aldehydes, is based on the GLC retention time data of Abenhaim.[16] The assignments of the exo and endo homoallylic alcohols from norcamphor were established as follows. The allylboration product was compared by GLC retention times (spiked injection) with the product from the Grignard allylation. It was assumed that the Grignard reaction would give almost exclusively the endo alcohol.[22] The ^{13}C NMR spectra of the allylboration product, and the Grignard allylation product, were identical and were consistent with the spectra expected for a single isomer. A sample of the exo alcohol was prepared from the endo alcohol by conversion to the tertiary chloride followed by solvolysis in an aqueous buffer [23]

Isolation and Characterization of 1. The white solid remaining after transesterification of a ketone allylboration was dissolved in THF, then reprecipitated by the addition of cold pentane. The solid

was filtered, washed twice with cold pentane, recrystallized from pentane–THF, and vacuum dried at 25 °C (15 mm) for 6 h (mp 202–203.5 °C with decomposition in a sealed evacuated capillary). Anal. Calcd for $C_{10}H_{20}BNO$ (181.092): C, 66.32; H, 11.13. Found: C, 66.25; H, 11.19. ^{11}B NMR (THF) δ −5.7. ^1H NMR (C_3D_6O) δ 4.9 (broad, ~2), 3.75 (t, 2, J = 6 Hz), 3.0 (m, 2), 1.77 (methylene envelope, ~12), 0.51 (m, ~2, bridgehead hydrogens). *m/e* M^+. Calcd for $^{12}C_{10}{}^1H_{20}{}^{11}B^{14}N^{16}O$: 181.1638. Found: 181.1644. This material underwent a partial reaction in the mass spectrometer: evidently two molecules of 1 combine with the elimination of ethanolamine to form



which gives high mass ions containing two boron atoms. M^+ calcd for $^{12}C_{18}{}^1H_{33}{}^{14}N^{16}O^{11}B_2$: 301.2748. Found: 301.2723. Calcd for $^{12}C_{18}{}^1H_{33}{}^{14}N^{16}O^{11}B^{10}B$: 300.2785. Found: 300.2762.

Allylboration of Aldehydes and Ketones. General Procedure (5-mmol Scale). To an oven-dried, nitrogen-flushed, flamed-out, 25-mL flask fitted with a septum inlet, a magnetic stirring bar, and topped with a connecting tube leading to a mercury bubbler, there was added a weighed amount of neat *B*-allyl-9-BBN derivative (~5 mmol). About 15 mL of dry, olefin-free pentane was added and 0.5 mL of the *n*-alkane (GLC internal standard). Stirring was begun, and the calculated amount of the neat carbonyl derivative (1 equiv) was added dropwise from a syringe.[24] The progress of the reaction was monitored by GLC. In most cases the reaction appeared to be complete in a few minutes, but the mixtures were generally allowed to stir for 2 h to ensure completion. One equivalent of neat ethanolamine was added from a syringe.[25] After stirring for about 1 h, the supernatant liquid was analyzed by GLC. The supernatant liquid was then decanted and the precipitate washed (2 × 10 mL) with pentane. The combined extracts were concentrated under a stream of nitrogen, then bulb-to-bulb distilled. The distillate, consisting normally of the homoallylic alcohol and the GLC internal standard, was subjected to a preparative GLC separation. The alcohol fraction, which was generally analytically pure, was used for the determination of spectra and the GLC correction factors. Even with product losses due to the small reaction scale and inefficiencies in the preparative GLC collections, the isolated yields were always over 60%. In preparative reactions, where no GLC internal standard is employed, the products are easily isolated in excellent yield by simple distillation. If the precipitate (1) is carefully removed, the products are normally analytically pure after removal of the pentane.

Allylboration of Pivaldehyde (23.3-mmol Scale). Following the general procedure given above, 3.775 g (23.3 mmol) of *B*-allyl-9-BBN was dissolved in about 25 mL of dry, olefin-free pentane in a 50-mL flask. This flask was immersed in a cold water bath where 2.60 mL (23.3 mmol) of freshly distilled pivaldehyde was added dropwise from a syringe to the stirred solution. The cooling bath was removed when the addition was complete, and the mixture was stirred for 1 h at 25 °C. Neat ethanolamine (1.40 mL, 23.3 mmol) was added dropwise from a syringe. After a few minutes, the thick, white precipitate of 1 had formed. This slurry was stirred for 0.5 h, then the contents of the reaction flask were poured into a 50-mL centrifuge tube. The flask was rinsed into the tube with ~10 mL of pentane. After centrifugation, the supernatant liquid was decanted and ~15 mL of pentane added to the tube. The solid was stirred, then the tube was centrifuged. This washing procedure was repeated three times. The combined extracts were concentrated under a stream of nitrogen and the residual oil subjected to simple vacuum distillation. Only one fraction, 2.53 g (85%), of a clear liquid, bp 55.5–56 °C (19 mm), was collected. GLC analysis of the product (n^{20}_D 1.4379) showed it to be 99.9+% pure. The IR and ^1H NMR spectra were consistent with the structure of 2,2-dimethyl-5-hexen-3-ol. The allylic methylene protons are not magnetically equivalent; therefore the α-hydroxy methine hydrogen appears as a doublet. ^1H NMR (CCl_4) δ 0.96 (s, 9, *t*-Bu), 1.97 (s, 1, OH), 2.25 (m, 2, allylic methylenes), 3.28 (dd, 1, J_1 = 8 Hz, J_2 = 2.5 Hz, methine), 5.02, 5.23, 5.9 (m, 3, terminal alkene); IR 3448 (OH), 1642 (C=C), 1381, 1368 (*t*-Bu), 995, 913 cm^{-1} (terminal double bond).

Allylboration of Acid Anhydrides, Esters, and *N,N*-Dimethylamides. General Procedure (5-mmol Scale). These reactions were carried out under essentially the same conditions as described above with the reaction stoichiometries adjusted as necessary. During the addition of the acid anhydrides, it was necessary to cool the reaction flask in a cold water or ice bath to prevent the solvent from boiling.

Allylboration of Acid Chlorides. General Procedure (5-mmol Scale). These reactions were carried out as described above up through the addition of the acid chloride. It was necessary to cool the reaction flask to prevent the solvent from boiling during this addition. The reaction mixture was allowed to stir for 1 h, and then 1 equiv of lithium isopropoxide in hexane was added dropwise from a syringe. After stirring for about 15 min, 2 equiv of ethanolamine was added and the reaction mixture worked up and analyzed in the usual manner.

In Situ Hydroboration–Allylboration Sequence. To an oven-dried, flamed-out, nitrogen-flushed, 25-mL flask fitted with a magnetic stirring bar, septum inlet, and topped with a connecting tube leading to a mercury bubbler, there were added 11.6 mL of 0.43 M 9-BBN in pentane (5.0 mmol), 0.5 mL of the GLC internal standard, and 5.0 mmol of the allene or diene. Stirring was begun and the progress of the hydroboration monitored by GLC. In all cases, the amount of residual diene remained constant after 24 h. Then 0.37 mL (5.0 mmol) of acetone was added. The mixture was worked up either by the usual transesterification procedure with ethanolamine or by the normal oxidative procedure using 3 M aqueous sodium hydroxide and 30% hydrogen peroxide.[7]

Acknowledgment. We thank the National Science Foundation for the support of this work under Grant GP 41169X. We also thank Professor R. A. Benkeser for helpful discussions involving this work.

Registry No.—**1**, 61967-22-4; 1 coordination form, 62059-31-8; *B*-allyl-9-BBN, 53317-08-1; pentanal, 110-62-3; pivalaldehyde, 630-19-3; benzaldehyde, 100-52-7; 2-butenal, 4170-30-3; acetone, 67-64-1; 3,3-dimethyl-2-butanone, 75-97-8; 1-phenylethanone, 98-86-2; diphenylmethanone, 119-61-9; 2,4-dimethyl-3-pentanone, 565-80-0; 2,2-dimethyl-3-hexanone, 5405-79-8; 2,2,4-trimethyl-3-pentanone, 5857-36-3; 2,2-dimethyl-1-phenyl-1-propanone, 938-16-9; 2,2,4,4-tetramethyl-3-pentanone, 815-24-7; cyclopentanone, 120-92-3; cyclohexanone, 108-94-1; cycloheptanone, 502-42-1; 4-*tert*-butylcyclohexanone, 98-53-3; norcamphor, 497-38-1; bicyclo[3.3.1]nonan-9-one, 17931-55-4; 3-buten-2-one, 78-94-4; 3-penten-2-one, 625-33-2; 4-methyl-3-penten-2-one, 141-79-7; *B*-crotyl-9-BBN, 61967-28-0; formaldehyde, 50-00-0; 2-methylallyl-9-BBN, 61967-13-3; 3,3-dimethylallyl-9-BBN, 55454-18-7; 3,3-dimethyl-1-isopropylallyl-9-BBN, 61967-14-4; 2-cyclohexen-1-yl-9-BBN, 61967-15-5; 2,4-dimethyl-4-penten-2-ol, 19781-53-4; 2,3,3-trimethyl-4-penten-2-ol, 36934-19-7; *trans*-2,3,3,6-tetramethyl-4-hepten-2-ol, 61967-16-6; *cis*-2,3,3,6-tetramethyl-4-hepten-2-ol, 61967-17-7; 2-(2-cyclohexenyl)-2-propanol, 5723-91-1; 1,3-cyclohexadiene, 592-57-4; 3-methyl-1,2-butadiene, 598-25-4; 2,5-dimethyl-2,4-hexadiene, 764-13-6; acetyl chloride, 75-36-5; benzoyl chloride, 98-88-4; acetic anhydride, 108-24-7; benzoic anhydride, 93-97-0; ethyl acetate, 141-78-6; ethyl benzoate, 93-89-0; *N,N*-dimethylacetamide, 127-19-5; *N,N*-dimethylbenzamide, 611-74-5; *B*-acetoxy-9-BBN, 62015-69-4; 4-methyl-1,6-heptadien-4-ol, 25201-40-5; 4-phenyl-1,6-heptadien-4-ol, 38400-77-0; 3,4,5-trimethyl-1,6-heptadien-4-ol, 756-43-4; BBN-9-ylaminoethoxy-9-BBN, 61967-18-8; ethanolamine, 141-43-5.

References and Notes

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(10) The remarkable air stability of this material is probably a result of the chelate structure.
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(14) The axial–equatorial ratio of products from the Grignard allylations is dependent on the reaction temperature.[15] It is reported to be 50.3:49.7 at 35 °C;[15] in our study we found it to be 54.3:45.7 in refluxing ether.
(15) M. Cherest and H. Felkin, *Tetrahedron Lett.*, 2205 (1968).
(16) D. Abenhaim, E. Henry-Basch, and P. Freon, *Bull. Soc. Chim. Fr.*, 4043,

4038 (1969).
(17) B. M. Mikhailov and V. F. Pozdnev, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1477 (1967), *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1428 (1967).
(18) it has recently been reported that *B*-vinyl derivatives of 9-BBN add in a 1,2 manner to unhindered aldehydes to give allylic alcohols after hydrolysis.[19] While no mechanism was postulated, it is interesting that the addition occurs with complete retention of the stereochemistry in the vinyl moiety.
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(22) M.-H. Rei, Ph.D. Thesis, Purdue University, West Lafayette, Ind., 1967.
(23) E. N. Peters, Ph.D. Thesis, Purdue University, West Lafayette, Ind., 1972; E. N. Peters and H. C. Brown, *J. Am. Chem. Soc.*, **96**, 265 (1974).
(24) Solid carbonyl compounds were dissolved in the minimum amount of pentane or benzene and added to the reaction mixture.
(25) Excess ethanolamine should be avoided, since it makes the precipitate of **1** sticky and renders more difficult the extraction of the products.
(26) ^{1}H NMR and infrared spectra of all the homoallylic alcohols prepared may be found in the Ph.D. Thesis of G. W. Kramer, Purdue University, 1976.

Selective Transformation of Vicinal-Disubstituted Epoxides into Ketones by Homogeneous Rhodium Catalysts[1]

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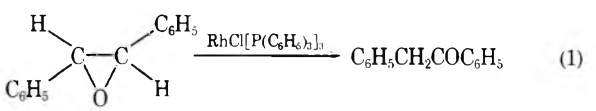
Chlorotris(triphenylphosphine)rhodium has been shown to catalyze the selective rearrangement of many vicinal-disubstituted epoxides to ketones between 150 and 210 °C. Kinetic measurements for various *trans*-1,2-diarylethylene oxides and $RhCl(PAr_3)_3$ catalysts were carried out. The reaction rate was shown to increase by introduction of electron-donating substituents into either the catalyst ligands or the substrate. The catalysis is inferred to proceed in the following order: (a) dissociation of $RhCl(PAr_3)_3$, (b) reversible nucleophilic cis addition of the epoxide to the activated catalyst to give a Rh(III) hydride, (c) intramolecular hydrogen transfer from the rhodium atom to the noncoordinated oxirane carbon, (d) reductive elimination to form the ketone and activated catalyst. The data are compatible with the expression rate = $k_1k_2[S][C]_0/(k_{-1} + k_2 + k_1[S])$ where [S] and $[C]_0$ are substrate and initial catalyst concentration, respectively. Step c is considered rate determining on the basis of kinetic isotope effect measurements. Complexes $RhCl(PAr_3)_3$ have been shown to catalyze also an unusual carbon–carbon bond cleavage in stilbene oxides having potent electron-attracting substituents to yield benzaldehydes and polymers. Epoxides in which one aromatic ring is more electron attracting than the other form aldehydes with the least electronegative groups.

Ring opening of epoxides by acids, bases, and salts has been extensively studied and reviewed.[2] In recent years some transition metal complexes have been shown to cleave catalytically C–O bonds in the oxirane system.[3] However, only in a few cases could the activities of the metal complexes be attributed to other than their acidic properties.

In this paper we present a detailed investigation on the transformation of vicinal-disubstituted ethylene oxides by the nonacidic $RhCl[P(C_6H_5)_3]_3$, including kinetic measurements and mechanistic studies on a selective isomerization of some stilbene oxides to deoxybenzoins. In addition we describe an epoxide system in which the C–C bond is cleaved in addition to the C–O linkage.

Results

Conversion of Epoxides to Ketones. While both acid- and base-catalyzed isomerization of *trans*-stilbene oxide gives usually diphenylacetaldehyde as the main product,[2c,4,5] the $RhCl[P(C_6H_5)_3]_3$-promoted reaction affords 88% deoxybenzoin, simply by heating 1 mol of the epoxide under N_2 with 2×10^{-2} mol of rhodium complex for 2 h at 210 °C. The only by-products in reaction 1 are diphenylmethane (7.9%),



(1)

trans-stilbene (2.8%), *cis*-stilbene (0.3%), and benzene (1.0%). Although $RhCl[P(C_6H_5)_3]_3$ has been assumed to liberate HCl in some other catalyses,[6] we could prove that no such decomposition is taking place in our system. The addition of a weak base to the reaction mixture that is able to remove any HCl that might have been formed, but is refractory toward the rhodium catalyst (e.g., 2,6-di-*tert*-butylpyridine), has no effect whatsoever on the results. On the other hand, addition of minute amounts of gasous hydrogen chloride causes the stilbene oxide to rearrange mainly to diphenylacetaldehyde.[7]

The high selectivity in our catalysis is conditioned by the existence of an absolutely inert atmosphere. Experiments performed under 90% N_2 and 10% O_2 gave no more than 26.5% of the ketone. *cis*-Stilbene oxide, which proved to undergo different transformations than the trans isomer by bases and acids,[5] gives the same yield of deoxybenzoin when the Wilkinson catalyst is employed.

The scope and potential synthetic application of the catalysis for selective conversion of stilbene oxides into the rearranged ketones are demonstrated by the examples listed in Table I.

While stilbene oxides with electron-donating groups give results similar to those with the unsubstituted parent compound, 4-nitrostilbene oxide forms only little of the expected ketone and 3,3′- as well as 4,4′-dinitrostilbene oxide give none at all. The negatively substituted epoxides undergo catalytic C–C bond cleavage which will be discussed below.

When two substituents of different electronic nature are being attached to the phenyl rings (one to each) the C–O bond that is closer to the more electron-donating group is expected to be the weaker one[2b] and to be cleaved preferentially. This is in fact observed in expt 5 and 6 (Table I): *trans*-4-chloro-4′-methylstilbene oxide yields 4-$ClC_6H_4COCH_2C_6H_4$-4-CH_3 and 4-$ClC_6H_4CH_2COC_6H_4$-4-CH_3 in ratio 7:3, and *trans*-4-

Table I. Catalytic Transformation of Stilbene Oxides $XC_6H_4\overline{CHOCHC_6H_4Y}$ in the Presence of $RhCl[P(C_6H_5)_3]_3$

Registry no.	Expt	Epoxide[a] X	Epoxide[a] Y	Reaction condition[b]	Products					
					$XC_6H_4CH_2COC_6H_4Y$	$XC_6H_4COCH_2C_6H_4Y$	$(XC_6H_4)(YC_6H_4)CHCHO$	$(XC_6H_4)(YC_6H_4)CH_2$	$XC_6H_4CH=CHC_6H_4Y$ Trans	$XC_6H_4CH=CHC_6H_4Y$ Cis
1439-07-2	1	H	H	A	87.9		0.0	7.9	2.8	0.3
1689-71-0	2	H[c]	H[c]	B	90.6		0.0	2.1	2.8	0.9
62006-50-2	3	4-Cl	4-Cl	C	80.3		0.2	3.5	4.7	0.0
62006-51-3	4	4-CH_3	4-CH_3	B	87.7		0.0	5.1	2.3	0.0
62006-52-4	5	4-CH_3	4-Cl	A	58.3	24.5	0.0	4.6	1.8	0.0
14985-26-3	6	4-NO_2	H	A	1.8	5.9	0.0	0.0	0.0	0.0

[a] Except in expt 2 trans oxides were used. [b] A, oxide to catalyst ratio $1:2 \times 10^{-2}$; 2 h at 210°C under N_2; no solvent. B, 1.5 M solution of oxide and 3×10^{-2} M catalyst in purified 1-methylnaphthalene; 2 h at 190°C under N_2. C, as in B at 210°C. [c] *cis*-Stilbene oxide.

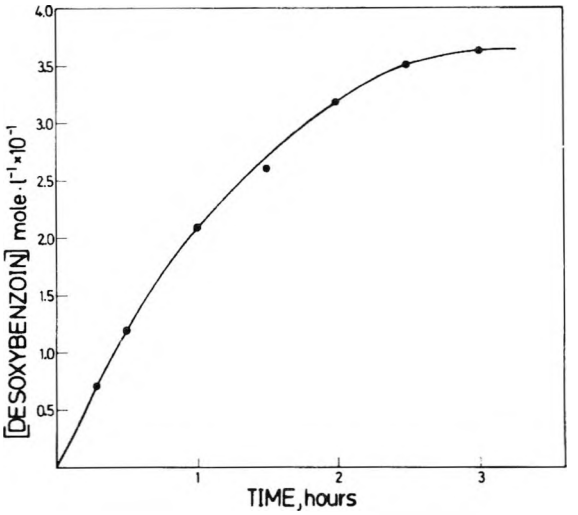


Figure 1. Concentration–time profile for deoxybenzoin formation: 0.382 M *trans*-stilbene oxide and 2.7×10^{-4} M $RhCl[P(C_6H_5)_3]_3$ in 1-methylnaphthalene at 200 °C.

nitrostilbene oxide gives 4-$NO_2C_6H_4COCH_2C_6H_5$ and 4-$NO_2C_6H_4CH_2COC_6H_5$ in ratio 13:4.

While many aromatic vicinal-disubstituted ethylene oxides react as smoothly as stilbene oxide in the presence of $RhCl[P(C_6H_5)_3]_3$, cycloalkene oxides open up rather slowly. Cyclohexene oxide, e.g., forms only 15, 22 and 36% of cyclohexanone when heated with the catalyst at 210 °C for 2, 3, and 15 h, respectively. (By-products in this reaction were 3.8–4.7% cyclopentane and 0.3–0.5% cyclopentanecarboxaldehyde.) This system, cleaves, however, more efficiently when $RuCl_2[P(C_6H_5)_3]_3$ is employed. (After 2 h, 1 mol of epoxide and 10^{-2} mol of catalyst give 67.8% ketone, 0.8% cyclopentane, 3.6% aldehyde, and 27.8% starting material.)

For kinetic measurements the isomerization of *trans*-stilbene oxide was chosen. A typical reaction curve for the transformation of 0.382 M epoxide by 2.7×10^{-2} M $RhCl[P(C_6H_5)_3]_3$ in 1-methylnaphthalene at 200 °C is shown in Figure 1. Changes in rate are shown to be very small in the initial stages of the reaction but become significant when the catalysis advances.

Dependence on Epoxide and Catalyst Concentration. A plot of the initial rate against epoxide concentration is shown in Figure 2. The rate is first order in the epoxide as long as the concentration does not exceed 150 mM. At higher concentrations the dependence of initial rate on concentration decreases and approaches a constant value above 1 M. Such a plot can be represented by the equation rate = $A[S]/(B + [S])$, where [S] is epoxide concentration and A and B are constants. (At high dilution $[S] \ll B$ rate = $A[S]/B$, and when $[S] \gg B$ rate = A). The reciprocal function, i.e., rate^{-1} vs. concentration^{-1}, is linear and has a positive intercept (see, e.g., Figure 4). It can thus be concluded that no higher order than 1 appear in the rate law (rate^{-1} = $\alpha/[S] + \beta$; $A = \beta^{-1}$ and $B = \alpha/\beta$).

The dependence on catalyst concentration (at 160 °C) is shown in Figure 3. In typical experiments, in which 0.877 M epoxide in 1-methylnaphthalene was treated with varying amounts of catalyst, a linear rate increase was observed for low catalyst concentration. Above 0.02 M the rate increase proved to diverge from linearity. For a 0.12 M solution the rate approached its maximum value but decreased on further addition of $RhCl[P(C_6H_5)_3]_3$ to the reaction mixture. Similar rate dependence was reported for several reactions in which rhodium– and ruthenium–phosphine complexes were used as catalysts. In $RhCl[P(C_6H_5)_3]_3$-catalyzed hydrogenation of olefins[8] or in $RuCl_2[P(C_6H_5)_3]_3$-catalyzed transfer hydroge-

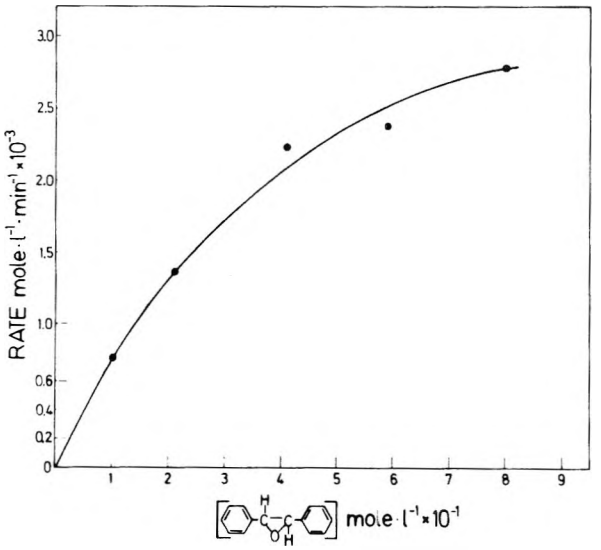


Figure 2. Dependence of initial rate of ketone formation on the concentration of *trans*-stilbene oxide in 1-methylnaphthalene at 200 °C. Catalyst concentration 1.125×10^{-4} M.

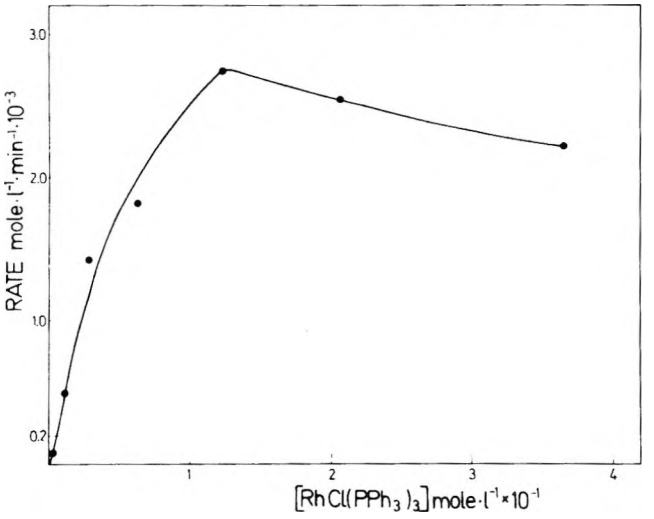


Figure 3. Rate dependence on the concentration of the rhodium catalyst at 160 °C. Initial concentration of *trans*-stilbene oxide 0.88 M.

nation of α,β-unsaturated ketones,[9] e.g., the relative slow increase in rate at high catalyst concentration was attributed to the low solubility of the catalysts[10] and to their tendency to form dimers and oligomers. Reaction 1 differs, however, from the reported ones in its *decrease* in rate after the maximum value has been reached. We assume that this phenomenon is associated with stilbene formation as a by-product (vide infra) which becomes of significance when the concentration of the phosphine-containing catalyst increases. The unsaturated hydrocarbon has been shown to react with the dissociated catalyst to give $(C_6H_5CH{=}CHC_6H_5)$-$RhCl[P(C_6H_5)_3]_2$ that has only low catalytic activity. (Cf. the inhibition of allylbenzene in $RuCl_2[P(C_6H_5)_3]_3$-catalyzed hydrogen transfer reactions.[9])

Dependence on Catalyst's Structure. The influence of the electronic structure of the catalyst was studied by utilizing complexes of the general formula $RhCl[4\text{-}X\text{-}C_6H_4)_3P]_3$ in reaction 1. The initial rates for a large range of epoxide concentration were recorded. The results of one set of experiments are listed in Table II.

Plots of the reciprocal of initial rate against the reciprocal of epoxide concentration are shown in Figure 4. The linear

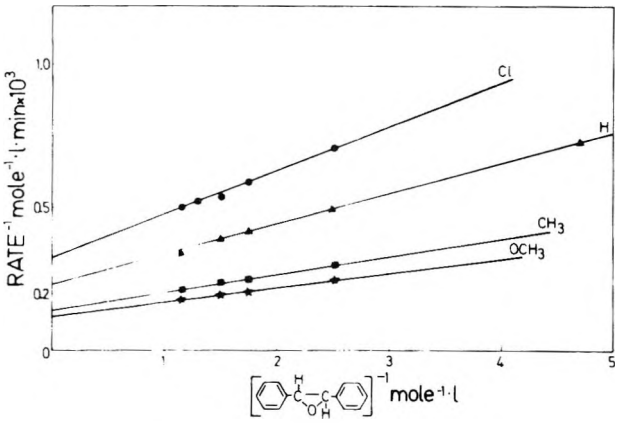


Figure 4. Plots of 1/initial rate against 1/epoxide 4-X-$C_6H_4CHOCHC_6H_4$-4-X concentration in the presence of 1.125×10^{-4} M catalyst in 1-methylnaphthalene at 200 °C (★, X = OCH_3; ■, X = CH_3; ▲, X = H; ●, X = Cl).

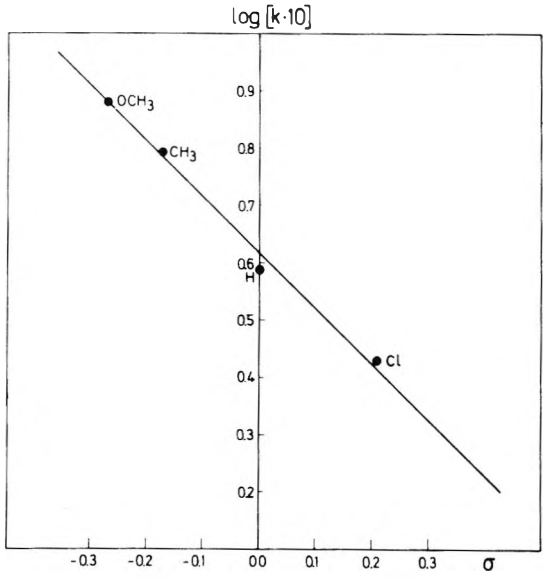


Figure 5. Hammett plot for reaction 1 using $RhCl[(4\text{-}X\text{-}C_6H_4)_3P]_3$ as catalysts. The σ values were taken from D. H. McDaniel and H. C. Brown, *J. Org. Chem.* **23**, 420 (1958).

Table II. Initial Rates of *trans*-Stilbene Oxide Rearrangement by Various Catalysts of Formula $RhCl[(4\text{-}X\text{-}C_6H_4)_3P]_3$ at 200 °C[a]

Registry no.	Substituent X	Initial rate, mmol L^{-1} min^{-1}
21481-17-4	OCH_3	5.60
24554-70-9	CH_3	4.67
16592-65-7	H	3.04
15008-65-8	Cl	1.89

[a] Reaction system was 0.877 M *trans*-stilbene oxide and 1.125×10^{-2} M rhodium catalyst in 1-methylnaphthalene.

dependence in all experiments suggests the same kinetics for the different catalysts employed. The rate constants k (see below) for the rate-determining step using 1.125×10^{-2} M $RhCl[(4\text{-}CH_3OC_6H_4)_3P]_3$, $RhCl[(4\text{-}CH_3C_6H_4)_3P]_3$, $RhCl[P(C_6H_5)_3]_3$, and $RhCl[(4\text{-}ClC_6H_4)_3P]_3$ at 200 °C are 0.76, 0.62, 0.39, and 0.27 min^{-1}, respectively. A quantitative representation of this electronic effect is obtained from the Hammett plot shown in Figure 5. The ρ value of −0.98 suggests partial positive charge stabilization on the rhodium atom in the rate-determining step.[11]

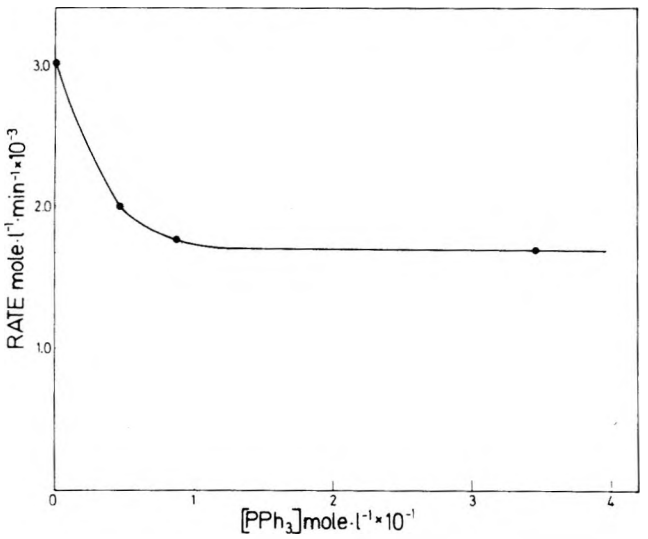


Figure 6. Effect of addition of triphenylphosphine on the initial rate. Reaction system: 0.986 M *trans*-stilbene oxide and 1.125×10^{-4} M catalyst in 1-methylnaphthalene at 200 °C.

Table III. Initial Rate of Rearrangement of Some Stilbene Oxides at 180 °C[a]

Epoxide	Initial rate, mmol L^{-1} min^{-1}
trans-4,4′-Dimethylstilbene oxide	4.77
trans-Stilbene oxide	2.46
trans-4,4′-Dichlorostilbene oxide	1.06

[a] Reaction system was 0.877 M epoxide and 2.055×10^{-2} M $RhCl[P(C_6H_5)_3]_3$ in 1-methylnaphthalene.

Dependence on Structure of the Epoxide. The data given in Table III indicate an increase in rate by introduction of electron-donating and decrease by electron-attracting substituents into the epoxide molecule. (The three epoxides listed were shown to have the same kinetics by virtue of the linear plots of rate^{-1} vs. concentration^{-1}.)

The rate constant for 4,4′-dimethyl-, unsubstituted, and 4,4′-dichlorostilbene oxide at (180 °C and 2.055×10^{-2} M rhodium catalyst) of 0.35, 0.18, and 0.07 min^{-1}, respectively, can be represented by a Hammett plot (log k vs. σ) with $\rho = -1.65$. This value suggests the formation of a *partial* positive charge rather than a real carbonium ion.[11]

The reaction rate is also affected by the *stereochemistry* of the substrate. For example, the initial rate of *cis*-stilbene oxide (0.850 M) isomerization at 170 °C by $RhCl[P(C_6H_5)_3]_3$ (2.25×10^{-2} M) in 1-methylnaphthalene is 13.8 mmol L^{-1} min^{-1}, while that of the trans isomer is only 1.50 mmol L^{-1} min^{-1} under the same conditions.

Kinetic Isotope Effect. The rates of isomerization of *trans*-stilbene oxide and of *trans*-α,α'-dideuteriostilbene oxide, $C_6H_5\overline{CDOCD}C_6H_5$, were compared at several concentrations. At 190 °C (substrate and catalyst concentration 0.85 and 1.125×10^{-2} M, respectively), e.g., the corresponding initial rates for the deuterated and nondeuterated compounds are 0.95 and 1.96 mmol L^{-1} min^{-1}. The ratio of reaction constants of the rate-determining step $k_H/k_D = 1.93$ ($k_H = 0.27$ and $k_D = 0.14$ min^{-1}, drawn, as shown below, from plots of rate^{-1} vs. concentration^{-1}) is typical for a hydride transfer reaction.[12] (Cf. also our study on $RuCl_2[P(C_6H_5)_3]_3$-catalyzed transfer hydrogenation reactions.[9]) This value diverges from those reported for proton transfer processes which usually have larger kinetic isotope effects.[12,13]

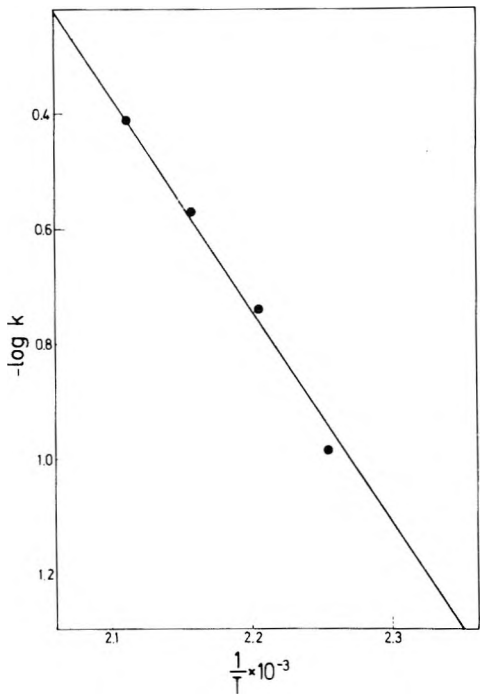


Figure 7. Arrhenius plot of *trans*-stilbene oxide rearrangement to deoxybenzoin at 170–200 °C.

Inhibition by Triphenylphosphine. The effect of addition of triphenylphosphine on the reaction rate is shown in Figure 6. The rate can be lowered to 0.56 of its original value but, in contrast to some other $RhCl[P(C_6H_5)_3]_3$-catalyzed reactions,[8,14,15] further addition of the phosphine has no effect on the catalysis.

Dependence on Temperature. Reaction 1 proved to take place under homogeneous conditions over a considerable range of temperatures, in essentially the same degree of selectivity. Initial rates were measured at 170, 180, 190, and 200 °C for several epoxide concentrations between 0.2 and 1 M. From the Arrhenius plot of log k against $1/T \times 10^{-3}$ (Figure 7) the activation energy $E_a = 17.1$ kcal mol^{-1} is obtained; $H^{\ddagger}$ (200 °C) = 16.2 kcal mol^{-1} and $S^{\ddagger}$ (200 °C) = −35.3 cal deg^{-1} mol^{-1}. Hence the general expression for $k = 5.14 \times 10^5 \cdot e^{-17.1/RT}$ s^{-1}. The greatly negative entropy of activation is uncommon for reactions in which both the starting material and the product are not polar. It may, therefore, be assumed that substantial increase in polarity and in steric strain is characteristic of the transition state of the catalysis.[16]

Side Reactions. Investigation of reaction 1 with 13 typical homogeneous catalysts (viz., $RhCl[P(C_6H_5)_3]_3$, $RhBr[P(C_6H_5)_3]_3$, $RhCl(CO)[P(C_6H_5)_3]_2$, $Rh[[(C_6H_5)_2PCH_2]_2]_2^+Cl^-$, $Rh_2(CO)_4Cl_2$, $RhCl_3[As(C_6H_5)_3]_3$, $RhCl_3 \cdot 3H_2O$, $RuCl_2[P(C_6H_5)_3]_3$, $IrCl(CO)[P(C_6H_5)_3]_2$, $PdCl_2[P(C_6H_5)_3]_2$, $PdCl_2$, $PtCl_2[P(C_6H_5)_3]_2$, and $Pt[P(C_6H_5)_3]_4$) revealed that transformation of the epoxide in high selectivity is limited to chloro- and bromotris(triphenylphosphine)rhodium(I) and chlorocarbonylbis(triphenylphosphine)rhodium(I). The other complexes gave a variety of products as shown in our preliminary report.[17]

The side products obtained from *trans*-stilbene oxide in the presence of $RhCl[P(C_6H_5)_3]_3$ are diphenylmethane (7.9%) and *trans*- and *cis*-stilbene (2.8 and 0.3%, respectively). The formation of the diphenylmethane is rationalized by assuming initial rearrangement of the epoxide to diphenylacetaldehyde followed by catalytic decarbonylation (eq 2).[18]

$$C_6H_5\underset{\diagdown O \diagup}{CH}—CHC_6H_5 \longrightarrow (C_6H_5)_2CHCHO \longrightarrow (C_6H_5)_2CH_2 + CO \quad (2)$$

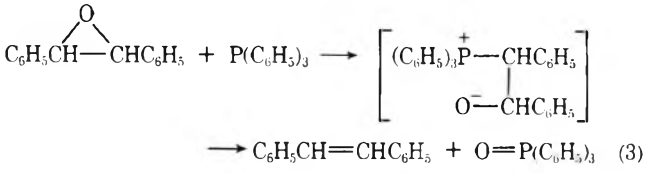
Table IV. Conversion of Some Substituted *trans*-Stilbene Oxides $XC_6H_4CHOCHC_6H_4Y$ into Benzaldehydes in the Presence of $RhCl[P(C_6H_5)_3]_3$[a]

Registry no.	Expt	Epoxide X	Epoxide Y	Products, % XC_6H_4CHO	XC_6H_5	YC_6H_4CHO	YC_6H_5
968-01-4	1	4-NO_2	4-NO_2	73.4	0.2		
	2	4-NO_2	H	5.2	0.1	0.5	25.6
13528-37-5	3	3-NO_2	3-NO_2	36.9	3.2		
	4	4-Cl	4-Cl	2.9	10.4		
	5	4-Cl	4-CH_3	0.0	0.1	0.0	5.5
	6[b]	H	H	0.0	1.0		

[a] Reaction conditions: 2 mmol of epoxide and 0.04 mmol of catalyst heated under N_2 (sealed pressure tube) at 210 °C for 2 h. [b] The cis isomer gives neither benzene nor benzaldehyde under these conditions.

In the rearrangement the rhodium catalyst is assumed to function as a weak Lewis acid. Therefore, it is not unexpected that catalysts of greater acidity than $RhCl[P(C_6H_5)_3]_3$ lead to higher yields of $(C_6H_5)_2CH_2$ and/or its precursor, $(C_6H_5)_2CHCHO$. For example, $RhCl_3[As(C_6H_5)_3]_3$, $Rh_2(CO)_4Cl_2$, $RhCl_3 \cdot 3H_2O$, and $PdCl_2$[19] give, under comparable conditions, 32.2, 36.4, 40.1, and 61.4% of $(C_6H_5)_2CH_2 + (C_6H_5)_2CHCHO$, respectively (see ref 17).

The formation of some stilbene along with the deoxybenzoin can be attributed to one or to several of the following processes: Wittig deoxygenation (eq 3)[20] may take place in the



$$C_6H_5CH(O)CHC_6H_5 + P(C_6H_5)_3 \longrightarrow [(C_6H_5)_3\overset{+}{P}-CHC_6H_5 \;\; O^{-}-CHC_6H_5] \longrightarrow C_6H_5CH{=}CHC_6H_5 + O{=}P(C_6H_5)_3 \quad (3)$$

presence of free triphenylphosphine liberated upon dissociation of the metal–phosphine complexes employed.[21,22]

The triphenylphosphine oxide formed may itself act as a deoxygenation agent.[23]

The stilbene obtained by the Wittig deoxygenation is expected to have the cis configuration;[24] however, the phosphine causes then isomerization to the trans compound. In a typical control experiment 1 mmol of *cis*-stilbene and 0.02 mmol of $P(C_6H_5)_3$ gave, at 210 °C (2 h, under N_2), a mixture of 96.8% *trans*- and 3.2% *cis*-stilbene. [Cf. also some other cis–trans interconversion reactions by $P(C_6H_5)_3$.[25]]

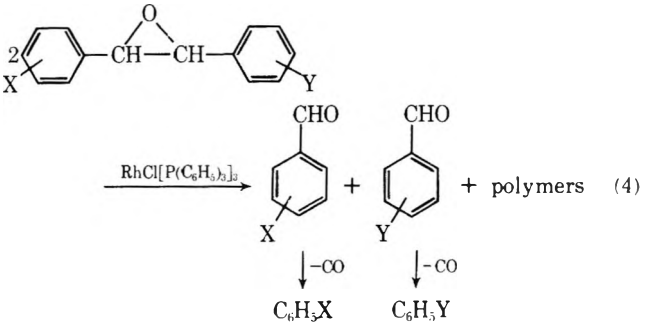
Since some complexes that do not have phosphate or arsine ligands prove also to deoxygenate stilbene oxide [$Rh_2(CO)_4Cl_2$,[17] $RhCl_3 \cdot 3H_2O$,[17] and $PdCl_2$[17] yield 12.4, 5.5, and 8.7% stilbene, respectively] it must be concluded that other than the Wittig deoxygenation takes part in olefin production as well. The formation of some CO_2 in the reaction tube suggests a mechanism which involves electrophilic attack of the metal at the epoxide oxygen, stepwise cleavage of the C–O bonds to give the olefin and a metal oxide, and oxidation of the CO [from $(C_6H_5)_2CHCHO$ decarbonylation] by the latter.[26,27]

Stilbene production by a few platinum metal complexes[17] (not $RhCl[P(C_6H_5)_3]_3$) may be attributed to their acidic properties[28] or to their ability to evolve hydrogen chloride at elevated temperatures.[6] (Cf. ref 7.)

By virtue of negative control experiments (at 210 °C) the possibility of thermal deoxygenation[29] in our catalysis must be excluded.

The most interesting side reaction is obviously a carbon–carbon bond cleavage in the oxirane ring.[30] Aldehydes and/or their decarbonylation products are formed in this process.

In stilbene oxides C–C cleavage is of significance only when electron-attracting substituents are present (see Table IV). Experiments 2 and 5 indicate that the cleavage of asymmetrically substituted epoxide yields preferentially the aldehyde with the less electronegative group. The *nitro*benzaldehydes proved to undergo least decarbonylation as expected from previous studies.[31]



$$2\,XC_6H_4CH(O)CHC_6H_4Y \xrightarrow{RhCl[P(C_6H_5)_3]_3} XC_6H_4CHO + YC_6H_4CHO + \text{polymers} \quad (4)$$

$$XC_6H_4CHO \xrightarrow{-CO} C_6H_5X \qquad YC_6H_4CHO \xrightarrow{-CO} C_6H_5Y$$

In contrast to *pyrolysis* of *trans*-stilbene oxide,[29] the benzylidene residues formed in reaction 4 do not yield the corresponding stilbenes but polymerize to macromolecular compounds. In expt 2, e.g., a polymer of mp 350 °C results which has the correct elemental analysis of $(CHC_6H_4NO_2)_n$.

Discussion

Following the mechanisms suggested for some other $RhCl[P(C_6H_5)_3]_3$-promoted reactions, we assume that (a) activation of the catalyst, (b) activation and reaction of the epoxide substrate, and (c) release of products are the major steps in our catalytic process.

Activation of the Catalyst. Controversial information on the dissociation of $RhCl[P(C_6H_5)_3]_3$ has been reported in the literature.[32] While, e.g., Arai and Halpern[33] found an equilibrium constant $K_{25} = 1.4 \times 10^{-4}$ M for reaction 5 in benzene, Tolman et al.[32] reported that $RhCl[P(C_6H_5)_3]_3$ does not dissociate to $RhCl[P(C_6H_5)_3]_2$ to a spectroscopically detectable extent at 25 °C but forms the chlorine-bridged dimer $[RhCl[P(C_6H_5)_3]_2]_2$.

$$RhCl[P(C_6H_5)_3]_3 \rightleftharpoons RhCl[P(C_6H_5)_3]_2 + P(C_6H_5)_3 \quad (5)$$

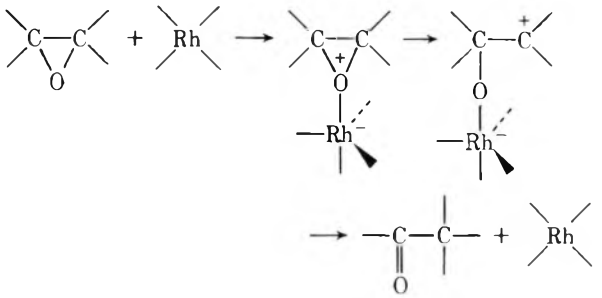
In our system, in which the trisphosphine complex is heated at ~170–220 °C *in the presence of an epoxide*, dissociation is fast and complete. The liberated $P(C_6H_5)_3$ is removed continuously as the oxide by reaction 3. On careful analysis of the reaction mixture of catalysis 1 nearly 1 mol of stilbene isomers and 1 mol of $O{=}PPh_3$ could be detected per each mol of $RhCl[P(C_6H_5)_3]_3$ employed. Owing to this phosphine–epoxide interaction even substantial quantities of added $P(C_6H_5)_3$ do not stop the catalysis (Figure 6) but cause formation of increasing amounts of stilbene which competes with the epoxide in occupying the active site in the catalyst. (Cf. the interference of ethylene in $RhCl[P(C_6H_5)_3]_3$-catalyzed hydrogenation[8] and the inhibition of catalytic transfer hydrogenation of chalcone by allylbenzene.[9])

The rhodium-containing complex formed on dissociation

of $RhCl[P(C_6H_5)_3]_3$ was subjected to molecular weight determination and found to be monomeric. We could show that no appreciable amounts of $[RhCl[P(C_6H_5)_3]_2]_2$ are formed. This observation has been confirmed by kinetic measurements which proved that in reaction 1 $RhCl[P(C_6H_5)_3]_3$ is a more active catalyst than the dimer.

In the presence of large excess of 1-methylnapththalene (solvent) the bisphosphine complex proved, by the mass spectrum, to be a solvate. We assume, therefore, that the active catalyst is—as originally proposed for other $RhCl[P(C_6H_5)_3]_3$-catalyzed reactions[14]—the solvate $RhCl[P(C_6H_5)_3]_2$solv, where "solv" represents either a molecule of the hydrocarbon or a non-fully coordinated epoxide.

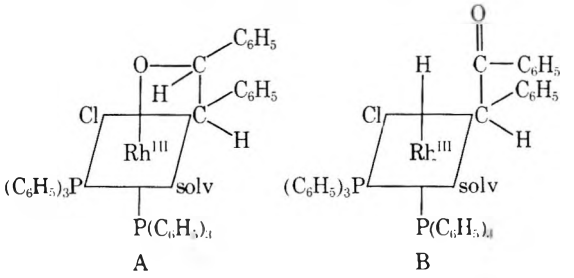
Coordination and Activation of the Epoxide. Initial coordination of the metal to the epoxide oxygen has been assumed[3n] to take place in the rearrangement of oxiranes by the Lewis acid[3k] $[Rh(CO)_2Cl]_2$ (eq 6). The intermediary of a stable



(6)

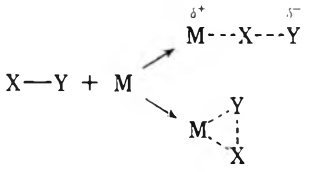
carbonium ion and migration of the most electron-releasing group to give an aldehyde can be regarded as a simple acid-catalyzed epoxide transformation. Chlorotris(triphenylphosphine)rhodium and the active solvated bisphosphine complex are, however, Lewis bases and therefore are not expected to coordinate in this manner to the epoxide heteroatom.

A second mechanism in which the relatively weak C–O bond[34] undergoes *oxidative addition* to the metal has been suggested for some iron-,[35] cobalt-,[3i] and nickel-catalyzed[30] transformations of the oxirane ring. Should $RhCl[P(C_6H_5)_3]_2$(solv) react in this way, one would expect a Rh(III) complex A to be formed that might in turn rearrange to complex B by β-hydrogen transfer. The ketone and regener-



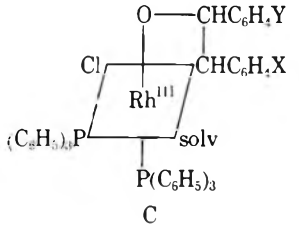
A B

ated active catalyst would then result by reductive elimination. In fact our results cannot be explained by such a mechanism. In consideration of the most probable intermediates in oxidative addition shown in eq 7,[36] the three-centered



(7)

mechanism must be ruled out right away on account of the observed electronic effect of substituents on the reaction rate. In the dipolar pathway, substituents that increase the nucleophilicity of the metal, or the electrophilicity of the substrate, should enhance the reaction rate. Assuming



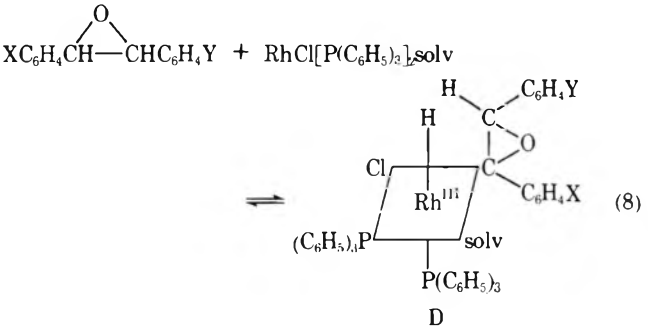
C

(X attracts electrons better than Y)

$RhCl[P(C_6H_5)_3]_2$(solv) to be a nucleophile in the oxidative addition of $XC_6H_4CHOCH_6H_4Y$ (X attracts electrons better than Y), the expected Rh(III) complex should have structure C and lead, upon reductive elimination, to $XC_6H_4CH_2CO$-C_6H_4Y and not to $XC_6H_4COCH_2C_6H_4Y$. We found, however, that the major product in the rearrangement of an asymmetrically substituted epoxide is the ketone which has the electronegative group closest to the carbonyl function (see Table I). Furthermore, Takegami et al.[35] have shown that the C–O bond in vicinal-disubstituted epoxides cannot undergo oxidative addition to iron carbonylates, owing to steric effects. It is thus obvious that C–O insertion cannot be an important step in our catalysis.

It is also improbable that insertion into the oxirane C–C bond occurs. Such oxidative addition is assumed to be the initial step in the cleavage of some stilbene oxides that form benzaldehydes as shown below.

The most probable mechanism that explains our results involves oxidative addition of an oxirane C–H bond to the rhodium catalyst.[37] Such addition to aliphatic and aromatic C–H linkages has been shown to be a nucleophilic process and to be promoted by electron-attracting groups.[37f] An oxirane C–H bond is by far a better electrophile than the corresponding aliphatic, or even aromatic, one. It can be compared in many respects to the C–H bond in aldehydes.[38] We suggest, therefore, that in our catalysis the epoxide is activated by *reversible*[37a] nucleophilic attack of the rhodium at the oxirane carbon atom having the lowest electron density as shown in eq 8.

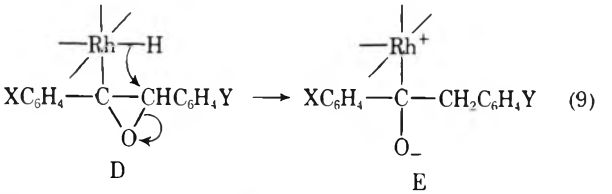


(8)

D

It should be noted, however, that while in such oxidative addition reactions the rate is expected to be increased by electron-attracting substituents, reaction 1 is accelerated by electron-releasing groups. Therefore, the epoxide activation cannot be the rate-determining step in the catalysis.

The Hydrogen Transfer Step. The rhodium intermediate D is now assumed to undergo a *slow* intramolecular β-hydride transfer from the metal to the noncoordinated oxirane carbon to yield a dipolar structure E. The observed kinetic isotope

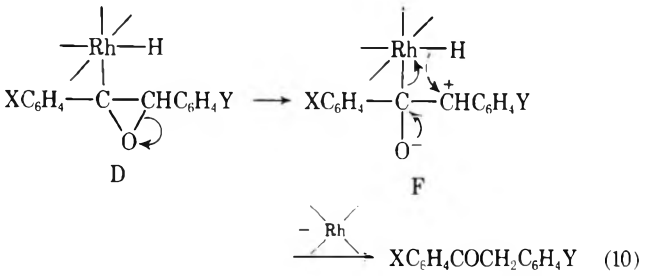


D E

(9)

effect supports this suggestion. α-Hydride transfer seems less probable as it would not account for the preferential formation

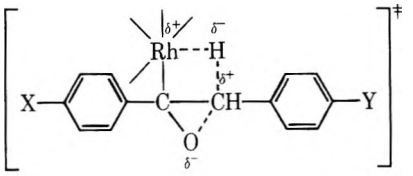
of deoxybenzoin with the electronegative group X attached to the *aroyl* moiety, and is also disfavored for steric reasons. Neither can *initial* C–O scission and formation of carbonium ion F (eq 10) rationalize our results. In this case the electronic



(10)

nature of the epoxide substituents is expected to affect primarily the formation of F, while it has already been shown, by virtue of the kinetic isotope effect (k_H/k_D = 1.93). that the rate-determining step is associated with the cleavage of a hydrogen linkage. Furthermore, the observed rate dependence on the electronic nature of the catalyst indicates that at least one ligand–rhodium bond is modified in the rate-controlling step (which is not the case when F is being formed). Both the calculated ρ value (−1.65) and the highly negative entropy of activation ($\Delta S^{\ddagger}$ = −35.3 cal deg^{-1} mol^{-1}) are uncommon in reactions that involve oxirane cleavage to a carbonium ion in the rate-determining step.[2b,11]

Acceleration of the catalysis by electron-donating groups on the substrate could indicate a *partial* positive charge on the activated complex of the hydrogen transfer step D → E, just as in the well-known "borderline S_N2" (or "loose S_N2") mechanism in which bond breaking has progressed further in the transition state than bond making.[39] Such a mechanism has often been suggested for nucleophilic substitution reactions in epoxides,[2b,c] and was attributed to the steric strain in the oxirane ring. These activated complexes were found to be always stabilized by incorporation of electron-releasing substituents into the substrate.



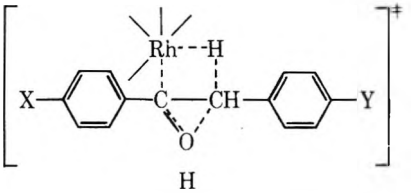
G

(X attracts electrons better than Y)

Structure G is thus the proposed transition state in step D → E. The C–O bond breaking is ahead of the C–H bond forming and, therefore, causes accumulation of a partial positive charge on the oxirane carbon atom. As expected, the formation of G is promoted by electron-releasing groups X and Y. This mechanism of hydrogen transfer in G is in full agreement with the observed kinetic isotope effect. It is known[40] that this effect results from changes in the activation energy of the process caused by differences in the zero-point energy when the reactants are converted to the activated complex, and it has been shown[8] that the zero-point energy of the C–H bond is larger than that of the Rh–H linkage by ~1.43 kcal/mol. Therefore, synchronous Rh–H breaking and C–H forming would lead to gain in zero-point energy and a reverse kinetic isotope effect (i.e., $k_H/k_D < 1$). The value k_H/k_D = 1.93 indicates that the C–H bond forming is less advanced than the Rh–H bond breaking and causes a partial negative charge location on the hydrogen. It is, however, unlikely that the hydrogen is being completely removed as H^- prior to some C–H bond formation, as this would give rise to a kinetic isotope effect of ~4 (as result of the difference of 0.86 kcal/mol in zero-point energy in Rh–H and Rh–D bonds[8]). The observed values suggests parallel, but not synchronous, formation of the C–H bond.

The assumption that a partial positive charge is formed on the rhodium atom in the rate-determining step is supported by the observation that substituents which increase the electron density on the metal accelerate the catalysis (ρ = −0.98). These groups stabilize the positive charge and facilitate hydride transfer.

An alternative five-centered mechanism for which structure H represents the transition state seems improbable. By this

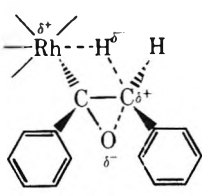


H

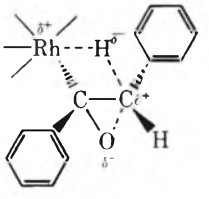
route the product would result by a single step reductive elimination coupled with nucleophilic attack on the oxirane ring, and groups that increase the electron density would be expected to decrease the reaction rate.

The highly negative entropy of activation ($\Delta S^{\ddagger}$ = −35.3 cal deg^{-1} mol^{-1}) may be rationalized by a combination of two factors: (a) increase in the polarity upon formation of the activated complex G from the reactants,[41] (b) the existence of a substantial steric hindrance. It must be assumed that the Rh–C bond is bent in the transition state, so that the heavily substituted rhodium atom is able to transfer its hydrogen to the oxirane carbon.

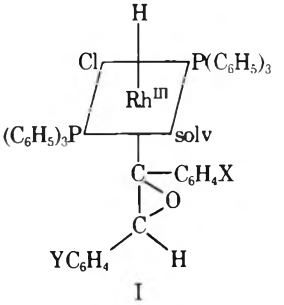
By comparison of $\Delta S^{\ddagger}$ for *trans*- and *cis*-stilbene oxide some interesting features of the stereochemistry of the corresponding activated complexes can be deduced. Since the cis oxide rearranges to deoxybenzoin 9.2 times faster than the trans isomer, it can be concluded that the activation entropy of *cis*-stilbene oxide is less negative than that of the trans compound, and the steric hindrance of the transition state of the latter is the greater one of the two. This is illustrated in structures G-c and G-t: in G-t hydrogen transfer from the substituted rhodium atom is hindered by a phenyl group; in G-c this interference does not exist. As G-c is derived from *cis*-stilbene oxide and G-t from the trans isomer, it can be concluded that the oxidative addition shown in eq 8 is cis addition, viz., hydride D is formed rather than I.



G-c

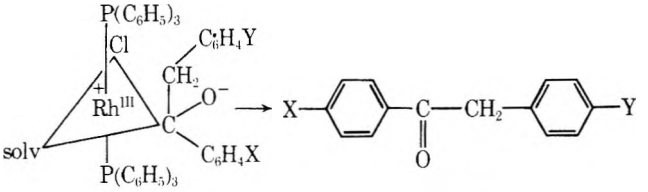


G-t



I

Release of the Product. In the final step E undergoes reductive elimination. The active Rh(I) catalyst is being reformed along with the rearranged ketone (eq 11).



E + $RhCl[P(C_6H_5)_3]_2solv$ (11)

(X attracts electrons better than Y)

The complete cycle of the catalytic rearrangement can thus be summarized by (a) fast oxidative cis addition of the epoxide to the active catalyst $RhCl[P(C_6H_5)_3]_2$, (b) slow intramolecular hydrogen transfer in D to give E, and (c) formation of product and active catalyst by fast reductive elimination.

Since under our experimental conditions $RhCl[P(C_6H_5)_3]_3$ dissociates completely in a practically irreversible fashion into the active catalyst, we can apply the kinetic Scheme I for our reaction.

Scheme I

$$C + S \underset{k_{-1}}{\overset{k_1\ (fast)}{\rightleftharpoons}} (CS)^1$$

$$(CS)^1 \xrightarrow{k_2\ (slow)} (CS)^2$$

$$(CS)^2 \xrightarrow{k_2\ (fast)} C + P$$

C, S, and P are catalyst, substrate, and product, respectively, and the rate law would be

$$\text{rate} = \frac{d[P]}{dt} = \frac{[k_2k_3/(k_2 + k_3)][C]_0[S]}{[(k_{-1} + k_2)/k_1][k_3/(k_2 + k_3)] + [S]}$$

where $[C]_0$ represents the initial concentration of $RhCl[P(C_6H_5)_3]_3$.

Since the first and final steps are much faster than the second one, i.e., $k_2 \ll k_3$ [though the relative rate of the reverse reaction $(CS)^1 \rightarrow C + S$ cannot be estimated], the rate law becomes

$$\text{rate} = \frac{k_2[C]_0[S]}{(k_{-1} + k_2)/k_1 + [S]}$$

and substituting $(k_{-1} + k_2)/k_1$ by K_A gives rate $= k_2[C]_0[S]/(K_A + [S])$. When $k_2 \ll k_1$, K_A represents the reciprocal of the equilibrium constant of the first step. This expression accounts for the observed rate dependence on the epoxide concentration shown in Figure 2. For very low concentration of the substrate ($[S] \ll K_A$) rate $= (k_2/K_A)[C]_0[S]$. This indicates that under these conditions the reaction is first order in the epoxide. When [S] increases ($[S] \gg K_A$) the rate approaches the constant $k_2[C]_0$ (see Figure 2).

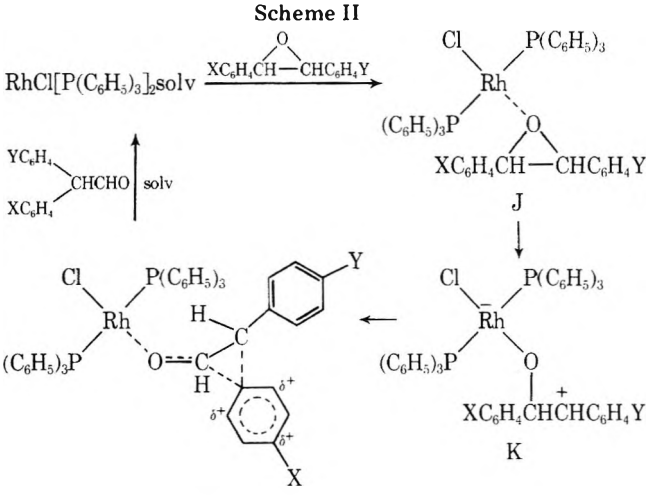
The rate expression is linear in the reciprocal form

$$\text{rate}^{-1} = [(K_A/k_2[C]_0)[S]^{-1}] + (k_2[C]_0)^{-1}$$

and $K_A/k_2[C]_0$ and $1/k_2[C]_0$ represent the corresponding terms α and β given above. The magnitude of k was thus obtained from the intercepts of the plot of rate^{-1} vs. epoxide concentration,[42] and K_A can be deduced from the gradient $K_A/k_2[C]_0$.

Finally we wish to comment upon the mechanisms of the main side reactions. As mentioned above the rearrangement of *trans*-stilbene oxide to diphenylacetaldehyde (eq 2) may be attributed to some Lewis acid character of the catalyst. Thus the mechanism of Grigg[3k,l,n] may be adopted: in the first step the active catalyst coordinates to the epoxide oxygen. Then the C–O bond that is closest to the electron-attracting group X is cleaved and aryl migration toward the electropositive center takes place (Scheme II).

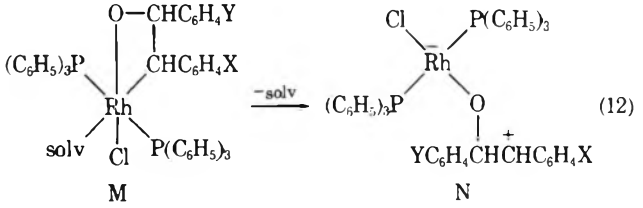
Scheme II



L

(X attracts electrons better than Y)

Formation of the dipolar structure may also result via an alternative route that includes oxidative addition to the C–O bond coupled with ring opening (M → N). However, since the nucleophilic nature of the oxidative addition would take place at the carbon atom that is closest to X and the resulting carbonium ion N is less stable than K, this mechanism is disfavored.



(12)

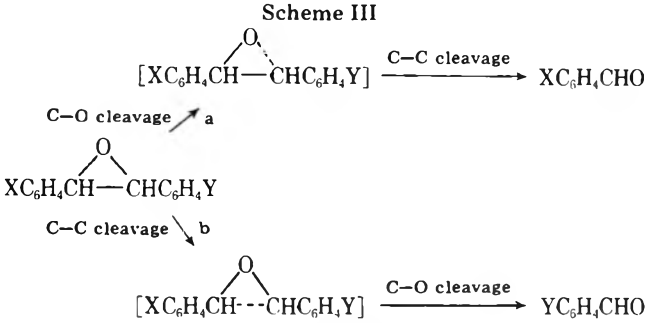
M N

The data given in Table IV indicate that the catalytic C–C bond cleavage in stilbene oxides (eq 4) depends strongly on the ability of substituents X and Y to withdraw electrons. A Hammett ρ value of +1.76 is obtained from a plot of log percentage C–C breaking vs. the sum of the substituent constants $\sigma_X + \sigma_Y$.

We have shown that reaction 4 is independent of reaction 1. The deoxybenzoins [e.g., 4-nitro-2-(4-nitrophenyl)acetophenone, $4\text{-}NO_2C_6H_4CH_2COC_6H_4\text{-}4\text{-}NO_2$] formed by the "normal" rearrangement of the epoxides, are not converted to benzaldehydes by $RhCl[P(C_6H_5)_3]_3$.

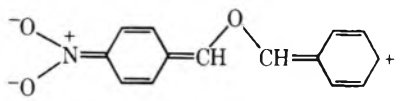
Upon transferring stilbene oxides to benzaldehydes the oxirane ring has to cleave both at the C–C and the C–O linkages. Thus, the question arises which of the two bonds is the first to break down. When it is the C–O bond the reaction follows *route* (*a*) in Scheme III and the resulting aldehyde

Scheme III

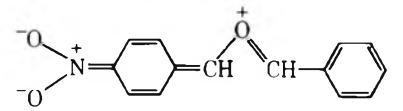


contains the utmost electron-attracting substituent X. As in fact the aldehyde with the least electron-attracting power is formed preferentially (see Table IV) it can be concluded that *route* (*b*) dominates the catalysis.

The weakness of the oxirane C–C bond in nitrostilbene has been explained by the mesomeric structures O and P.[43,44]

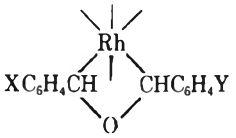


O



P

Since the analogue of P, in which a double bond is located between O^+ and the second methine group, is of low probability, the C–O bond that is closer to the nitrophenyl moiety is expected to cleave preferentially. The role of the metal catalyst in reaction 4 seems, therefore, to be associated primarily with the "trapping" or "freezing out" of the noncyclic epoxide mesomers, probably by formation of complexes of type Q. A platinum(II) analogue of Q has been isolated from the reaction of $Pt[P(C_6H_5)_3]_4$ and tetracyanoethylene oxide.[45]



Q

The C–O bond breaking is assumed to follow next; however, with the available evidence it seems premature to give the mechanism of this step.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are not corrected. Infrared and ultraviolet spectra were measured with Perkin-Elmer spectrophotometers Models 257 and 402, respectively. Proton magnetic resonance spectra were run using Varian EM-360 and HA-100 spectrometers. Mass spectra were recorded with a Varian MAT-311 spectrometer or directly from a gas chromatograph using a Varian MAT-111 instrument. Gas chromatography was performed with F & M Model 810 and Hewlett-Packard Model 7620A instruments (equipped with both thermal conductivity and flame ionization detectors).

The catalysts $RhCl[P(C_6H_5)_3]_3$,[8] $RhBr[P(C_6H_5)_3]_3$,[8] $RhCl[P(4\text{-}ClC_6H_4)_3]_3$,[47] $RhCl[P(4\text{-}CH_3C_6H_4)_3]_3$,[47] $RhCl[P(4\text{-}CH_3OC_6H_4)_3]_3$,[47] $RuCl_2[P(C_6H_5)_3]_3$,[48] $IrCl(CO)[P(C_6H_5)_3]_2$,[49] $PtCl_2[P(C_6H_5)_3]_2$,[50] and $Pt[P(C_6H_5)_3]_4$[50] as well as the starting and reference compounds *trans*-4-$ClC_6H_5CH{=}CHC_6H_4$-4-Cl,[51] *trans*-4-$CH_3C_6H_4CH{=}CHC_6H_4$-4-CH_3,[52] *trans*-4-Cl-$C_6H_4CH{=}CHC_6H_4$-4-CH_3,[53] *trans*-4-$NO_2C_6H_4CH{=}CHC_6H_4$-4-NO_2,[54] 4-$NO_2C_6H_4COCH_2C_6H_4$-4-NO_2,[55] 4-$NO_2C_6H_4CH_2COC_6H_5$,[55] 4-$NO_2C_6H_4COCH_2C_6H_5$,[55] $(4\text{-}ClC_6H_4)_2CHCHO$,[56] $(4\text{-}ClC_6H_4)_2CH_2$,[57] $(4\text{-}CH_3C_6H_4)_2CH_2$,[57] and 4-$ClC_6H_4CH_2C_6H_4$-4-$CH_3$[58] were prepared as previously described.

The following stilbene oxides were prepared by 3-chloroperbenzoic acid oxidation of the olefins.[59] ***trans*-Stilbene oxide:** mp 69–70 °C (lit.[60] 69–70 °C); ν_{C-O} (Nujol) 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.88 (s, 2), 7.38 ppm (s, 10). ***cis*-Stilbene oxide:** mp 38–39 °C (lit.[60] 37–37.5 °C); ν_{C-O} (Nujol) 892 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.37 (s, 2), 7.20 ppm (s, 10). ***trans*-4,4′-Dichlorostilbene oxide:** mp 120–121 °C (lit.[51] 123–124 °C); ν_{C-O} (Nujol) 840 cm^{-1}; ^1H NMR ($CDCl_4$) δ 3.67 (s, 2), 7.28 ppm (s, 8). ***trans*-3,3′-Dinitrostilbene oxide:** mp 157–159 °C (lit.[61] 156–158 °C); ν_{C-O} (Nujol) 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.03 (s, 2), 7.67 (m, 4), 8.22 ppm (m, 4).

***trans*-4,4′-Dimethylstilbene Oxide.** A solution of 2.08 g (10 mmol) of *trans*-4,4′-dimethylstilbene and 2.18 g (10.8 mmol) of 3-chloroperbenzoic acid (85%) in 40 mL of methylene chloride was stirred at 25 °C. TLC analysis [SiO_2, *n*-hexane–ethyl acetate (10:1) as eluent] indicated that the oxidation was completed after 20 h. The acids were extracted with 5% aqueous sodium bicarbonate; the organic layer was washed with water, dried, and concentrated. The residue was recrystallized (three times) from petroleum ether to yield 1.8 g (76%) of colorless needles: mp 92–93 °C; ν_{C-O} (Nujol) 875 cm^{-1}; ^1H NMR (CCl_4) δ 2.35 (s, 6), 3.65 (s, 2), 7.13 ppm (s, 8). Anal. Calcd for $C_{16}H_{16}O$: C, 85.7; H, 7.1. Found: C, 85.4; H, 7.2.

***trans*-4-Chloro-4′-methylstilbene Oxide.** A solution of 1.01 g (4.42 mmol) of *trans*-4-chloro-4′-methylstilbene and 0.99 g (4.87 mmol) of 3-chlorobenzoic acid (85%) in 40 mL of $CHCl_3$ and 5 mL of CH_2Cl_2 was stirred at 25 °C for 52 h and worked up as above to give 0.92 g (85%) of colorless plates: mp 96–97 °C; ν_{C-O} (Nujol 878 cm^{-1}; ^1H NMR ($CDCl_3$) δ 237 (s, 3), 3.83 (m, 2), 7.23 (s, 4), 7.33 ppm (s, 4). Anal. Calcd for $C_{15}H_{13}ClO$: C, 73.6; H, 5.4; Cl, 14.5. Found: C, 73.9; H, 5.4; Cl, 14.7.

***trans*-4,4′-Dinitrostilbene Oxide.** To a solution of 12.8 g of 4-nitrobenzaldehyde in 100 mL of benzene was added, at −70 °C, a solution of 6.8 g of tris(dimethylamino)phosphine in 15 mL of the same solvent. The mixture was brought slowly to 23 °C and stirred at this temperature for 18 h. The white precipitate (mp 203–204 °C) was recrystallized from ethyl acetate to give 5.6 g (46%) of isomerically pure trans epoxide (cf. ref 61) as colorless needles: mp 204–205 °C (lit.[61] 202–203 °C); ν_{C-O} (Nujol) 855 cm^{-1}; ^1H NMR ($AsCl_3$) δ 4.05 (s, 2), 7.88 ppm (q $A_2'B_2'$, 8).

***trans*-4-Nitrostilbene oxide** was prepared according to Bergmann and Hervey[62] from benzaldehyde and 4-nitrobenzyl chloride: mp 124.5–125.5 °C (lit.[62] 125–126 °C); ν_{C-O} ($CHCl_3$) 850, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.90 (d, 1, J = 2 Hz), 4.03 (d, 1, J = 2 Hz), 7.43 (s, 5), 7.93 ppm (q $A_2'B_2'$, 4).

***trans*-α,α′-Dideuteriostilbene Oxide.** A solution of 7.12 g (0.04 mol) of diphenylacetylene in 100 mL of *n*-hexane was converted into *cis*-α,α′-dideuterostilbene (95%) by 0.04 mol of D_2 in the presence of 0.6 g of Pd/C (10%). The catalyst was filtered off, the solvent was removed, and a crystal of iodine was added. The mixture was heated at 200 °C for 10 min and cooled to room temperature and the solid *trans*-α,α′-dideuteriostilbene was recrystallized from EtOH, yield 6.1 g (83%) of colorless prisms, mp 123–124 °C (lit.[63] 123.8–125 °C). To a solution of 4 g (22 mmol) of this compound in 100 mL of CH_2Cl_2 was added 4.8 g (24 mmol) of 3-chloroperbenzoic acid (85%) and the mixture left at 25 °C for 22 h. After neutralization with 5% aqueous $NaHCO_3$ and the usual workup the residue was chromatographed on Florisil (petroleum ether as eluent) to give 3.2 g (69%) of *trans*-α,α′-dideuteriostilbene oxide (90% d_2): mp 69–70 °C; ν_{C-O} 895 cm^{-1}; ^1H NMR (CCl_4) δ 7.30 ppm (s) (traces of ^1H compound showed up at 3.73 ppm); *m/e* 198 (M^+). Anal. Calcd for $C_{14}H_{10}D_2O$: C, 84.8; H + D,[64] 6.1. Found: C, 84.5; H + D, 6.2.

The catalytic transformation of the various vicinal-disubstituted epoxides studied is illustrated by the following example.

Reaction of *trans*-Stilbene Oxide and $RhCl[P(C_6H_5)_3]_3$. A pressure tube (wall thickness 5 mm) was carefully dried, washed with N_2, and charged with 196 mg (1 mmol) of freshly chromatographed *trans*-stilbene oxide and 18.5 mg (2×10^{-2} mmol) of $RhCl[P(C_6H_5)_3]_3$. Any traces of oxygen were removed from the reaction tube with the aid of a high vacuum line, and nitrogen was introduced at 1 atm, sealed, and immersed into an oil bath thermostat at 210 °C. The clear red-brown solution was cooled to room temperature and dissolved in CCl_4 (total volume 5 mL). GLC analysis was carried out with a 2-m long column packed with 15% stabilized DEGS on Chromosorb ST-164 operated at 228 °C, carrier gas (He) 70 mL/min. The reaction mixture proved to consist of 87.9% deoxybenzoin (retention time 490 s), 7.9% diphenylmethane (retention time 120 s), 2.8% *trans*-stilbene (retention time 370 s), and 0.3% *cis*-stilbene (retention time 145 s). The different products were isolated either by preparative GLC or by PLC on silica gel [EtOAc–*n*-hexane (1:4) as eluent].

The following substituted deoxybenzoins were isolated on 1-m long Apiezon L (20%) on Anakrom ABS (60–70 mesh) operated at 210–230 °C.

4-Chloro-α-(4′-chlorophenyl)acetophenone: mp 111–112 °C; $\nu_{C=O}$ (Nujol) 1688 cm^{-1}; ^1H NMR (CCl_4) δ 4.10 (s, 2), 7.12 (m, 4), 7.68 ppm (q $A_2'B_2'$, 4). The compound was compared with an authentic sample prepared according to Bergmann et al.[65]

4-Chloro-α-(4′-tolyl)acetophenone: mp 102–103 °C; $\nu_{C=O}$ (CCl_4) 1690 cm^{-1}; ^1H NMR (CCl_4) δ 2.30 (s, 3), 4.19 (s, 2), 7.12 ppm (s, 4). Anal. Calcd for $C_{15}H_{13}ClO$: C, 73.6; H, 5.3; Cl, 14.5. Found: C, 73.3; H, 5.1; Cl, 14.6. For comparison the ketone was prepared by the following procedure. 4-Chlorophenylacetyl chloride (prepared from 1.7 g of acid and 0.9 g of phosphorus trichloride at 100 °C) in 10 mL of dry toluene was poured, with cooling and agitation, onto 1.9 g of powdered anhydrous $AlCl_3$. The mixture was heated at 100 °C for 1 h, cooled, decomposed with ice and hydrochloric acid, and worked up in the usual manner. Upon recrystallization from MeOH (three times) there was obtained 1.95 g (80%) of the pale yellow ketone.

4-Methyl-α-(4′-chlorophenyl)acetophenone: mp 111.5–112 °C; $\nu_{C=O}$ (CCl_4) 1685 cm^{-1}; ^1H NMR (CCl_4) δ 2.39 (s, 3), 4.21 (s, 2), 7.20 (m, 6), 7.88 ppm (m, 2). Anal. Calcd for $C_{15}H_{13}ClO$: C, 73.6; H, 5.3; Cl, 14.5. Found: C, 73.4; H. 5.3; Cl, 14.3. The compound was also prepared by the Friedel–Crafts reaction described for the foregoing ketone from chlorobenzene and 4-tolylacetic acid.

α,α′-Dideuteriodeoxybenzoin: mp 59–60 °C; $\nu_{C=O}$ (CCl_4) 1680 cm^{-1}; ^1H NMR (CCl_4) δ 7.27 (s, 5), 7.37–7.60 (m, 3), 7.93–8.10 ppm

(m, 2). An authentic sample was prepared for comparison according to Corey and Schaefer.[66]

Kinetic Measurements. Typically there was prepared a 20-mL solution of the epoxide (freshly chromatographed on Florisil) and the rhodium catalyst in 1-methylnaphthalene (vacuum distilled over Na and chromatographed on alumina). Each of 19 ampules was charged with 1 mL of this solution, sealed under 1 at N_2 (purity 99.99%), and immersed into an oil bath thermostat (accuracy ±0.05 °C). During the first 1 h one ampule was withdrawn each 10 min and immediately frozen to −78 °C to await GLC analysis. The initial rate was calculated in each case from the average of at least three experiments.

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Registry No.—Bromotris(triphenylphosphine)rhodium(I), 14973-89-8; chlorocarbonylbis(triphenylphosphine)rhodium(I), 13938-94-8; *trans*-stilbene, 103-30-0; *cis*-stilbene, 645-49-8; *trans*-4,4′-dichlorostilbene, 1657-56-3; *trans*-3,3′-dinitrostilbene, 62006-53-5; *trans*-4,4′-dimethylstilbene, 18869-29-9; *trans*-4-chloro-4′-methylstilbene, 3041-83-6; 4-nitrobenzaldehyde, 555-16-8; benzaldehyde, 100-52-7; 4-nitrobenzyl chloride, 100-14-1; *trans*-α,α′-dideuteriostilbene oxide, 62006-54-6; *cis*-α,α′-dideuteriostilbene, 3947-91-9; *trans*-α,α′-dideuteriostilbene, 5284-44-6; 4-chloro-α-(4′-chlorophenyl)acetophenone, 51490-05-2; 4-chloro-α-(4′-tolyl)-acetophenone, 15221-84-8; 4-methyl-α-(4′-chlorophenyl)acetophenone, 62006-19-3; α,α′-dideuteriodeoxybenzoin, 62006-20-6.

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Transfer Hydrogenation and Transfer Hydrogenolysis. 14. Cleavage of Carbon–Halogen Bond by the Hydrogen Transfer from Organic Compounds Catalyzed by Noble Metal Salts

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It is shown that in the presence of Pd(II) salts the carbon–halogen bond of aryl halides is cleavaged to give the corresponding aryl compounds and hydrogen halides by hydrogen transfer from organic compounds. Secondary cyclic amines have excellent hydrogen-donating ability, and the ability decreases in the order indoline > tetrahydroquinoline > pyrrolidine > *N*-methylpyrrolidine > 3-pyrroline > piperidine > 2,5-dihydrofuran. The addition of bases, such as potassium hydroxide, sodium acetate, sodium carbonate, cyclohexylamine, and *n*-propylamine, promoted the hydrogenolysis. The addition of potassium halides, hydrogen halides, and triphenylphosphine retarded the reaction. Several alcohols were examined as a solvent, and methanol was found to be an excellent one. When chlorobenzene, indoline, and palladium chloride were heated in methanol, the initial rate of the formation of benzene was independent of the concentration of chlorobenzene and can be expressed as $r = k$[indoline][$PdCl_2$].

There are few studies about the catalytic hydrogenolysis of the carbon–halogen bond by hydrogen transfer from organic compounds. In heterogeneous systems, cyclohexene, limonene, and *p*-menthene have been reported to donate hydrogen to halides in the presence of palladium carbon.[1] For homogeneous systems, polychloroalkyl compounds have been reported to be hydrogenolyzed with alcohols in the presence of $RuCl_2(PPh_3)_3$.[2] In this case, aryl halides were not hydrogenolyzed.[2] Further, it has been reported that in some reactions of aryl halides in the presence of palladium[3] or nickel compounds[4] the corresponding aromatic hydrocarbons were detected, but in these reactions the sources of hydrogen were not identified. So far as we know, no systematic studies of the transfer hydrogenolysis seem to have yet been reported.

In the course of the transfer hydrogenation of olefins, we found that aryl halides were hydrogenolyzed to the corresponding aryl compounds and this study was undertaken to examine the transfer hydrogenolysis of aryl halides in detail.

Results and Discussion

Catalytic Activity. The catalytic activity of several transition metal salts and phosphine complexes was investigated. In the reaction system in which chlorobenzene (0.5 M), indoline (0.5 M), and a catalyst (0.056 M) in methanol were heated at 140 °C for 4 h, the activity decreased in the order $PdCl_2$ (76%), $(NH_4)_2PdCl_4$ (75%), $RhCl_3 \cdot 3H_2O$ (59%), $PdBr_2$ (50%), $IrCl_3$ (32%), K_2PtCl_4 (12%), $RuCl_3 \cdot nH_2O$ (3%), K_2PtCl_6 (3%). Here, the percentages shown in the parentheses are the yield of benzene. Phosphine complexes, such as $RhCl(PPh_3)_3$, $RhH(PPh_3)_4$, $RuCl_2(PPh_3)_3$, $RuH_2(PPh_3)_4$, $PdCl_2(PPh_3)_2$, and $PtCl_2(PPh_3)_2$ hardly catalyzed the hydrogenolysis, and $ReCl_5$, $FeCl_2 \cdot 2H_2O$, $NiCl_2 \cdot 6H_2O$, and $CoCl_2 \cdot 6H_2O$ showed no catalytic activity under these reaction conditions. The reason why the catalytic activity of $PdBr_2$ was lower than that of $PdCl_2$ may be that the retarding effect of HBr, which was formed in the generation of Pd(0) species, was larger than that of HCl, as described later.

When a reaction mixture was cooled after hydrogenolysis, a black precipitate was obtained in all the reaction systems in which noble metal salts were used as a catalyst and a metallic mirror was found in some reaction systems. The reactions are inferred to proceed homogeneously, because the precipitates and mirrors collected hardly catalyzed the hydrogenolysis. All the transfer hydrogenolyses described hereafter were carried out using $PdCl_2$ as a catalyst.

Hydrogen-Donating Ability of Some Organic Compounds. The hydrogen-donating ability of several organic compounds to chlorobenzene was examined. When a methanol solution of $PdCl_2$ (0.056 M), chlorobenzene (0.5 M), and a hydrogen donor (0.5 M) was heated at 140 °C for 4 h, the hydrogen-donating ability of several organic compounds decreased in the order indoline (76%), tetrahydroquinoline (42%), pyrrolidine (28%), *N*-methylpyrrolidine (25%), 3-pyrroline (24%), piperidine (16%), 2,5-dihydrofuran (7%), *N*-methylpiperidine (4%). Here, the percentages shown in the parentheses are the yield of benzene. The high hydrogen-donating power of these amines may be attributable at least partly to the basic nature of the compounds. Methanol, ethanol, 1-propanol, 1-butanol, 2-propanol, 2-butanol, cyclohexanol, cyclohexylamine, morpholine, tri-*n*-propylamine, dioxane, tetrahydrofuran, tetralin, indan, and formic acid had no hydrogen-donating ability. Except for amines, only 2,5-dihydrofuran showed a weak hydrogen-donating ability. The addition of bases promoted the reaction as described later, and it was thought that the removal of the free HX formed was the important step of the hydrogenolysis of halides. When sodium carbonate (0.25 M) was added to the reaction systems in which tetralin or 2-propanol was used as a hydrogen donor, the hydrogenolysis proceeded to give 16% or 3% yield of benzene, respectively. However, in the case of 2,5-dihydrofuran the addition of sodium carbonate hardly affected the yield of benzene.

When chlorobenzene (0.5 M), indoline (0.5 M), and $PdCl_2$ (0.056 M) were heated in methanol at 140 °C for 4 h, benzene (0.38 M) and indole (0.44 M) were confirmed and some substrate (0.12 M) and hydrogen donor (0.05 M) survived. This result is summarized as follows. (1) The amount of indole was equal to that which is needed to form benzene and to reduce Pd(II) to Pd(0) species within experimental error. (2) The total amount of benzene formed and the surviving chlorobenzene was equal to the amount of the charged chlorobenzene. (3) The total amount of the surviving donor and indole equaled the amount of the charged donor within experimental error. This result shows that the following reactions proceeded without remarkable side reactions.

$$\text{Pd(II)} + \text{indoline} \rightarrow \text{Pd(0)} + \text{indole} + 2\text{H}^+$$

$$\text{PhCl} + \text{indoline} \rightarrow \text{PhH} + \text{HCl} + \text{indole}$$

In this study, indoline was used as a hydrogen donor.

Table I. Transfer Hydrogenolysis of Halides[a]

Registry no.	Substrate	Product, % yield
108-90-7	Chlorobenzene	Benzene, 76
591-50-4	Iodobenzene	Benzene, 53
100-44-7	Benzyl chloride	Toluene, 45
108-86-1	Bromobenzene	Benzene, 39
104-92-7	*p*-Bromoanisole	Anisole, 38
104-83-6	*p*-Chlorobenzyl chloride	Toluene, 14; benzyl chloride, 24
622-24-2	β-Phenethyl chloride	Ethylbenzene, 37
106-41-2	*p*-Bromophenol	Phenol, 34
106-43-4	*p*-Chlorotoluene	Toluene, 34
672-65-1	α-Phenethyl chloride	Toluene, 32
106-48-9	*p*-Chlorophenol	Phenol, 28
106-39-8	*p*-Chlorobromobenzene	Chlorobenzene, 26
106-46-7	*p*-Dichlorobenzene	Benzene, 18; chlorobenzene, 2
106-37-6	*p*-Dibromobenzene	Bromobenzene, 20
90-11-9	α-Bromonaphthalene	Naphthalene, 20
541-73-1	*m*-Dichlorobenzene	Benzene, 12; chlorobenzene, 3
95-50-1	*o*-Dichlorobenzene	Benzene, 10; chlorobenzene, 2
104-88-1	*p*-Chlorobenzaldehyde	Chlorobenzene, 6
98-56-6	*p*-Chloro benzotrifluoride	Benzotrifluoride, 4
106-47-8	*p*-Chloroaniline	Aniline, trace
99-91-2	*p*-Chloroacetophenone	Acetophenone, trace
111-85-3	*n*-Octyl chloride	*n*-Octane, trace
	Chlorobenzene[b]	Benzene, 74
	Bromobenzene[b]	Benzene, 40
	Iodobenzene[b]	Benzene, 46

[a] The substrate (0.5 M), indoline (0.5 M), and $PdCl_2$ (0.056 M) were heated in methanol at 140 °C for 4 h. [b] The substrate (0.5 M), indoline (0.5 M), $PdCl_2$ (0.056 M), and cyclohexylamine (0.25 M) were heated in methanol at 140 °C for 1 h.

Transfer Hydrogenolysis of Halides. In the presence of $PdCl_2$, aryl halides were hydrogenolyzed to give the corresponding aryl compounds and hydrogen halides (Table I). The susceptibility of substituted halobenzenes to hydrogenolysis was influenced by the kind of substituents, but there seems to be no clear relation between the susceptibility and the electronic nature of the substituents. The yield of products increased in the order for *p*-X-C_6H_4Cl, X = $COCH_3$ < NH_2 < CF_3 < Cl < OH < CH_3 < H, and for *p*-Y-C_6H_4Br, Y = Br < Cl < OH < OCH_3 < H. It has been reported that oxidative addition of aryl halides with electron-withdrawing substituents to Pd(0) species occurs faster than that of those with electron-donating substituents.[5] In our reaction system, the electronic nature of the substituents is considered to influence the following steps: (1) the oxidative addition of the halobenzenes; (2) the reductive elimination of the products; and (3) the coordination and the dehydrogenation of the hydrogen donor. Moreover, it is also possible that the substrates coordinate through the substituent group. The yield of products may be affected by the total results of these effects and this is the reason why the substituent effect is complicated. In the case of *p*-chlorobenzaldehyde, decarbonylation occurred to form chlorobenzene, and the chlorobenzene formed did not undergo hydrogenolysis. *p*-Chlorobromobenzene was selectively hydrogenolyzed to chlorobenzene and chlorobenzene formed did not undertake further reduction. The affinity of C–Br bond to palladium species seems to be larger than that of C–Cl bond. The reactivity of benzyl chloride was lower than that of chlorobenzene. The reactivity of chloro compounds decreased in the order $PhCl > PhCH_2Cl > PhCH_2CH_2Cl > PhCHClCH_3$. The reactivity of α-phenethyl chloride, which has a benzyl-substituted chloride, is inferior to that of β-phenethyl chloride. Aliphatic halides were hardly hydrogenolyzed.

As to halobenzenes, PhX, the yield of benzene decreased in the order X = Cl > I > Br. Fluorobenzene did not react under these reaction conditions. The ease of oxidative addition of PhX to palladium complex has been reported to be in the order X = Cl < Br < I.[5] The hydrogen halides formed poison the catalytic species and deactivate indoline by salt formation. The amine hydrochloride may be sufficiently acidic to deactivate the catalytic species.[6] The poisoning effect of the hydrogen halides is presumed to increase in the order HCl < HBr < HI, because the retarding effect caused by the addition of HX and KX increased in that order, that is, HCl < HBr < HI and KCl < KBr < KI, as described later. Therefore, the yield of benzene is inferred to be realized by the balance between the ease of the oxidative addition of PhX to the palladium species and the poisoning power of HX formed.

Unless otherwise noted, all the experiments discussed in the following sections were carried out using chlorobenzene as a hydrogen acceptor.

Table II. Effect of Additives[a]

Additive	Yield of benzene, %
None	27
Potassium hydroxide	64
Sodium acetate	61
Sodium carbonate	56
n-Propylamine	54
Cyclohexylamine	53
N,N-Dimethylcyclohexylamine	48
Sodium bicarbonate	46
Morpholine	45
Tri-*n*-propylamine	33
Water	31
Acetonitrile	30
Potassium chloride	24
Acetic anhydride	22
Pyridine	19
Potassium bromide	14
Hydrochloric acid	5
Dimethyl sulfoxide	5
Hydrobromic acid	2
Potassium iodide	trace
Hydriodic acid	trace
Triphenylphosphine	0

[a] Chlorobenzene (0.5 M), indoline (0.5 M), $PdCl_2$ (0.056 M), and the additive (0.25 M) were heated in methanol at 80 °C for 1 h.

Effect of Additives. The effect of several additives on the reaction system was examined at 80 °C (Table II) and varies with their concentration. Under conditions given in Table II, the effectiveness of the additives was in the order potassium hydroxide > sodium acetate > sodium carbonate > *n*-propylamine > cyclohexylamine > *N,N*-dimethylcyclohexylamine > sodium bicarbonate > morpholine. This result indicates that the addition of bases promotes the hydrogenolysis. The role of base is the removal of hydrogen halides formed, which is the poison of the catalytic species and the hydrogen donor, indoline, by salt formation.

$$Pd^0 + HCl \rightarrow HPdCl$$

$$HPdCl + base \rightarrow Pd^0 + base{\cdot}HCl$$

$$indoline{\cdot}HCl + base \rightarrow indoline + base{\cdot}HCl$$

When amines, such as *n*-propylamine, cyclohexylamine,

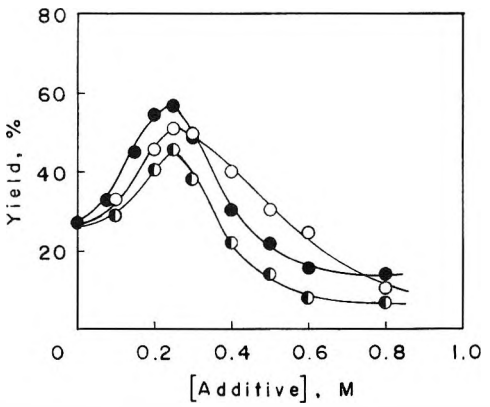

Figure 1. Dependence of the yield of benzene on the concentration of additives. Chlorobenzene (0.5 M), indoline (0.5 M), $PdCl_2$ (0.056 M), and the additive were heated in methanol at 80 °C for 1 h: ○ cyclohexylamine; ◐ *N,N*-dimethylcyclohexylamine; ● *n*-propylamine.

Table III. Effect of Reaction Solvents[a]

Solvent	Yield of benzene, %
Methanol	76
Cyclohexanol[b]	68
N,N-Dimethylacetamide	45
2-Propanol	42
Ethanol	40
1-Propanol	37
2-Butanol	32
N,N-Dimethylformamide	20
1-Butanol	12

[a] Chlorobenzene (0.5 M), indoline (0.5 M), and $PdCl_2$ (0.056 M) were heated in the designated solvent at 140 °C for 4 h. [b] Cyclohexene, 0.22 M, was obtained as the dehydration product of cyclohexanol.

and *N,N*-dimethylcyclohexylamine, were added to the reaction system, the yield of benzene showed the maximum values in the concentration range 0.2–0.3 M; that is, the concentration of the additives is 3.5–5.4 times as high as that of the catalyst (Figure 1). The yield of benzene rapidly decreased when more than 0.4 M of the amines were added. This shows that at higher concentration amines themselves coordinate on the catalyst to depress the hydrogenolysis. The promoting power of *N,N*-dimethylcyclohexylamine was lower than that of *n*-propylamine and cyclohexylamine, and the effective range of the concentration of the first is narrower than that of the latter two.

The addition of water hardly affected the hydrogenolysis. The addition of hydrochloric acid, hydrobromic acid. and hydriodic acid retarded the reaction in the order HCl < HBr < HI. The addition of potassium halides also gave the same result; that is, the retarding effect on the reaction increased in the order KCl < KBr < KI. The inference based on this result has been mentioned in the previous sections. The poisoning effect of triphenylphosphine, dimethyl sulfoxide, pyridine, and acetic anhydride was also confirmed.

Reaction Solvents. Several alcohols and amides were examined as solvents (Table III). When the reaction was carried out in alcohols, the yield of benzene decreased in the order methanol > cyclohexanol > 2-propanol > ethanol > 1-propanol > 2-butanol > 1-butanol. This result suggests that long chain or normal alcohols are less suitable solvents. In *N,N*-dimethylformamide and *N,N*-dimethylacetamide, a metallic mirror was formed as the reaction proceeded. When the hydrogenolysis was carried out in aromatic hydrocarbons, such as toluene and cumene, a Friedel–Crafts reaction occurred as

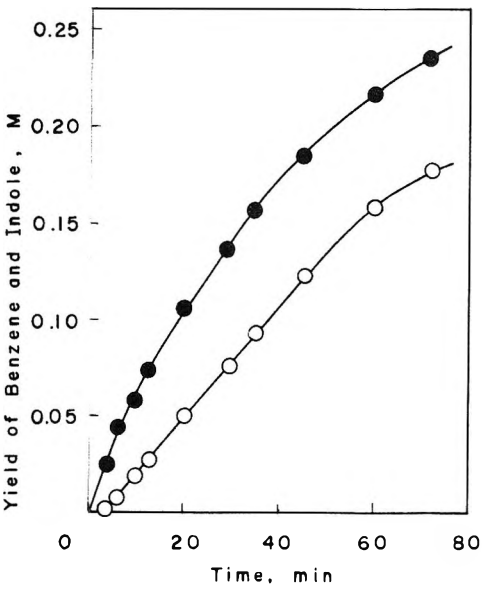

Figure 2. Dependence of yield on reaction time. Chlorobenzene (0.5 M), indoline (0.5 M), and $PdCl_2$ (0.056 M) were heated in methanol at 70 °C: ○ benzene; ● indole.

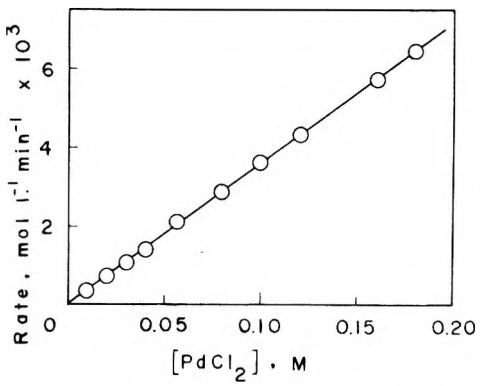

Figure 3. Dependence of the rate of hydrogenolysis of chlorobenzene on catalyst concentration. Chlorobenzene (0.5 M), indoline (0.5 M), and the catalyst were heated in methanol at 70 °C.

a side reaction. So, these solvents were not suitable for the transfer hydrogenolysis of aryl halides. In this study, methanol was used as a solvent.

The Measurement of Initial Rate. Chlorobenzene (0.5 M), indoline (0.5 M), and $PdCl_2$ (0.056 M) were heated in methanol at 70 °C, and the dependence of the yield of benzene and indole on the reaction time is shown in Figure 2. Hydrogenolysis of chlorobenzene hardly occurred until the yield of indole became about 0.02 M. This suggests that the first step of this reaction is the activation of $PdCl_2$, that is, the reduction of Pd(II) to Pd(0) species. After the yield of indole became more than 0.03 M, that of benzene increased linearly with time until it reached 0.13 M. After 15 min, the amount of indole equaled the total amount of benzene formed and the catalyst. This result also suggests that indoline reduced the Pd(II) species to the Pd(0) species. The yield of benzene deviated from the linear relationship in more than 0.13 M yield, and this deviation is caused by the deactivation effect of the hydrogen chloride formed and by the consumption of the reactants. The reaction rate of the hydrogenolysis of chlorobenzene was derived from the gradient of the linear part.

The initial rate of the hydrogenolysis was found to be proportional to the concentration of the catalyst, and the extrapolation of the line to lower concentration passes through the origin as shown in Figure 3. The reaction rate has a linear relationship with the concentration of indoline over the range

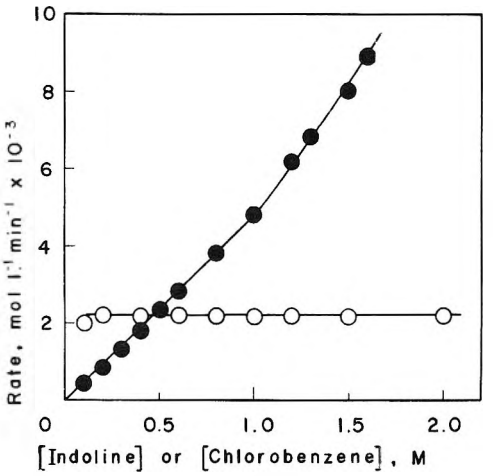

Figure 4. Dependence of the rate of hydrogenolysis of chlorobenzene on the concentration of indoline (0.5 M chlorobenzene), ●, and the halides (0.5 M indoline), ○, in methanol at 70 °C with 0.056 M $PdCl_2$.

of 0–1.0 M. However, in higher concentration more than 1.0 M the linearity no longer held and the rate deviated upwards (Figure 4). In higher concentration more than 1.0 M, the volume of indoline occupies more than 10% volume of the total solution, and the deviation seems to be caused by the solvent effect of indoline to stabilize palladium active species.

The reaction rate was independent of the concentration of chlorobenzene in the range examined (Figure 4). As the concentration of chlorobenzene was increased, the induction period became longer.

Reaction Temperature. The hydrogenolysis of chlorobenzene proceeded even at 60 °C, but that of bromobenzene and iodobenzene hardly occurred below 100 °C with or without added base. The rate of the hydrogenolysis of chlorobenzene was measured at 60, 70, 80, 90, 100, and 110 °C, and those of bromobenzene and iodobenzene were done at 110, 120, 130, and 140 °C. In all cases, the plots of log (rate) vs. $1/T$ showed good linear relationship, indicating uncomplicated reaction kinetics. From the plots, activation energies of 14.5, 14.4, and 13.5 kcal mol^{-1} are obtained for chlorobenzene, bromobenzene, and iodobenzene, respectively.

Discussion of Kinetics

As can be seen from Figure 1 and the result of quantitative relation, the first step of this transfer hydrogenolysis was the reduction of $PdCl_2$ to form the Pd(0) species (Scheme I).

Scheme I

$$PdCl_2 \overset{\text{indoline}}{\rightleftharpoons} PdCl_2(\text{indoline}) \rightarrow Pd^0 + 2HCl + \text{indole}$$

Since the initial rate of the hydrogenolysis was derived from the linear part of time vs. conversion curve, the kinetic discussion in this paper concerns the process after the activation of $PdCl_2$. It has been reported that aryl halides oxidatively add to the Pd(0) species.[5-7] Based on this inference, the results described earlier, and the comparison with the mechanism of transfer hydrogenation of olefins,[8] the following two catalytic cycles are reasonably considered as the mechanism of the transfer hydrogenolysis of chlorobenzene (Schemes II and III).

Scheme II

$$Pd^0 \overset{PhCl,\ K_1}{\rightleftharpoons} Pd(Ph)(Cl) \xrightarrow{\text{indoline},\ k_2} Pd^0 + HCl + PhH + \text{indole}$$

Scheme III

$$Pd^0 \xrightarrow[-\text{indole}]{\text{indoline},\ k_3} PdH_2 \xrightarrow{PhCl,\ k_4} Pd^0 + HCl + PhH$$

From Scheme II, the rate is expressed as

$$R = \frac{k_2 K_1 [PhCl][\text{indoline}][PdCl_2]}{1 + K_1[PhCl]} \quad (1)$$

where K_1 is an equilibrium constant and k_2 is a rate constant, respectively. Since the rate was independent of the concentration of chlorobenzene, the following relation should be satisfied in the numerator of eq 1; $1 \ll K_1[PhCl]$, that is, $[Pd^0] \ll [Pd(Ph)(Cl)]$. Biphenyl was not obtained in the hydrogenolysis of chlorobenzene, and the concentration of the phenyl palladium species was negligible in the reaction system. It has been also reported that the rate of the oxidative addition of chlorobenzene to the Pd(0) species was relatively slow.[5] Therefore, Scheme II is unreasonable for the catalytic cycle of the hydrogenolysis of chlorobenzene.

From Scheme III, the rate expression becomes as follows

$$R = k_3[\text{indoline}][PdCl_2] \quad (2)$$

where k_3 is a rate constant. In order to derive this equation, it is assumed that the indole formed was not hydrogenated. This assumption was not so unreasonable because the indole is an aromatized product and the addition of indole to the reaction system did not reduce the reaction rate. Equation 2 is found to accommodate all of the other experimental observations described earlier. (1) The dependence of the rate on the concentration of the catalyst should be linear and this agrees with the result as shown in Figure 3. From this figure, 7.6×10^{-2} mol^{-1} L min^{-1} was obtained as the value of k_3. (2) The rate should be proportional to the concentration of indoline, and this is in agreement with the result in Figure 4. From this figure, the same value, 7.6×10^{-2} mol^{-1} L min^{-1}, was obtained as the value of k_3. (3) The rate is independent of the concentration of chlorobenzene, and this agrees with the result shown in Figure 4. As the value of k_3, 7.6×10^{-2} mol^{-1} L min^{-1} was obtained. Then, the overall rate expression at 70 °C is formulated as follows.

$$R = 0.076[PdCl_2][\text{indoline}] \quad (3)$$

The oxidative addition of chlorobenzene may not be the rate-determining step, because the coordinating power of chlorobenzene was not so large and the rate of the hydrogenolysis was independent of the concentration of chlorobenzene. As hydrogenolysis proceeded, hydrogen halide accumulated to deactivate the catalytic species. When bases were added to the reaction system, the induction period became shorter, but the initial rate of the hydrogenolysis was scarcely changed. The addition of bases promotes the activation of $PdCl_2$ to Pd(0) species in the initial reaction stage, and did not affect the rate-determining step. The rate-determining step of the transfer hydrogenolysis of chlorobenzene seems to be the dehydrogenation of the hydrogen donor, that is, the formation of the palladium dihydride species. There is no evidence to decide whether the hydrogenolysis proceeds via the Pd(IV) species, $H_2Pd(Ph)(Cl)$, or the Pd(II) species with four-center transition state.

When chlorobenzene (0.5 M), bromobenzene (0.5 M), indoline (0.5 M), and $PdCl_2$ (0.056 M) were heated at 70 °C in methanol for 1 h, neither benzene nor indole was obtained. In the case of chlorobenzene and iodobenzene, the same result was confirmed. These results show that bromobenzene and iodobenzene act as poisons at 70 °C. The reaction mechanism of the hydrogenolysis of bromobenzene and iodobenzene may be different from that of chlorobenzene.

Experimental Section

Materials. Palladium chloride, ammonium palladous chloride, rhodium trichloride, palladium bromide, iridium trichloride, platinum(II) potassium chloride, ruthenium trichloride, and platinum(IV) potassium chloride were purchased and used without purification. Alcohols and amines were purified by distillation. Aryl halides were purified by distillation or recrystallization.

An Example of Transfer Hydrogenolysis. Chlorobenzene (28 mg, 0.25 mmol), indoline (30 mg, 0.25 mmol), and $PdCl_2$ (5 mg, 0.028 mmol) were put into a Pyrex tube which had been sealed at one end, and the total volume of the solution was made 0.5 mL by the addition of methanol as a solvent. The tube was cooled with liquid nitrogen and sealed under vacuum. The sealed tube was heated for 4 h in a polyethylene glycol bath kept at 140 ± 1 °C. The reaction mixture was submitted to GLC analysis, which was performed at 90 °C using 2 m × 6 mm stainless steel column packed with 15% of Silicone DC-11 on Diasolid L and 30 μL of *n*-heptane as an internal standard. The amount of indoline and indole was measured by the use of a 2 m × 6 mm stainless steel column packed with 10% diethylene glycol succinate on Diasolid L and dibenzyl ether as an internal standard.

Other transfer hydrogenolyses were carried out in a similar way.

An Example of Kinetic Runs. Ten samples, prepared by the method described above, were heated at 70 ± 1 °C for 3, 6, 10, 15, 20, 30, 37, 45, 60, and 75 min. The reaction mixtures were submitted to GLC analysis.

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Anodic Oxidation of Cyclohexene in the Presence of Cyanide Ion

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The electrochemical oxidation of cyclohexene in methanol solution of sodium cyanide results in isocyanation as well as cyanation and methoxylation. The current efficiency of isocyanide increases outstandingly with increasing electrode potential. Current–potential data suggest adsorption of a product of the electrolysis on the electrode. The current efficiencies of products are dependent on the cyclohexene concentration, whereas the product distribution is found to be independent of the relative concentration of both electroactive species, i.e., CN^- and C_6H_{10}, on the electrode which changes with changing bulk concentration of cyclohexene. These observations indicate that a primary electron transfer from cyclohexene adsorbed while expelling an electrolysis product adsorbed is a key step to derive organic products.

Cyanation of olefins or dienes has been thus far unsuccessful. We previously reported on the products obtained from the electrochemical reaction of methanol solution of cyclohexene in the presence of mercuric cyanide and proposed simultaneous operation of both the substrate oxidation reaction and the ion discharge reaction to account for low yields of cyanated products.[1] Recently, however, several types of experimental evidence in favor of direct anodic oxidation of the substrate have been presented.[2-9]

Anodic oxidation of cyclohexene has received a great deal of recent attention.[10-23] Much of the interest in this compound has been due to the fact that it serves as an easily studied model for both addition and allylic substitution reactions to olefins. The present paper describes a careful study of the products of cyclohexene oxidation in the presence of cyanide. Some mechanistic experiments will also be reported and the formation of isocyanide will be discussed.

Results

Products. The electrolyses were conducted in methanol solution of sodium cyanide using a two-compartment cell under a nitrogen atmosphere in the potential region 1.9–2.7 V vs. SCE at platinum electrode. The products formed were identified as such from comparisons with the authentic samples prepared by other routes, and determined by VPC. Isolation of the various products was performed using preparative VPC techniques. Besides 3-methoxycyclohexene (1) and dimethoxymethylcyclopentane (2), 3-isocyanocyclohexene (3), 2-cyclohexene-1-carbonitrile (4), isocyanocyclohexane (5), cyclohexanecarbonitrile (6), and *trans*-2-methoxycyclohexanecarbonitrile (7) were found together with bis-2-cyclohexen-1-yl (8) and unidentified minor components. Traces of methoxycyclohexane and *trans*-1,2-dimethoxycyclohexane were also noted.

Current–Potential Data. Figure 1 presents current–potential curves for oxidation of sodium cyanide in methanol and for the same solution with added cyclohexene. As can be seen in Figure 1, a methanolic solution of sodium cyanide is discharged at about 1.5 V,[4] whereas the addition of cyclohexene results in a remarkable decreasing of the current in the region of 1.6–1.9 V. Under experimental conditions cyclohexene begins to be oxidized at about 2.0 V ($E_{1/2}$ = 1.89, 2.05, and 2.16 V vs. Ag,Ag^+,[10,17,24] 2.14 and 2.35 V vs. SCE[16,20]).

Cyclic voltammograms were taken at a platinum electrode in a solution of 0.1 M tetraethylammonium fluoroborate within the range of 1.0–2.2 V vs. SCE at 0.1 V/s. The background current is not affected by added sodium cyanide (concentration $\sim 10^{-2}$ M). With cyclohexene added (concentration $\sim 10^{-2}$ M) the current decreases instantaneously at essentially the same potential and the curve of current vs. potential falls below that for the system without the substrate. The trend does not change even when the order of addition of the substrate and the cyanide is inverted. This suggests that a product of the electrolysis would be adsorbed on the anode, thus decreasing the area available for the normal electrochemical reaction.

Influence of the Concentration. Table I summarizes the results of controlled potential electrolyses performed with

Table I. Anodic Oxidation of Cyclohexene in Methanolic Sodium Cyanide Solution [a]

[Cyclohexene], M	Oxidation potential, V vs. SCE	Anode material	Electricity, Faradays	*n* Faradays/mol	Current efficiency and yield,[d] % 1	2	3	4	5	6	7	8	3/4
0.08	2.0	Pt	0.011	9.7	5.9 (28.6)	2.5 (12.1)	0.40 (1.94)	0.21 (1.02)	0.02 (0.10)	0.02 (0.10)	0.02 (0.10)	0.01 (0.10)	1.9
0.40	2.1	Pt	0.030	5.3	13.6 (36.0)	5.0 (13.3)	0.74 (1.96)	0.39 (1.03)	0.08 (0.21)	0.06 (0.16)	0.02 (0.05)	0.04 (0.21)	1.9
0.80	2.1	Pt	0.030	3.9	24.0 (46.8)	9.6 (18.7)	1.09 (2.13)	0.64 (1.25)	0.08 (0.16)	0.07 (0.14)	0.05 (0.10)	0.21 (0.82)	1.7
1.60	2.1	Pt	0.020	2.4	20.0 (24.0)	7.0 (8.4)	1.30 (1.56)	0.68 (0.82)	0.13 (0.16)	0.09 (0.11)	0.07 (0.08)	0.75 (1.80)	1.9
2.40	2.1	Pt	0.015	1.7	19.6 (16.7)	6.4 (5.4)	1.72 (1.46)	0.75 (0.64)	0.15 (0.13)	0.10 (0.09)	0.09 (0.08)	2.12 (3.60)	2.3
0.80	2.4	Pt	0.035	3.7	25.1 (46.4)	9.9 (18.3)	2.50 (4.63)	0.74 (1.37)	0.27 (0.50)	0.11 (0.20)	0.10 (0.19)	0.14 (0.52)	3.4
0.80	2.7	Pt	0.025	3.2	24.4 (39.0)	10.3 (16.5)	3.83 (6.13)	0.82 (1.31)	0.43 (0.69)	0.23 (0.37)	0.10 (0.16)	0.17 (0.54)	4.7
0.80	2.1	C	0.014	3.2	21.5 (34.4)	7.2 (11.5)	0.94 (1.50)	0.51 (0.82)	0.05 (0.08)	0.06 (0.10)	trace	0.09 (0.29)	1.8
0.80[b]	2.0	Pt	0.037	1.8	57.5 (51.8)	26.7 (24.0)							
0.80[c]	1.4	Pt	0.028	13.8	0.6 (4.1)	0.1 (0.7)							

[a] [NaCN] = 0.80 M; temperature, 25 °C. Minor products: methoxycyclohexane, *trans*-1,2-dimethoxycyclohexane. [b] Methanolic sodium perchlorate solution (0.80 M). [c] Methanolic sodium methoxide solution (0.80 M). [d] The value in parentheses represents the chemical yield based on unrecovered cyclohexene.

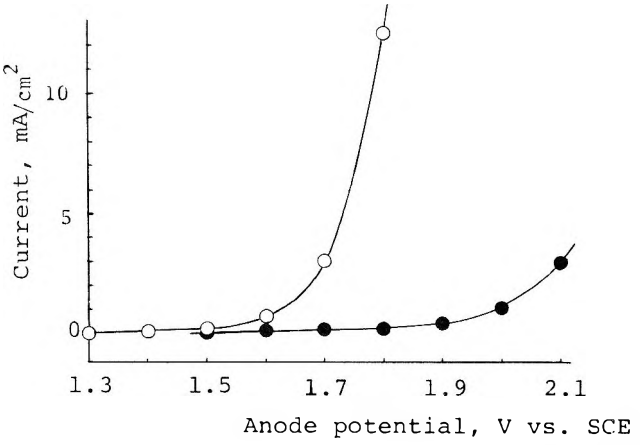


Figure 1. Plots of current vs. anode potential for electrolyses of solutions containing 0.8 M sodium cyanide in methanol at smooth platinum (8 cm^2) at 25 °C (solution magnetically stirred): ○, without cyclohexene; ●, with 0.8 M cyclohexene.

various initial concentrations of cyclohexene. Each current efficiency represents an average of three or more experiments conducted at the same potential.

The data listed in Table I clearly show that the current efficiency of products increased with increasing concentration of the substrate used; especially the current efficiency of formation of **8** is increased conspicuously. The chemical yield of products (based on unrecovered cyclohexene) increased with increasing cyclohexene concentration. Coulombic *n* value increases with decreasing cyclohexene concentration, whereas the product distribution is relatively constant with cyclohexene concentration from 2.40 M decreasing to 0.08 M (except for **8**, whose formation is second order in cyclohexene). Hence cyanide ion discharges concurrently at the lower concentration of cyclohexene probably to produce cyano radical, which does not enter into organic products but would attack the coexisting cyanide ion to form cyanogen anion radical[5] or dimerize to cyanogen.[25] The current efficiency for the reaction at the lower concentration of cyclohexene was 10% or so and the remainder of the current would be consumed with these inorganic electrode processes.

Influence of the Anode Potential. Comparative experiments were also carried out at different anode potential. The initial concentrations of sodium cyanide and cyclohexene were both fixed at 0.80 M. It is seen from Table I that the current efficiency of each product again increased with increasing potential. This observation taken together with the influence of bulk concentration of cyclohexene supports adsorption of the substrate on the electrode.[8,26] The current efficiency for the production of isocyanide increased outstandingly.

Influence of the Anode Materials and the Solvent. The electrooxidations were carried out at carbon and gold anodes in methanolic sodium cyanide solution to compare the role of anode materials. The current efficiencies for the production of the products are as shown in Table I. It is seen that at a carbon anode all the products are formed in almost the same current efficiencies as at a platinum anode. At gold, the electrode itself began to dissolve in the solution with the passage of a current. A trace amount of isocyanide **3** was detected, along with the methoxylated products (**1** and **2**).

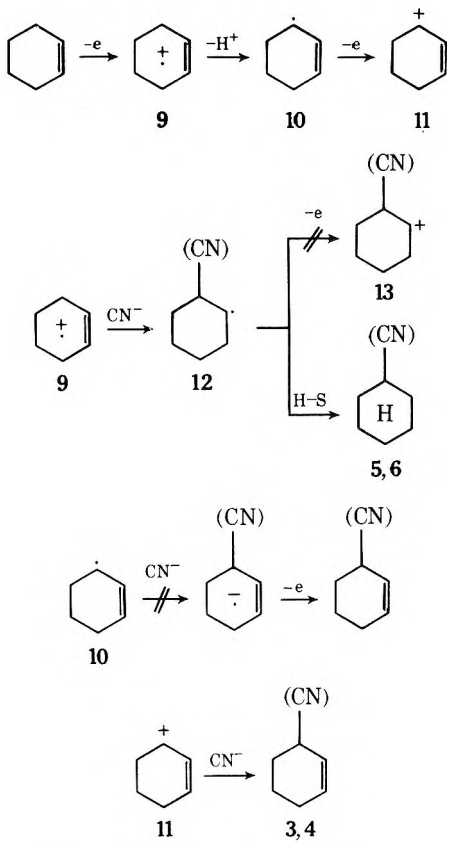
To study the influence of solvent, the anodic oxidation of cyclohexene was performed in acetonitrile containing tetraethylammonium cyanide. Neither cyanation nor isocyanation was observed, but a significant amount of tarry products was obtained.

Discussion

The observed products are formally a 2-equiv change. A mechanism involving direct anodic oxidation of the substrate is reasonable to account for the electrochemical behavior of cyclohexene and the relation between products and the cyclohexene concentration. Some of the current is consumed via electron transfer from the cyanide ion and this process does not produce isolable cyanated products.

According to the proposed mechanism in Scheme I, three types of intermediates are conceivable: cyclohexene cation radical **9** produced by an initial one-electron oxidation, 3-cyclohexenyl radical **10** produced by deprotonation of initially

Scheme I

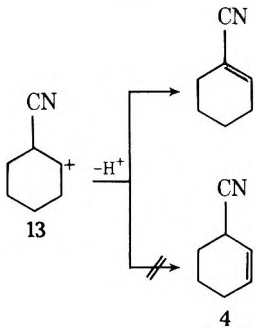


generated cation radicals, and 3-cyclohexenyl cation **11** formed by further anodic oxidation.

The anodically generated cation radical **9** is attacked by the cyanide ion to produce the radical **12,** followed by hydrogen atom abstraction from cyclohexene or the solvent methanol. Ionization energy of cyclohexene is moderately low[27-32] and the cyclohexene cation radical **9** has clearly been recognized in the gas phase.[33,34] Intervention of **9** has also been proposed to account for the products obtained from the oxidation reaction by means of cobaltic acetate[35] as well as anodic process.[17,20]

The radical **12** could be oxidized to the cation **13,** followed by proton release, thus leading to the allylic substitution

Scheme II



products.[1,20] This possibility is ruled out from the fact that the solvolysis of *trans*-2-cyanocyclohexyl tosylate in methanolic cyanide solution produces 1-cyclohexene-1-carbonitrile at 25 °C exclusively. Under these conditions, the rate of isomerization of 2-cyclohexene-1-carbonitrile (**4**) to 1-cyclohexene-1-carbonitrile is extremely slow. The conjugated isomer was not detected in the electrochemical experiment. Anodically generated 2-methylcyclohexyl cation produces 1-methylcyclohexene.[36]

Neutral radicals can couple with nucleophiles such as cyanide ion.[37] 3-Cyclohexenyl radical **10** was generated from cyclohexene by irradiation of a solution containing di-*tert*-butyl peroxide and sodium cyanide. In this case, the allylic hydrogen abstraction is effected by *tert*-butoxy radicals from the photodissociation of the peroxide. A Pyrex filter was used in all experiments to ensure that direct excitation of alkene and/or adduct did not occur.[38-41] Bis-2-cyclohexen-1-yl (**8**) was formed effectively, whereas no cyanated or isocyanated product was observed.

Table II. Product Ratio in Allylic Substitution of Various Reactions

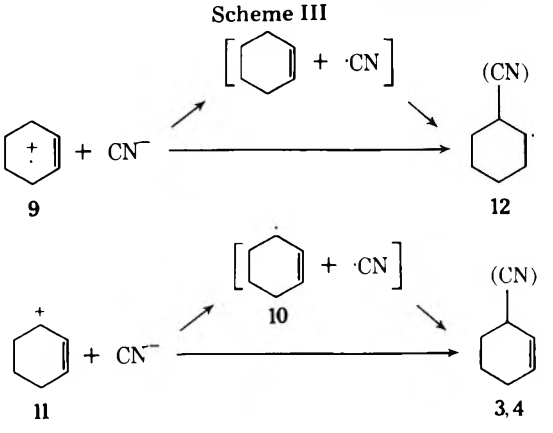
Reaction	3/4	1/4
Cyclohexene–NaCN–CH_3OH, 2.7 V	4.7	30
3-Bromocyclohexene–NaCN–CH_3OH, reflux	0.4	40
3-Bromocyclohexene–AgCN, room temp	9.2	

The reaction of the various cations with the cyanide nucleophile has been studied extensively.[42-44] 3-Cyclohexenyl cation **11** combines with cyanide ion to form the isocyanide **3** or the cyanide **4.** For comparison, the reaction of 3-bromocyclohexene with metallic cyanides was examined. The results are shown in Table II, together with the result of a potentiostatic experiment conducted at a higher potential. With sodium cyanide in methanol, cyanation surpassed isocyanation. On the contrary, with silver cyanide, isocyanation was brought about predominantly. Of interest are the results obtained with increased anode potential. The data listed in Table I clearly show that the relative ratio of two products (**3** and **4**) significantly increases as the electrode potential is made positive. The predominance of isocyanation in the present anodic reaction performed at relatively high electrode potentials would be ascribable to the interaction of cyanide ion with electrode surface (with a covalent bond character such as that in silver cyanide) and the different reactivity of anodically excited species.

In the anodic addition[4,6,8,9] or the substitution[7,43,45-48] involving aromatic cation radical intermediates, the carbon atom of cyanide ion acts as the nucleophilic center. A few reports have mentioned the coexistence of isocyanide in the reaction mixture from IR data.[49-51] The hard–soft acids–bases (HSAB) principle has been used with considerable success in rationalizing the reactivity pattern of ambident anions.[52-54] From the general experience the carbon nucleophiles are soft, as are carbanions, and nitrogen nucleophiles are hard, although the hardness is less pronounced when the nucleophilic nitrogen atom is part of a polarizable aromatic system as in pyridine. One may consider the carbon end the softer end, and the nitrogen end the harder end of the cyanide ion. In addition, cyclohexene cation radical **9** as well as π-3-cyclohexenyl cation **11** in question is harder than are the aromatic cation radicals concerned in cyanation, in which positive charge spreads over the whole molecule.

Scheme III is an attempt to describe the anodically gener-

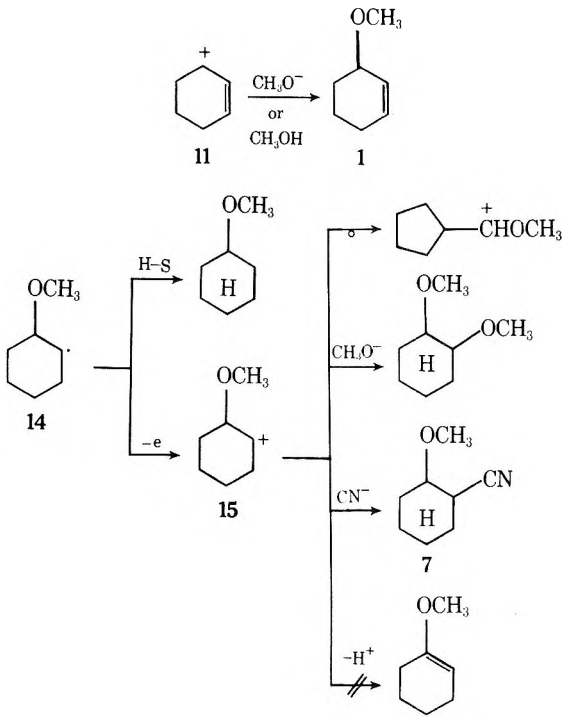
Scheme III



ated cationic species–cyanide anion combination reaction in more detail. The cationic species, **9** and **11**, would combine with cyanide anion directly or via an electron-transfer process.[55] In practice, a stable cation radical such as tri-*p*-anisylamine can oxidize cyanide ion to cyano radical,[7,25] whereas cyano radical can couple with cyclohexene or 3-cyclohexenyl radical **10**.[56] The reaction of perylene perchlorate with cyanide ion may be via the electron-transfer reaction in view of the stability of the former compound.[57] The cation radical–nucleophile combination reaction has attracted continuous attention.[58,59]

As in the cyanation and isocyanation reactions, methoxylation would proceed via the substrate discharge mechanism. There are some mechanistic works concerning the anodic methoxylation of cyclohexene[15,20] and consequently, an attempt was made to avoid repetition. The cation **11** combines with methoxide ion or the solvent methanol. Since an ionization potential of 2-methoxycyclohexyl radical **14** is lower than that of 2-cyanocyclohexyl radical **12**, the former radical would mainly be oxidized to the cation **15**, followed by a rearrangement of the carbon skeleton.[14,15,20,60] *trans*-2-

Scheme IV



Methoxycyclohexanecarbonitrile must come from the combination of the cation **15** and cyanide ion, because the foregoing solvolysis of *trans*-2-cyanocyclohexyl tosylate did not yield the cyanomethoxylation product. Unfortunately, the reaction between the cation **15** and cyanide ion could not be observed directly, since *trans*-2-methoxycyclohexyl tosylate did not undergo solvolysis in methanolic sodium cyanide solution.

The product **8** arises from the dimerization of the radical **10**. This reaction competes with that of cationic species, **9** and **11**, with the electrolyte or the solvent. The second-order reaction is affected to a greater extent by an increase in the cyclohexene concentration on the electrode; thus a relatively high current efficiency for the formation of **8** is favored by the use of a concentrated solution of cyclohexene and a higher anode potential.

In conclusion, the anodic oxidation of cyclohexene in methanolic cyanide solution results in isocyanation as well as cyanation and methoxylation. Isocyanation is highly potential dependent. Current–potential data show that a product of the electrolysis is adsorbed on the anode. The substrate discharge mechanism can account well for the electrochemical behavior of cyclohexene and the observed products.

Experimental Section

Controlled potential electrolyses were performed by using a divided cell with a platinum wire electrode in the cathode compartment and the saturated calomel reference electrode, a platinum plate electrode having an area of 8 cm^2, and a magnetic stirrer bar in the anode compartment. Anode potential was controlled by means of a Yanaco Model VE-3 controlled potential electrolyzer.

Coulometry was carried out with a Hokuto Denko Model HF 108A current integrator.

Cyclic voltammetry was performed in a two-compartment cell in which the calomel reference electrode with an agar bridge was separated from the platinum anode and the cathode by a glass frit. The working electrode was a 1-cm platinum wire. A Hokuto Denko HB-107A voltage scanner, HA-104 potentiostat, and Yokogawa Type 3083 XY recorder were used. All measurements were carried out at 25 °C.

Materials. Methanol was purified by fractional distillation from magnesium methoxide. Reagent grade sodium cyanide was used with no purification other than drying. Tetraethylammonium cyanide was prepared according to the method given by Andreades and Zahnow.[5] Cyclohexene was prepared from cyclohexanol by dehydration with concentrated sulfuric acid[61] and was purified by distillation over sodium. *trans*-2-Methoxycyclohexyl tosylate was obtained from the standard procedure.[62] *trans*-2-Cyanocyclohexyl tosylate was also prepared from *trans*-2-hydroxycyclohexanecarbonitrile[63,64] and recrystallized from petroleum ether, mp 50–54 °C.

The following reference materials were prepared according to the literature: methoxycyclohexane,[65] 1-methoxycyclohexene,[66] cyclopentanecarboxyaldehyde,[67] cyclohexanemethanol,[68] dimethoxymethylcyclopentane,[69] cyclohexanecarbonitrile,[70] 1-cyclohexene-1-carbonitrile,[71] and isocyanocyclohexane.[72]

3-Methoxycyclohexene was obtained from 3-bromocyclohexene[73] by a modification of the method of Vogel,[65] bp 46 °C (27 mm) (lit.[14] bp 139–141 °C).

cis- and *trans*-1,2-dimethoxycyclohexane were prepared from the corresponding 1,2-diol[74,75] by the procedure of Hanze, Conger, Wise, and Weisbalt.[76]

2-Cyclohexene-1-carbonitrile was obtained by the reaction of 3-bromocyclohexene and potassium cyanide in acetone–water by the method of Mousseron, Winternitz, Jullien, and Jacquier.[77] The nitrile was obtained together with cyclohex-2-enol[78,79] and 3-isocyanocyclohexene (product ratio 7:11:1).

3-Isocyanocyclohexene was prepared by the reaction of 3-bromocyclohexene and silver cyanide according to a modification of the method of Jackson and McKusick.[80] Relative ratio of 3-isocyanocyclohexene and 2-cyclohexene-1-carbonitrile was 9:1. This isocyanide has not been reported previously.

trans-2-Methoxycyclohexanecarbonitrile was prepared from *trans*-2-hydroxycyclohexanecarbonitrile,[63,64] which was made by cyanation of *trans*-2-bromocyclohexanol,[81] according to the known procedure.[82,83]

Bis-2-cyclohexen-1-yl was obtained by the reaction of 3-bromocyclohexene and metallic sodium in ether by stirring at room temperature for several days, bp 120–125 °C (25 mm) [lit.[14] bp 106–107 °C (10 mm)].

Potentiostatic Oxidations of Cyclohexene. The anolyte (50 mL) was made up of various amounts of cyclohexene in 0.80 M methanolic sodium cyanide solution. The catholyte was a methanolic solution of sodium cyanide. The anode and cathode compartments were crudely purged with nitrogen in most experiments. This did not affect the electrode process. The reaction was carried out at a controlled anode potential at 25 °C. During the electrolysis, the solution was stirred magnetically. To the electrolyzed mixture were added internal standards for VPC analyses, the mixture was treated with water, and the organic material was extracted with ether. The ethereal solution was analyzed by VPC using a PEG 6000 column.

Each product was separated in pure form by preparative VPC and the IR and NMR spectra of the products were compared with those of the corresponding authentic sample. These products are listed below in order of increasing retention time: methoxycyclohexane, 3-methoxycyclohexene (**1**), dimethoxymethylcyclopentane (**2**), *trans*-1,2-dimethoxycyclohexane, isocyanocyclohexane (**5**), 3-isocyanocyclohexene (**3**), cyclohexanecarbonitrile (**6**), 2-cyclohexene-1-carbonitrile (**4**), bis-2-cyclohexen-1-yl (**8**), *trans*-2-methoxycyclohexanecarbonitrile (**7**), and unidentified minor components.

Solvolysis of *trans*-2-Cyanocyclohexyl Tosylate in Methanolic Cyanide Solution. Solvolysis of *trans*-2-cyanocyclohexyl tosylate (0.28 g, 0.001 mol) was carried out in 20 mL of methanolic sodium cyanide solution (0.1 M) at room temperature for several days. The reaction mixture was treated with water and the organic material was extracted with ether. The ether was removed by distillation under reduced pressure. VPC analysis showed only the presence of 1-cyclohexene-1-carbonitrile. Neither 2-cyclohexene-1-carbonitrile nor *trans*-2-methoxycyclohexanecarbonitrile was detected.

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Registry No.—**1**, 2699-13-0; **2**, 20117-79-7; **3**, 62126-66-3; **4**, 13048-17-4; **5**, 931-53-3; **6**, 766-05-2; **7**, 62126-67-4; **8**, 1541-20-4; cyclohexene, 110-83-8; sodium cyanide, 143-33-9; *trans*-2-cyanocyclohexyl tosylate, 62126-68-5.

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Reaction of Atomic Oxygen with Alkanes. Regioselective Alcohol Formation on γ-Radiolysis of Liquid Carbon Dioxide Solutions of Alkanes

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γ-Radiolysis of liquid carbon dioxide in the presence of cyclohexane, methylcyclohexane, and *cis*- or *trans*-decalin has been studied at 0 °C. The main products were corresponding alcohols and carbonyl compounds. The oxidizing species from carbon dioxide apparently shows selective attack on C–H bonds of alkane in the order tertiary > secondary > primary. The observed tendency could be rationalized in terms of the reaction of ground state triplet oxygen atoms, $O(^3P)$, with alkane in liquid carbon dioxide. In the case of *cis*- and *trans*-decalin, highly configurational retention of decalol-9 was observed. The formation of a dimer of alkane was negligibly small. The rapid recombination of radical pairs initially formed by the reaction of $O(^3P)$ atoms with alkane in a solvent cage is proposed. In addition, the production of cyclohexanone from cyclohexanol is described.

Reactions of ground state $O(^3P)$ atoms, generated by the mercury photosensitized decomposition of nitrous oxide, with organic molecules, such as alkenes,[1] arenes,[2] alkynes,[3] and alcohols,[4] have been extensively studied by Cvetanović et al., by other workers,[1f,2c,3] and recently by Havel et al., in gas phase. However, the reactions of $O(^3P)$ atoms in condensed phase have drawn little attention, possibly owing to the absence of a convenient method of producing oxygen atoms in condensed phase.[5]

On the other hand, the radiolysis of carbon dioxide has been extensively studied and carbon monoxide is known to be produced from liquid and solid carbon dioxide.[6] Baulch, Dainton, and Willix reported $G(CO) = 5.0–3.5$, $G(O_2) = 0.2–0.6$, and $G(O_3) \leq 0.7$ for ^{60}Co γ-irradiation on liquid carbon dioxide.[6a] The production of O_2 and O_3 suggests that atomic oxygen is an intermediate. We recently investigated the radiolysis of liquid carbon dioxide in the presence of an alkene and observed the formation of the corresponding oxirane and carbonyl compounds.[7] The similarity of the products to that of the gas-phase reaction of photochemically produced $O(^3P)$ atoms with alkene[1] was observed and we suggested that the most appropriate, main oxidizing species from liquid carbon dioxide is a ground state $O(^3P)$ atom. Further, formation of a phenylketene on γ-radiolysis of a phenylacetylene in liquid carbon dioxide indicates that the reaction of $O(^3P)$ atoms with a phenylacetylene has occurred via a ketocarbene intermediate.[8,9] Recently, Wojnarovits, Hirokami, and Sato also indicated the formation of $O(^3P)$ atoms in γ-radiolysis of a cyclohexene–liquid carbon dioxide mixture.[10] Therefore, it seems that the γ-radiolysis of liquid carbon dioxide is the most convenient method to approach the reactivity of $O(^3P)$ atoms with a variety of organic molecules in liquid phase. This paper attempts to obtain the available information on the behavior of the oxidizing species from carbon dioxide, such as $O(^3P)$ atoms, in the reaction with an alkane.

The reaction of $O(^3P)$ atoms with alkane in liquid phase has been attempted by photolysis of nitrous oxide and ozone. However, competitive reactions of $O(^3P)$ and $O(^1D)$ atoms were unavoidable in the case of nitrous oxide[11] and the reaction of $O(^3P)$ atoms with alkane was hardly observed in the case of ozone,[12,13] presumably by the effective scavenging of $O(^3P)$ atoms by oxygen molecules which is the by-product in the photolysis of ozone.

Results

Cyclohexane. γ-Radiolysis of liquid carbon dioxide (1.4 mol) in the presence of low molar concentrations of cyclohexane (lower than 0.32) was carried out in a stainless steel autoclave using a ^{60}Co (7000 Ci) source at 0 °C for 0.5–2 h. Products were cyclohexanol, cyclohexanone, cyclohexene oxide,[14] and bicyclohexyl, of which G values were 2.0–3.1, 0.5–1.3, less than 0.4, and less than 0.3, respectively. The total G value of oxygenated product is 2.9–4.7 (molecule/100 eV), which agreed with that of oxygen atoms estimated from $G(CO)$ obtained by Baulch et al. in γ-radiolysis of liquid carbon dioxide.[6a] These data are summarized in Table I. The relative yield of cyclohexanol was about 65% of the products and almost independent of irradiation time and concentration of cyclohexane.

Methylcyclohexane. The products in the radiolysis of liquid carbon dioxide (1.4 mol) in the presence of methylcyclohexane (7.1–9.7 mmol) were methylcyclohexanols and cyclohexylcarbinol (their combined G value was 2.8–3.2) and three isomers of methylcyclohexanone ($G = 0.5–1.0$). The total G value of product was 3.4–4.2 (molecule/100 eV). These data and the distribution of alcohols are shown in Table II. A pronounced selectivity of the attack of $O(^3P)$ atoms on three types of C–H bonds of methylcyclohexane was observed.

***cis*- and *trans*-Decalin.** Radiolysis of liquid carbon dioxide (1.4 mol) in the presence of *cis*-decalin (6.6 mmol) produced isomers of decalol ($G = 2.5$) and decalone ($G = 0.2$), and in the presence of *trans*-decalin (9.4 mmol) produced isomers of decalol ($G = 2.5$) and decalone ($G = 0.7$). The total G values of product in the case of *cis*- and *trans*-decalin were 2.8 and 3.2, respectively. From the proportion of *cis*- or *trans*-decalol-9 in produced *cis*- and *trans*-decalol-9, retention of configuration at the tertiary position has been calculated. The distribution of alochols and retention of configuration are summarized in Table II. Formation of decalol-9 occurs with predominant stereoselectivity on the reaction of $O(^3P)$ atoms with *trans*-decalin.

Cyclohexanol. By the radiolysis of cyclohexanol (2.2 mmol) in liquid carbon dioxide (1.4 mol), cyclohexanone ($G = 6.0$) was obtained as a sole product (Table IV).

Discussion

Alcohol Formation. As described above, alkanes were easily oxidized to the corresponding alcohols. Our previous reports[7,8] indicate that the oxidizing species produced from liquid carbon dioxide by γ-irradiation should be ground state $O(^3P)$ atoms. The data of Table II shows the distribution of alcohols by the attack of the $O(^3P)$ atoms on C–H bonds of alkane. The distribution per C–H bonds for methylcyclohexane and decalin apparently shows greater preferential attack of $O(^3P)$ atoms on C–H bonds in the order tertiary > secondary > primary. The relative reactivity among the three

Table I. Products of γ-Radiolysis of Cyclohexane in Liquid Carbon Dioxide at 0 °C

mmol	Irradiation time, h	Product G value, molecule/100 eV[a] Cyclohexanol	Cyclohexanone	Cyclohexene oxide	Bicyclohexyl
8.9	0.5	2.71 (65.9)	0.93 (22.6)	0.32 (7.8)	0.15 (3.6)
8.8	1	3.14 (65.6)	1.18 (24.6)	0.40 (8.4)	0.07 (1.5)
8.7	2	2.19 (63.3)	1.27 (36.7)	*b*	*b*
2.0	1	2.01 (66.3)	0.53 (17.5)	0.37 (12.2)	0.12 (4.0)
18.9	1	2.37 (68.1)	0.56 (16.1)	0.30 (8.6)	0.25 (7.2)

[a] Relative yields are shown in parentheses. [b] Not detected.

Table II. Products of γ-Radiolysis of Alkanes in Liquid Carbon Dioxide at 0 °C

Registry no.	Alkane	mmol	Irradiation time, h	Product G value: Alcohols	Product G value: Ketones	Alcohol distribution, %: Prim	Alcohol distribution, %: Sec	Alcohol distribution, %: Tert	Alcohol distribution per C–H bonds: Prim	Alcohol distribution per C–H bonds: Sec	Alcohol distribution per C–H bonds: Tert	Retention of configuration, %
108-87-2	Methylcyclohexane	7.1	1	3.22	0.95[a]	0.6	47.8	51.6	0.05	1	10.8	
		6.6	2	2.97	0.48[a]	2.0	52.2	45.8	0.13	1	8.78	
		9.7	3	2.81	0.56[a]	2.1	55.2	42.7	0.13	1	7.74	
493-01-6	*cis*-Decalin	6.6	3	2.54	0.21[b]		28.7	71.3		1	19.8	83
493-02-7	*trans*-Decalin	9.4	3	2.54	0.65[b]		39.0	61.0		1	12.5	93

[a] Three isomers of methylcyclohexanone. [b] Isomers of decalone.

Table III. Relative Reactivity of C–H Bonds by the Attack of Active Species

Active species	Substrate	Condition	Relative reactivities per C–H bonds: Prim	Sec	Tert	Ref
$O(^3P)$	Methylcyclohexane	Liq CO_2, γ ray, at 0 °C	1	9	80	This work
$O(^3P)$	*cis*-Decalin	Liq CO_2, γ ray, at 0 °C		1	20	
$O(^3P)$	*trans*-Decalin	Liq CO_2, γ ray, at 0 °C		1	13	
t-BuO·	*n*-Butane[a] and 2,3-dimethylbutane[b]	*t*-BuOCl, $h\nu$, at 0 °C in several solvents	1	11–14	69–89	15
$O(^1D)$	Propane[c] and isobutane[d]	Ozone, 2537 Å, at 87 K in liq argon	1	0.9	1.0	17
$O(^1D)$	Methylcyclohexane	N_2O, 1849 Å, at 0 °C	1	1.1	1.4	11
O^-	Aliphatic alcohols and monocarboxylic acids	Aqueous solution, at high pH, pulse radiolysis	1	4.8		18

[a] Registry no., 106-97-8. [b] Registry no., 79-29-8. [c] Registry no., 74-98-6. [d] Registry no., 75-28-5.

types of C–H bonds of methylcyclohexane can be presented: primary C–H bond:secondary C–H bond:tertiary C–H bond = 1:9:80 (Table III). Similar results were obtained by *cis*- and *trans*-decalin. The relative reactivity of the three types of C–H bonds on hydrogen abstraction by *tert*-butoxy radical in several solvents (*n*-butane and 2,3-dimethylbutane) at the same temperature as our experiment were reported by Walling and Jacknow[15] (see Table III). Our result is in excellent agreement with that obtained by the hydrogen abstraction of *tert*-butoxy radical from alkane. Therefore, the present alcohol formation would be caused by hydrogen abstraction and followed by the recombination of radical pair. In contrast to this, excited singlet state $O(^1D)$ atoms are well known to exhibit little discrimination in their attack on the primary, secondary, and tertiary C–H bonds of alkane in gas phase[16] and condensed phase.[11,17] Hydrogen abstraction by oxygen radical anion, O^-, from saturated compounds shows preferential attack on C–H bonds in the same order by the attack of *tert*-butoxy radical, but the relative reactivity of secondary C–H bond against primary C–H bond for hydrogen abstraction with O^- anion is about half as high as the relative reactivity with *tert*-butoxy radicals.[18] Further, it seems that alkyl radical and OH^- anion thus formed do not take part in alcohol formation. Thus, these results exclude the possibility of O^- anion as well as $O(^1D)$ atoms from the precursor of alcohols.

There are reports of carbon trioxide, CO_3, formation by the reaction of singlet $O(^1D)$ atoms with carbon dioxide in gas phase and condensed phase.[19] Excited carbon trioxide stabilizes either by collisional deactivation forming ground state CO_3 or by decomposition producing carbon dioxide and $O(^3P)$ atoms. In liquid phase, excited carbon trioxide may be effectively deactivated by collision. It would be difficult to demonstrate the possibility of the participation of CO_3 in the present reaction without the knowledge of the reactivity of CO_3 with organic compounds, such as alkane.

It seems likely that hydrogen abstraction from an alkane by $O(^3P)$ atoms results in the formation of an alkyl radical and OH radical. In the case of cyclohexane, only a trace amount of bicyclohexyl was obtained. Any dimer was not detected even in the case of methylcyclohexane or decalin. Therefore, we assume that the rapid recombination of radical pair in a solvent cage may occur and result in the formation of the corresponding alcohol.

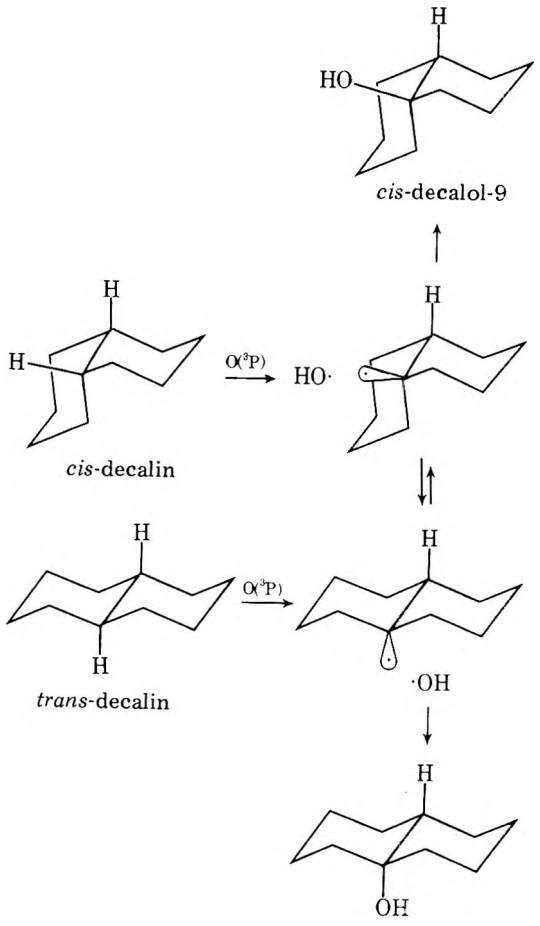
$$RH + O(^3P) \rightarrow [R\cdot + \cdot OH]_{cage} \rightarrow ROH$$

Table IV. γ-Radiolysis of Cyclohexane and Cyclohexanol in Liquid Carbon Dioxide[a]

Cyclohexane, mmol	Cyclohexanol, mmol	Product G value			
		Cyclohexanol	Cyclohexanone	Cyclohexene oxide	Bicyclohexyl
2		2.7	0.9	0.3	0.2
2	0.2		2.5	*b*	*b*
	2		6.0	*b*	*b*

[a] Irradiation; 0.5 h, in liquid carbon dioxide (1.4 mol) at 0 °C. [b] Not detected.

With regard to further details of the alcohol formation, it would be interesting to know the recombination process of the radical pair in liquid carbon dioxide. It was observed in the radiolysis of liquid carbon dioxide with decalin that the distribution of tertiary alcohols shows excellent retention of configuration at the tertiary positions of *cis*- and *trans*-decalin. On the hydrogen abstraction of $O(^3P)$ atoms from the tertiary position of *cis*-decalin, *cis*-9-decalyl radical must be formed initially. 9-Decalyl radicals were examined by various methods, and conformational conversion from *cis*-9-decalyl radical to the more stable *trans*-9-decalyl radical has been known to occur easily.[20] It seems likely that *cis*-9-decalyl radical which formed initially from *cis*-decalin may recombine with OH radical in a solvent cage to give *cis*-decalol-9. The recombination of *cis*-9-decalyl radical with OH radical may compete with the conversion of *cis*-9-decalyl radical to *trans*-9-decalyl radical to some extent. In the case of *trans*-decalin, 9-decalol was obtained with higher retention of configuration as the equilibrium between the two 9-decalyl radicals lies to *trans*-9-decalyl radical.



Ketone Formation. In all runs, small amounts of ketones were formed as a by-product. The *G* values of the formation of cyclohexanone from cyclohexane are approximately constant regardless of dose (Table I). It seems likely that ketones were formed as a primary product from alkanes. Nevertheless, a slight increase in *G* value of cyclohexanone as dose was observed. We would like to suggest that a secondary reaction of cyclohexanol with $O(^3P)$ atoms might be involved. Actually, radiolysis of a cyclohexane–cyclohexanol mixture (10:1) in liquid carbon dioxide resulted in a remarkable increase in *G* value of cyclohexanone formation (Table IV). Further, radiolysis of cyclohexanol in liquid carbon dioxide gave cyclohexanol as a sole oxidized product in high yield ($G = 6.0$). The oxidation process of cyclohexanol can be accounted for by an initial α-hydrogen abstraction by $O(^3P)$ atoms, followed by the fast recombination of geminate radical pairs in a solvent cage to form unstable *gem*-diol which was easily dehydrated, or followed by disproportionation of the radical pairs in a solvent cage producing cyclohexanone and water.

Experimental Section

General Procedure. γ-Radiolysis of liquid carbon dioxide (1.4 mol) in the presence of 0.03–0.3 M concentrations of an alkane was carried out in a stainless steel autoclave (65 mL) using a ^{60}Co (7000 Ci) source at 0 °C for 0.5–3 h. Reactions were run to less than ca. 10% completion to avoid secondary oxidation. The dose rate, measured with the Fricke dosimeter solution, was 1.7×10^{19} eV/g·h. The products were identified by comparison of retention times of GLC and mass spectra (Hitachi RMS-4 GC/MS, Carbowax 20M, 6 m) with those of authentic samples.

Air in an autoclave was replaced with about 20 g of carbon dioxide three times in every experiment before the autoclave was filled out with liquid carbon dioxide. The loss of alkane after this procedure was negligible. The solubilities were checked by quartz autoclave (12 mL).

Materials. Carbon dioxide (99.99%, Fuji Koatsu Gasu Co. Ltd.) from the tank was used without further purification. Cyclohexane and methylcyclohexane used were of spectral grade and were purified by distillation in a spinning band column (60 cm). Analysis by GLC indicates less than 0.01% impurities. *cis*- and *trans*-decalin were obtained commercially and were distilled. The purity of *cis*- and *trans*-decalin, as determined by GLC, was 96 and 99%, respectively. Cyclohexanol was obtained commercially, and was purified by distillation in a spinning band column followed by further purification by preparative GLC. Analysis by GLC indicates about 0.05% cyclohexanone.

Authentic Samples. Cyclohexanone, cyclohexene oxide, 2-, 3-, and 4-methylcyclohexanol, and 2-, 3-, and 4-methylcyclohexanone were obtained commercially (Tokyo Kasei Kogyo Co. Ltd.). Bicyclohexyl was prepared by hydrogenation of biphenyl over Raney nickel W-6 at 160 °C under 150 atm of hydrogen.[21] Cyclohexylcarbinol was prepared by the reaction of cyclohexylmagnesium chloride with formaldehyde.[22] 1-Methylcyclohexanol was prepared by the reaction of cyclohexanone with methyl magnesium iodide in ether.[23] *cis*- and *trans*-decalol-9 were prepared by oxidation of *cis*- and *trans*-decalin with ozone.[24] *cis*- and *trans*-decalol-1- and -2 were prepared by hydrogenation of 1- and 2-naphthol over Raney nickel W-7 at 170 °C under 180 atm of hydrogen.[25] 1- and 2-decalone were prepared by oxidation of 1- and 2-decalol with potassium dichromate and concentrated sulfuric acid.[26] All the products were identified by those boiling points and NMR and IR spectra or by elemental analysis.

Registry No.—Cyclohexane, 110-82-7; carbon dioxide, 124-38-9.

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Notes

A Facile and General Pyridazine Synthesis from α-Diketone Monohydrazones and β-Keto Esters or β-Diketones

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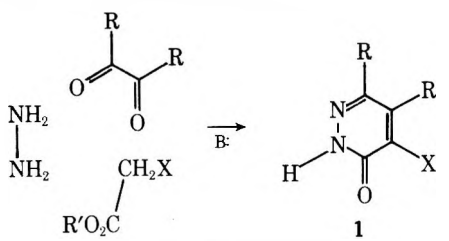
The Schmidt pyridazine synthesis[2] formally involves the base-catalyzed condensation of hydrazine, an α-diketone, and an ester activated methylene compound yielding substituted pyridazinones (**1**). In conjunction with this work, Schmidt and



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X = CO_2R', COR", CN, etc.

Druey[2] reported that, in the abscence of a basic catalyst, reaction of benzil monohydrazone (**7**) with ethyl acetoacetate (**8a**) yields the "azine" **9a** which could not be converted into a ring-closed product (i.e., **10a**) although no details were given. There are, however, examples in the literature of similar cyclizations. Reaction of α-diketone monohydrazones (**2**) with dimethyl acetylenedicarboxylate (DMAD) yields[3] dicarbomethoxypyridazines **3**, presumably via the azines **4** which are also isolated along with several other products (reaction 1). In addition, we have shown[4] that the stabilized phosphorane **5** yields the pyridazinylmethyltriphenylphosphonium salt **6** on heating (reaction 2).

In the course of another investigation we had occasion to synthesize "azine" **9a**. Azine is actually a misnomer since the molecule exists completely (as determined by NMR and IR spectroscopy) in the enamine tautomer, presumably stabilized by intramolecular hydrogen bonding to the benzoyl carbonyl oxygen. To our knowledge, this represents the first example of preference for the enamine tautomer in an azine, although the intermediacy of the enamine form has been postulated[5] in the α-alkylation of aliphatic ketazines by electron-deficient dienophiles (e.g., maleic anhydride). Throughout this discussion, we will refer to these molecules as azines, although their tautomeric structure should be kept in mind.

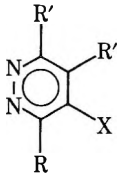
Our original intention was to carry out a series of transformations involving the carboethoxy moiety of **9a** beginning with saponification. When **9a** is heated in aqueous ethanol containing potassium hydroxide a deep red color develops which fades to a very pale yellow after 10 min. The single, colorless product formed retains the carboethoxy group and spectral (IR, NMR, mass spectrum) and elemental analyses indicate that the product is the pyridazine carboxylic ester **10a**. The rapidity and efficiency (>90% isolated yield of **10a**) of this reaction stands in marked contrast to the earlier reports of the inertness of **9a** toward ring closure.[2]

It is not necessary to isolate **9a** and, in fact, considerable

losses result during purification. We have adopted a one-pot procedure consisting of initial formation of the azine by heating the reactants in benzene with azeotropic removal of water, removal of benzene in vacuo, and treatment of the crude azine with a catalytic amount of KOH in hot ethanol. The isolated yield of **10a** based on **7** by this method is 93%. Following the same procedure we have prepared 3,4,6-triphenyl-5-carboethoxypyridazine (**10d**) in 55% overall yield from **7** and ethyl benzoylacetate (**8b**).

Further confirmation of the structures of **10a** and **10d** is provided by their transformation into the known 5-unsubstituted pyridazines **10c** and **10f.** Saponification of the esters **10a** and **10d** yields the acids **10b** and **10e** which readily decarboxylate on heating. The physical and spectral parameters for **10c** and **10f** prepared in this manner are identical with those reported in the literature.[6]

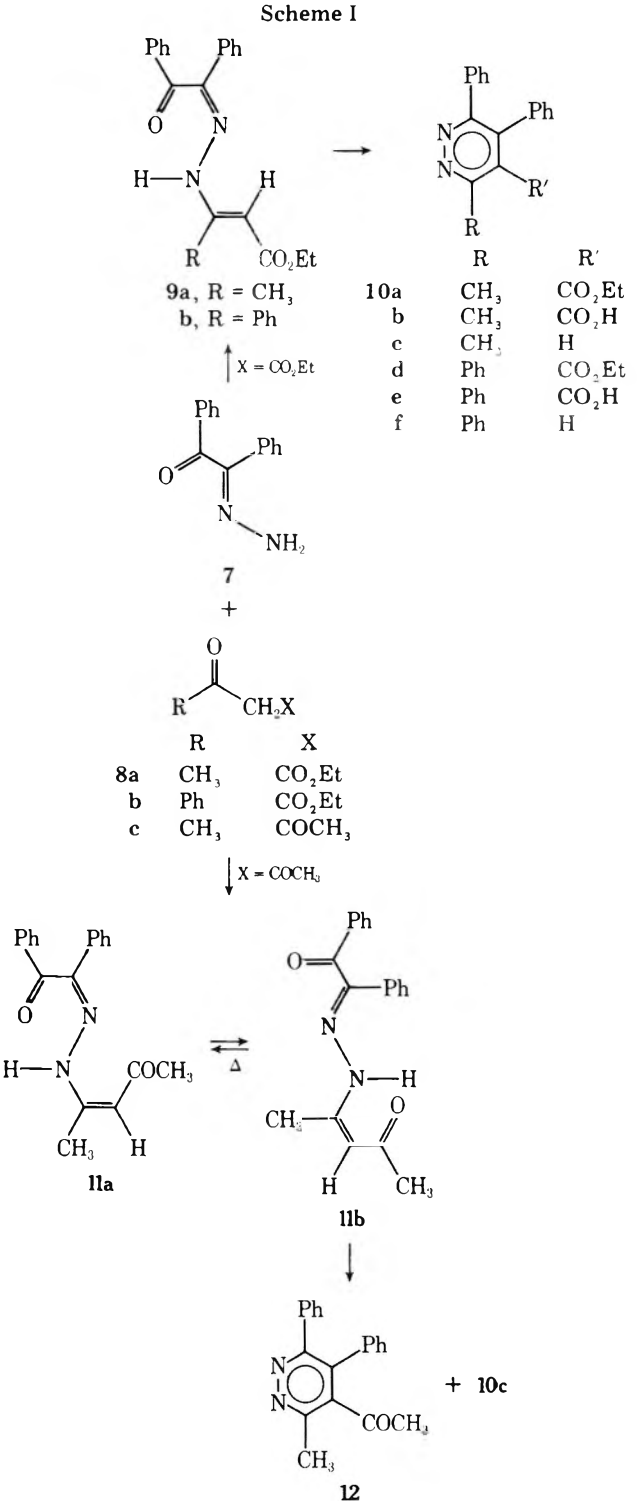
In theory, any carbonyl activated methylene compound of the type **8** (X = any carbanion stabilizing group) should be readily convertible to the corresponding pyridazine **13** by



13

dehydrative ring closure of its azine with an α-diketone (R′COCOR′). To investigate the generality of the reaction, we have examined the reaction of acetylacetone **8c** with **7.** Complex, tarry reaction mixtures result from the attempted one-pot reaction as outlined above. Thus, we prepared and isolated the azine in an initial step prior to its ring closure. The azine, **11,** can be isolated in sufficient purity for further reaction as an orange solid in 73% yield. As in the case of **9a, 11** is completely in the enamine form. However, it consists of a mixture of two thermally interconvertible isomers (A and B) in approximately a 1.5:1 ratio. The IR and NMR spectra are very similar, suggesting the same gross structure. A reasonable explanation is that A and B are syn and anti isomers about the

Scheme I

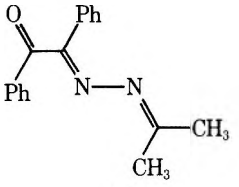


C–N double bond (i.e., **11a** and **11b**). In the anti isomer (**11b**) hydrogen bonding is possible only with the acetyl carbonyl. Similar interactions are possible with either the benzoyl or acetyl carbonyl in the syn isomer **11a;** however, the distinct spectral differences in the methyl, vinyl, and N–H regions of the NMR spectra suggest that the interaction is with the benzoyl carbonyl in this case. We are unable to assign either structure (**11a** or **11b**) unambiguously to either isomer A or B on the basis of the data in hand. Synthetically, the existence of the two isomers presents no difficulty since both yield the same products in the next step.

The ring closure of **11** proves to be more interesting than anticipated. Whereas the cyclizations of **9a** and **9b** to **10a** and **10d** require only a catalytic amount of base, nearly a full equivalent is needed to convert **11** to products. Unlike **9,**

treatment of **11** with hydroxide under a variety of conditions yields a mixture of two products. The expected 3,4-diphenyl-5-acetyl-6-methylpyridazine (**12**) is the minor (10–15%) product. The major (75–80%) product is the 5-unsubstituted pyridazine **10c**. Spectral and analytical data support the acetyl pyridazine structure for **12**. The mass spectrum is particularly useful as a strong peak at *m/e* 245 $(M - CH_3CO)^+$ is observed. Pyridazine **10c** isolated from this reaction is identical in all respects with **10c** prepared above by decarboxylation of **10b**.

There are several reasonable mechanisms to be considered for the formation of **10c** in this reaction. First, it is possible that it arises from **12** by deacylation, a known reaction in pyridazine *N*-oxide chemistry.[7] However, neither shortening the reaction time nor lowering the temperature leads to an increase in the amount of **12** formed. Also, **12** is recovered unchanged after heating with alcoholic KOH for an extended period of time. Alternatively, **10c** could be the result of "deacylation" of **11** to **14**, but **14** is also inert to the reaction



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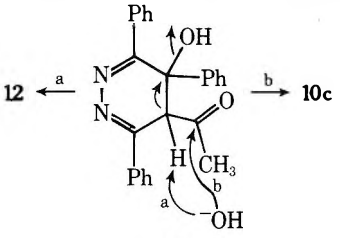
conditions. The evidence suggests a reactive intermediate as the source of **10c**. We believe the probable origin of the mixture of products in this reaction to be competing eliminations from an intermediate dihydropyridazine **15**. Elimination of



15

water (path a) gives the expected **12**, while attack of hydroxide at the acetyl carbonyl (path b) yields the "deacylated" product **11a** by elimination of acetic acid and hydroxide. Steric crowding coupled with the increased electrophilicity of the ketone carbonyl carbon compared with that of an ester may be responsible for the favorable competition of the "abnormal" elimination in this system.

We have demonstrated that azines derived from α-diketones and either β-keto esters or β-diketones exist predominantly in the unique enamine tautomeric form and are useful precursors for the pyridazine ring system. The ready availability of active methylene compounds of the type **8** should make this an attractive route to a variety of pyridazine derivatives.

Experimental Section

Benzilacetone azine (**14**) was prepared by heating benzil monohydrazone in acetone containing a catalytic amount of glacial acetic acid, a modification of the method of Taylor et al.[8] All other reagents were commercial (Aldrich) products and used as received. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 337 instrument referenced to polystyrene film. A Perkin-Elmer R12b nuclear magnetic resonance spectrometer was used to obtain the ^1H NMR data. Spectra were recorded as 5–10% solutions in $CDCl_3$ except as noted and chemical shifts are reported as parts per million (δ) vs. Me_4Si as an internal standard. Mass spectra were recorded on a Du Pont CEC21-110D instrument with a resolution of 1000 (30% valley). Elemental analyses were performed by Micro-Analysis Inc., Wilmington, Del.

Preparation of Benzilethylacetoacetate Azine (9a). To 75 mL of benzene is added 3.5 g (0.027 mol) of ethyl acetoacetate and 5.6 g (0.0246 mol) of benzil monohydrazone and a catalytic amount (10–20 mg) of *p*-toluenesulfonic acid. A Dean-Stark water collector, condenser, and $CaCl_2$ drying tube are attached and the reaction mixture heated at reflux until the theoretical amount of water has collected (~2 h). The benzene is removed in vacuo and the residual golden oil triturated with cold methanol to yield 6.2 g (75%) of a yellow solid, mp 85–100 °C.

The NMR spectrum indicates that this material is essentially pure despite the wide melting point range and it can be converted in high yield to the pyridazine **10a** upon treatment with alcoholic KOH. Repeated crystallization from ethanol yields an analytical sample: mp 110.5–112.5 °C; IR 3190 (br), 1660, 1615, 1565, 1350 cm^{-1}; ^1H NMR δ 1.10 (t, J = 7 Hz, 3 H, $-OCH_2CH_3$), 2.01 [s, 3 H, $CH_3C(NH)=CH-$], 3.89 (q, J = 7 Hz, 2 H, $-OCH_2CH_3$), 4.37 (br s, 1 H, C=CH), 7.3 (br s, 8 H, aromatic), 7.8 (m, 2 H, aromatic ortho to C=O), 11.42 (br s, 1 H, NH). Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99. Found: C, 71.12; H, 6.05.

Preparation of 3,4-Diphenyl-5-carboethoxy-6-methylpyridazine (10a). The crude oily azine (above) from 2.7 g (0.021 mol) of ethyl acetoacetate and 4.5 g (0.02 mol) of benzil monohydrazone is dissolved in 75 mL of hot ethanol and 0.2 g of potassium hydroxide is added. A deep red color develops which fades on gentle boiling for 10 min to a pale yellow. The ethanol is removed in vacuo and the residue is partitioned between 50 mL of ether and 10 mL of 5% NaOH. The layers are separated and the ether layer extracted with 10 mL of 5% NaOH, 2 × 10 mL of 5% HCl, and 10 mL of H_2O, dried (Na_2SO_4), and evaporated in vacuo to yield 5.92 g (93%) of **10a**, mp 78–80 °C. Recrystallization from methylene chloride/heptane affords a colorless analytical sample: mp 85.5–86.5 °C; IR (KBr) 1725, 1490, 1440, 1370, 1305, 1225 cm^{-1}; ^1H NMR δ 0.92 (t, J = 7 Hz, 3 H, $-OCH_2CH_3$), 2.74 (s, 3 H, ring CH_3), 4.02 (q, J = 7 Hz, 2 H, $-OCH_2CH_3$), 7.1 (br s, 10 H, aromatic); mass spectrum *m/e* (% base) 318 (41.6) M^+, 289 (100), 178 (49.2). Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70. Found: C, 75.41; H, 5.49.

Saponification of 10a. Preparation of 3,4-Diphenyl-6-methyl-5-pyridazinecarboxylic Acid (10b). Ester **10a** (1.5 g, 4.7 mmol) is heated for 15 h in 40 mL of 50% alcohol containing 0.6 g (~8.9 mmol) of potassium hydroxide. The bulk of the ethanol is removed in vacuo and the residue acidified to pH ≃2 with 5% HCl and thoroughly extracted with methylene chloride. After drying (Na_2SO_4) and removal of the solvent in vacuo, the combined CH_2Cl_2 extracts yield 1.25 g (86%) of **10b** as a white solid. Crystallization from acetonitrile yields an analytical sample: mp 180–181 °C dec (with gas evolution); IR (KBr) 3500 (br), 1720, 1440, 1380 cm^{-1}; ^1H NMR ($CDCl_3$ + Me_2SO-d_6) δ 2.74 (s, 3 H, ring CH_3), 7.16 (br s, 10 H, aromatic), 10.07 (br s, 1 H, $-CO_2H$); mass spectrum *m/e* (% base) 290 (0.3) M^+, 289 (1.2), 246 (94.4), 245 (100), 178 (93.5). Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86. Found: C, 74.27; H, 4.81.

Decarboxylation of 10b. Preparation of 3,4-Diphenyl-6-methylpyridazine (10c). In a 10-mL round-bottom flask fitted with a $CaCl_2$ drying tube is placed 400 mg of acid **10b**. The flask is immersed in an oil bath held at 200 °C for 30 min. As the sample melts it darkens and gas is evolved. The crude tan residue (0.34 g, 99%, mp 119–122 °C) is dissolved in 15 mL of 95% ethanol, treated with Darco G-60 activated carbon, and filtered and the solvent removed. The resulting light yellow solid is recrystallized from methylene chloride/heptane to yield **10c** as an off-white solid: mp 121–123 °C (lit.[5] 122–123 °C); IR (KBr) 1580, 1565, 1400 cm^{-1}; ^1H NMR δ 2.71 (s, 3 H, ring CH_3), 7.16 (m, 11 H, aromatic + pyridazine ring H); mass spectrum *m/e* (% base) 246 (62.0) M^+, 245 (100), 178 (82.3).

Preparation of 3,4,6-Triphenyl-5-carboethoxypyridazine (10d). The procedure is identical with that described above for the preparation of **10a**, except that 15 h is required to collect the theoretical amount of water in the initial step of the reaction. The crude "azine" thus obtained from 2.25 g (0.01 mol) of benzil monohydrazone and 2.3 g (0.012 mol) of ethyl benzoylacetate is heated in 40 mL of ethanol containing 0.36 g of KOH for 20 min. Again a deep red color which fades as the reaction proceeds is noted. Workup as above and crystallization from ethanol yields 2.08 g (55%) of **10d** as a pale yellow solid, mp 120–124 °C. Recrystallization from ethanol yields a colorless analytical sample: mp 124–125 °C; IR 1730, 1380, 1295 cm^{-1}; ^1H NMR δ 0.78 (t, J = 7 Hz, 3 H, $-OCH_2CH_3$), 3.83 (q, J = 7 Hz, 2 H, $-OCH_2CH_3$), 7.2 (br m, 13 H, aromatic), 7.7 (br m, 2 H, ortho protons in 6-phenyl ring); mass spectrum *m/e* (% base) 380 (36.5) M^+, 351 (74.6), 178 (100). M^+, calcd for $C_{25}H_{20}N_2O_2$: 380.09. Found: 380.15.

Saponification of 10d. Preparation of 3,4,6-Triphenyl-5-pyr-

idazinecarboxylic Acid (10e). Saponification and workup as above for the hydrolysis of **10a** yields, from 1.0 g (2.64 mmol) of pyridazine ester **10d**, 0.75 g (81%) of acid **10e** as an off-white solid, mp 214–215 °C dec (with gas evolution). Crystallization from ethanol yields a colorless analytical sample: mp 215–215.5 °C dec (with gas evolution); IR ~3500 (br), 1710, 1370, 1280 (br), 1220 cm^{-1}; ^1H NMR ($CDCl_3$ + Me_2SO-d_6) δ 7.3 (m, 13 H, aromatic), 7.8 (m, 2 H, ortho protons, 6-phenyl), 9.09 (br s, 1 H, CO_2H); mass spectrum *m/e* (% base) 352 (12.7) M^+, 308 (90.3), 307 (100), 178 (99.0). M^+, calcd for $C_{23}H_{16}N_2O_2$: 352.12. Found: 352.15.

Decarboxylation of 10e. Preparation of 3,4,6-Triphenylpyridazine (10f). In a 25-mL round-bottom flask fitted with a $CaCl_2$ drying tube is placed 300 mg (0.855 mmol) of pyridazinecarboxylic acid **10e**. The flask is immersed in a 220 °C oil bath for 30 min. As the sample melts, vigorous gas evolution is observed. The yield of slightly yellow solid, mp 170–175 °C, is 0.26 g (99%). Recrystallization from ethanol affords colorless material: mp 170–172 °C (lit.[5] 171–172 °C); IR (KBr) 1580, 1560, 1395 cm^{-1}; ^1H NMR δ 7.2 (br m, 13 H, aromatic), 7.59 (s, 1 H, pyridazine ring H), 7.97 (m, 2 H, ortho protons, 6-phenyl ring); mass spectrum *m/e* (% base) 309 (54.0), 308 (99.6), 307 (100), 178 (99.4).

Preparation of Benzilacetylacetone Azine (11). A mixture of 4.5 g (0.02 mol) of benzil monohydrazone and 4.0 g (0.04 mol) of acetylacetone (**8c**) is heated at reflux in ethanol containing 100 mg of benzoic acid for 60 h. On cooling an orange solid precipitates which is isolated by filtration, yielding 4.48 g (73%) of **11**, mp 122–159 °C. ^1H NMR indicates that this is a 1.5:1 mixture of two isomers, A and B. Careful fractional crystallization from ethanol or carbon tetrachloride allows the isolation of both isomers. Isomer A: light yellow plates, mp 161–162 °C; IR ($CHCl_3$) 3100 (br), 3010, 1635, 1565, 1490 cm^{-1}; ^1H NMR δ 1.90 (s, 3 H, CH_3C=C), 1.99 (s, 3 H, $COCH_3$), 5.11 (s, 1 H, C=CH), 7.3 (m, 8 H, aromatic), 7.8 (m, 2 H, aromatic ortho to C=O), 12.91 (br s, 1 H, NH). Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92. Found: C, 74.25; H, 5.90. Isomer B: orange-yellow chunky crystals, mp 146–149 °C; IR ($CHCl_3$) 3100 (br), 3020, 1675, 1620, 1570 cm^{-1}; ^1H NMR δ 1.88 (s, 3 H, CH_3C=C), 2.18 (s, 3 H, CH_3C=O), 5.00 (s, 1 H, C=CH), 7.3 (m, 8 H, aromatic), 7.8 (m, 2 H, aromatic ortho to C=O), 13.47 (br s, 1 H, NH). Either pure isomer is converted to the equilibrium mixture (~1.5:1, A:B) on heating in ethanol for several hours.

Cyclization of 11. Preparation of 3,4-Diphenyl-5-acetyl-6-methylpyridazine (12) and 3,4-Diphenyl-6-methylpyridazine (10c). To a gently boiling solution of 115 mg (~1.78 mmol) of potassium hydroxide in 15 mL of ethanol is added 0.46 g (1.50 mmol) of azine **11** (mixture of isomers). A deep red color develops which fades rapidly. After heating for 5 min, the bulk of the ethanol is removed in vacuo and the residue partitioned between ether and 5% NaOH. The layers are separated, the organic layer thoroughly extracted with 5% HCl, and the acid extracts reserved. The ether layer is dried (Na_2SO_4) and evaporated in vacuo to yield 50 mg (12%) of **12** as a pale yellow solid. Purification by sublimation (140 °C, 1 mm) and recrystallization (CH_2Cl_2/heptane) yields an analytical sample: mp 131.5–132.5 °C; IR (KBr) 1695, 1440, 1375 cm^{-1}; ^1H NMR δ 1.86 (s, 3 H, CH_3C=O), 2.62 (s, 3 H, ring CH_3), 7.2 (br s, 10 H, aromatic); mass spectrum *m/e* (% base) 288 (87.9) M^+, 287 (100), 245 (75.1), 178 (28.3). Anal. Calcd for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59. Found: C, 79.17; H, 5.86.

Basification of the acid extracts (above) and extraction with methylene chloride yields, after drying (Na_2SO_4) and removal of the CH_2Cl_2 in vacuo, 0.29 g (79%) of **10c**, identical in all respects with the material prepared by decarboxylation of **10b**.

Registry No.—**7**, 5344-88-7; **8a**, 141-97-9; **8b**, 94-02-0; **8c**, 105-45-3; **9a**, 62139-81-5; **10a**, 62139-82-6; **10b**, 62139-83-7; **10c**, 13340-82-4; **10d**, 62139-84-8; **10e**, 62139-85-9; **10f**, 2272-58-4; **11a**, 62139-86-0; **11b**, 62139-87-1; **12**, 62139-88-2.

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2-Phenylthio-2-cyclopentenone, a Useful Synthon for 2,3-Disubstituted Cyclopentanones. Synthesis of *dl*-Methyl Dehydrojasmonate

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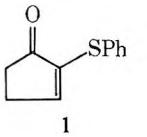
Recently, there has been an increasing amount of research devoted to the development of useful synthetic routes to 2,3-disubstituted cyclopentanones, mainly because of the interest in the pharmacologically important prostaglandins. However, most of the published routes either use as starting material the commercially expensive 2-cyclopentenone[1] or 2-alkylated 2-cyclopentenones,[2] which are not themselves readily available. 2-Phenylthio-2-cyclopentenone (**1**) is expected to be a very useful synthon for the preparation of several 2,3-disubstituted cyclopentanones, since it bears the adequate functionalities for conjugate alkylations,[1,3] or Michael-type additions followed by a regiospecifically directed[4] alkylation at the 2 position ensured by the thioether function. The described[5] syntheses of **1** are too laborious and expensive; therefore, a facile preparation was sought.

Oki[6] described the formation of 2-methylthio-2-cyclohexenone by the reaction of phenylsulfenyl chloride with 2-methylthiocyclohexanone, but did not exploit the preparative aspects of this interesting transformation. We reasoned that, since 2-phenylthiocyclopentanone is expected[7] to be the primary product from the reaction of phenylsulfenyl chloride with cyclopentanone, **1** could be prepared in a single step by reaction of the ketone with an excess of the sulfenyl chloride. Indeed, treatment of cyclopentanone with phenylsulfenyl chloride in dry acetonitrile, followed by chromatography on silica gel, afforded 55–65% yields of the pure unsaturated ketone **1**, based on cyclopentanone. The method[8] is quite economical, since the diphenyl disulfide formed in the reaction can be recovered and reconverted into phenylsulfenyl chloride.

Initial alkylation experiments of **1** with *n*-amylmagnesium



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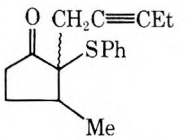

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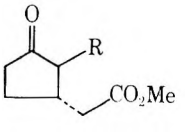

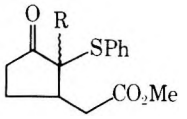

3, R = CH_2CH=CHEt-*cis* **5**, R = H
4, R = CH_2C≡CEt **6**, R = CH_2C≡CEt

bromide without copper salt catalysis resulted in about a 45% yield of 1,4-addition, as evidenced by spectroscopic analyses of the reaction products. This large proportion of conjugate addition may be possibly caused by the inductive or steric effects of the 2-phenylthioether group.

On the other hand, alkylation of **1** with lithium dimethylcuprate followed by quenching of the enolate with 2-pentynyl bromide, according to Coates' procedure,[3a] afforded, after preparative TLC, good yields of the ketone **2** as an epimeric mixture. No 5-alkylated ketone could be detected among the minor products, indicating that enolate equilibration[1,4] does not take place under the reaction conditions.

To further test the synthetic potentialities of the ketone **1**,

and also encouraged by its ready availability, we turned our attention to a practical synthesis of methyl jasmonate (3), a useful raw material in the perfume industry.[9]

Michael reaction of 1 with dimethyl malonate and sodium methoxide in methanol, followed by acid hydrolysis and decarboxylation of the crude adduct, and subsequent esterification of the resulting acid with methanol gave the expected ester 5 in 84% overall yield. The phenylthioether group in 5 was ready to serve its purpose, which was to guarantee the regiospecific alkylation[4] at the sulfur bearing carbon atom. Thus, alkylation of the keto ester 5 with 2-pentynyl bromide and sodium hydride in glyme gave the expected ester 6, which was isolated from polymeric and other, nonidentified, minor products on preparative TLC, in 63% yield. Although compound 6 appeared homogeneous on analytical TLC, its NMR spectrum showed it to be a mixture of the two expected epimers at the newly alkylated center in the approximate ratio of 1.6:1. As the phenylthioether grouping was to be removed in the next step, generating a new epimeric center susceptible to equilibration, no endeavor was made to separate and further characterize the isomers. Instead, the epimeric mixture of 6 was treated with aluminum amalgam, a smooth cleavage of the thioether function taking place to afford, after purification on preparative TLC, a 92% yield of pure *dl*-methyl dehydrojasmonate (4), which was identical with the material previously prepared by other workers.[9a-c,g] Since 4 can be readily hydrogenated to *dl*-methyl jasmonate (3),[9a-c,g] its synthesis of the above procedure constitutes a new and efficient route to that interesting substance, and exemplifies a useful method of preparation of 2,3-disubstituted cyclopentanones.

Experimental Section

General. All solvents were distilled before use. Melting points were measured in a Kofler block and are uncorrected. Analytical and preparative TLC were run on fluorescent (GF_{254}) or Rhodamine 6G dyed Merck silica gel plates. ^1H NMR spectra were recorded on a Varian A-60D spectrometer using carbon tetrachloride as solvent and tetramethylsilane as internal standard. Infrared spectra were recorded on a Perkin-Elmer 137 instrument. Mass spectra were obtained on Varian MAT CH-5 and 731 spectrometers.

2-Phenylthio-2-cyclopentenone (1). Phenylsulfenyl chloride (4.40 g, 33 mmol) was added to a solution of cyclopentanone (0.84 g, 10 mmol) in dry acetonitrile (15 mL), cooled by a water bath. After stirring at room temperature for 2 h, the mixture, protected from moisture, was filtered and the residue washed with acetonitrile. The filtrate was evaporated under vacuum on the steam bath. To the residue was added boiling methanol (20 mL), the mixture reevaporated under vacuum, and the whole process repeated a second time. Chromatography of the oily residue on a silica gel column (eluting solvents: petroleum ether and petroleum ether–ether, 9:1) gave diphenyl disulfide (1.58 g) and 1 (1.07 g, 56.5%), identical with the authentic material.[5]

2-Phenylthio-2-(2′-pentynyl)-3-methylcyclopentanone (2). A solution of the ketone 1 (190 mg, 1.0 mmol) in anhydrous ether (5 mL) was added dropwise, under stirring and argon, to a chilled solution of lithium dimethylcuprate prepared from methyllithium (2.2 mL of 1.1 M ether solution, 2.4 mmol) and cuprous iodide (230 mg, 1.2 mmol) in dry ether (5 mL). After the addition, the bath was removed and the solvent evaporated almost to dryness under vacuum. The flask was again chilled, and the residue dissolved in dry glyme (5 mL). 2-Pentynyl bromide (500 mg, 3.4 mmol) was then added, and the mixture left stirring at room temperature for 2 h. After cooling in an ice bath, the reaction was quenched with aqueous saturated NH_4Cl and extracted with ether. The extract was washed successively with brine and 5% NaOH, dried (Na_2SO_4), and evaporated. Preparative TLC of the oily residue (eluting solvent: ether–petroleum ether, 1:9) yielded 2 (176 mg, 65%). An analytical sample was prepared by bulb-to-bulb distillation at 0.005 mm (120 °C bath temperature): IR (film) 1740 cm^{-1}; ^1H NMR 0.95–1.40 (m, 6 H, CH_3CH_2 and CH_3CH), 1.50–2.70 (m, 9 H), 7.10–7.60 ppm (m, 5 H, Ar). Anal. Calcd for $C_{17}H_{20}OS$: *m/e* 272.1230. Found: *m/e* 272.1242.

2-Phenylthio-3-methoxycarbonylmethylcyclopentanone (5). Dimethyl malonate (393 mg, 2.98 mmol) was added to a solution of sodium (65 mg, 2.82 mmol) in methanol (5 mL). To this mixture, under argon and chilled in an ice bath, was added a solution of 1 (500 mg, 2.63 mmol) in methanol (4 mL). After stirring for 1.5 h, the reaction was quenched with 10 N HCl (10 mL), the methanol distilled off, and the aqueous mixture refluxed for 24 h. The cold reaction mixture was extracted with ether, the ethereal extracts washed with 10% $NaHCO_3$, and the basic washings acidified with 10 N HCl. Extraction with ether, followed by washing of the organic phase with brine, drying (Na_2SO_4), and evaporation under vacuum, gave the crude acid. The residue was dissolved in dry methanol (6 mL) containing a drop of concentrated sulfuric acid. After standing overnight under argon at room temperature $NaHCO_3$ (200 mg) was added, and the methanol removed under vacuum. The oily residue was taken into ether, washed successively with 10% $NaHCO_3$ and brine, and dried (Na_2SO_4). Evaporation of the solvent left practically pure 5 (586 mg, 84%). An analytical sample was prepared by bulb-to-bulb distillation at 0.005 mm (125 °C bath temperature): IR (film) 1740 cm^{-1}; ^1H NMR 1.17–3.22 (m, 8 H), 3.47 (s, 3 H, CH_3O), 7.12–7.57 ppm (m, 5 H, Ar). Anal. Calcd for $C_{14}H_{16}O_3S$: *m/e* 264.0816. Found: *m/e* 264.0855. Semicarbazone: mp 185–187 °C (from MeOH). Anal. Calcd for $C_{15}H_{19}N_3O_3S$: *m/e* 321.1147. Found: *m/e* 321.1151.

2-Phenylthio-2-(2′-pentynyl)-3-methoxycarbonylmethylcyclopentanone (6). Sodium hydride (89 mg, 3.70 mmol) was added to a solution of 5 (890 mg, 3.37 mmol) in dry glyme (10 mL), kept in an ice bath with efficient stirring under an argon atmosphere. After the evolution of hydrogen subsided, 2-pentynyl bromide (660 mg, 4.50 mmol) was added, and the mixture left stirring for 2 h at 0 °C and 16 h at room temperature. The dark brown reaction mixture was then chilled in an ice bath, quenched with saturated aqueous NH_4Cl, and extracted with ether. The ether extracts were washed successively with brine, 5% NaOH, and brine, and dried (Na_2SO_4). Evaporation of the solvent under vacuum gave a dark oil, which was extracted with hot *n*-hexane. Evaporation of the hexane extract and preparative TLC (eluting solvent: ether–petroleum ether, 3:7) gave 6 (696 mg, 63%). An analytical sample was prepared by bulb-to-bulb distillation at 0.001 mm (125 °C bath temperature): IR (film) 2250, 1740 cm^{-1}; ^1H NMR 1.12, 1.17 (two overlapping t, 3 H, J = 7 Hz, CH_3CH_2), 1.75–3.15 (m, 11 H), 3.67, 3.70 (two overlapping s, 3 H, CH_3O), 7.32 ppm (s, 5 H, Ar). Anal. Calcd for $C_{19}H_{22}O_3S$: *m/e* 330.1284. Found: *m/e* 330.1261.

2-(2′-Pentynyl)-3-methoxycarbonylcyclopentanone (*dl*-Methyl Dehydrojasmonate, 4). A solution of 6 (162 mg, 0.49 mmol) in 10% aqueous THF (50 mL) was added to aluminum amalgam (1.75 g, 65 mmol) prepared according to Fieser and Fieser.[10] The mixture was stirred at room temperature until complete dissolution of the metal. Saturated NH_4Cl was added, the organic layer decanted, and the aluminum hydroxide slurry further extracted with ether. The combined extracts were washed with saturated NH_4Cl, dried (Na_2SO_4), and evaporated. Preparative TLC (eluting solvent: ether–petroleum ether, 2:8) afforded *dl*-methyl dehydrojasmonate (4, 100 mg, 92%). Bulb-to-bulb distillation at 0.01 mm (90 °C bath temperature) gave an analytical sample: IR (film) 1740 cm^{-1}; ^1H NMR 1.08 (t, 3 H, J = 7 Hz, CH_3CH_2), 1.68–2.97 (m, 12 H), 3.63 ppm (s, 3 H, CH_3O). Semicarbazone: mp 167–168 °C (from MeOH) (lit. 169–171,[9a] 168–169 °C[9c]).

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Registry No.—1, 34780-08-0; *cis*-2, 62067-30-5; *trans*-2, 62067-31-6; 4, 29119-47-9; 5, 62067-32-7; 5 semicarbazone, 62067-33-8; *cis*-6, 62067-34-9; *trans*-6, 62067-35-0; phenylsulfenyl chloride, 931-59-9; cyclopentanone, 120-92-3; 2-pentynyl bromide, 16400-32-1; dimethyl malonate, 108-59-8.

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A New Synthesis of *dl*-Muscone

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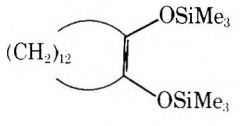
We wish to report a convenient synthesis of *dl*-muscone (**7**),[1] employing as its key step the $FeCl_3$ induced ring expansion of bis(trimethylsilyloxy)bicyclo[*n*.1.0]alkanes (e.g., **3** → **4**) which was found by us.[2] Our synthesis started from electrolysis of methyl hydrogen suberate producing dimethyl tetradecanedioate (**1**),[3] of which the silyl acyl condensation according to the Rühlmann procedure[4] afforded 1,2-bis(trimethylsilyloxy)cyclotetradecene (**2**). Cyclopropanation of **2**



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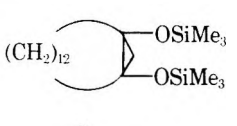

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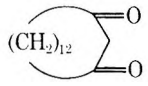

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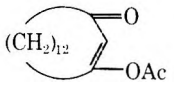

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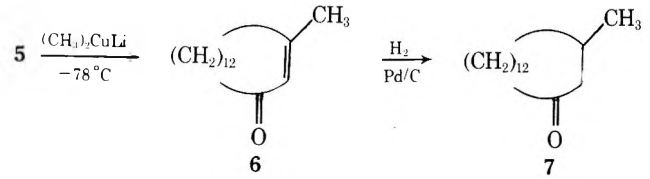
with diethylzinc and methylene diiodide[5] furnished a high yield of 1,14-bis(trimethylsilyloxy)bicyclo[12.1.0]pentadecane (**3**). But use of the conventional Simmons–Smith reagent, zinc–copper couple and methylene diiodide,[6] for cyclopropanation of **2** produced a complex mixture including **3**. A solution of **3** (10 mmol) in DMF (5 mL) was added to a stirring solution of anhydrous $FeCl_3$ (20 mmol) in DMF (25 mL) at room temperature, and the mixture was heated at 60 °C for 3 h. Acid workup and column chromatography on silica gel (benzene eluent) furnished cyclopentadecane-1,3-dione (**4**) as a keto–enol tautomer mixture in 88% yield. Conjugate addition[7] of lithium dimethylcopper to the enol acetate (**5**),



6 **7**

which was readily derived by the reaction of **4** with isopropenyl acetate in the presence of *p*-toluenesulfonic acid,[8] followed by the workup with aqueous NH_4Cl and the subsequent hydrogenation with Pd/C of the resulting 3-methyl-2-cyclopentadecenone (**6**), yielded *dl*-muscone (**7**) as a light yellow oil (78%). The overall yield of *dl*-muscone from the readily available methyl hydrogen suberate is about 23%.

Experimental Section

Materials. Anhydrous $FeCl_3$ was prepared by treating $FeCl_3 \cdot 6H_2O$ with thionyl chloride. Diethylzinc[9] was prepared by the reaction of zinc–copper couple with ethyl iodide and ethyl bromide. Dimethyl tetradecanedioate (**1**) was synthesized in 65% yield by electrolysis of methyl hydrogen suberate according to the procedure[3] employed for decarboxylative dimerization of methyl hydrogen sebacate producing dimethyl octadecanedioate.

1,2-Bis(trimethylsilyloxy)cyclotetradecene (2). Under a nitrogen atmosphere, a solution of 13.7 g (48 mmol) of dimethyl tetradecanedioate (**1**) in 50 mL of xylene was added dropwise into a stirring mixture of a fine dispersion of molten sodium (5.75 g, 0.25 g-atom) and 28.2 g (260 mmol) of trimethylchlorosilane in 200 mL of xylene at 40–50 °C over 3 h, and then the reaction mixture was heated at reflux for 5 h. After cooling, the reaction mixture was filtered to remove sodium chloride and concentrated in vacuo. The residue was subjected to Kugelrohr distillation to afford 11.2 g (63% yield) of 1,2-bis(trimethylsilyloxy)cyclotetradecene (**2**): bp 100–110 °C (1 mm); IR (neat) 1672, 1250, 1210, 850 cm^{-1}; NMR (CCl_4) δ 0.14 (s, 18 H), 1.20–1.70 (m, 20 H), 1.80–2.20 (m, 4 H).

Anal. Calcd for $C_{20}H_{42}O_2Si_2$: C, 64.80; H, 11.42. Found C, 64.92; H, 11.38.

Cyclopentadecane-1,3-dione (4). Under a nitrogen atmosphere, 8.61 g (32 mmol) of methylene diiodide was added dropwise to a stirring mixture of 3.95 g (32 mmol) of diethylzinc[9] and 5.92 g (16 mmol) of 1,2-bis(trimethylsilyloxy)cyclotetradecene (**2**) in 50 mL of benzene at room temperature and then the mixture was heated at reflux for 3 h. The reaction mixture was worked up with aqueous NH_4Cl and extracted with benzene. The benzene extract was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Kugelrohr distillation of the residue afforded 4.98 g (81% yield) of 1,14-bis(trimethylsilyloxy)bicyclo[12.1.0]pentadecane (**3**): bp 110–120 °C (1 mm); IR (neat) 3070, 1250, 1220, 840 cm^{-1}; NMR (CCl_4) δ 0.12 (s, 18 H), 0.30–0.70 (m, 2 H), 0.70–2.00 (m, 24 H).

A solution of 3.84 g (10 mmol) of **3** in 5 mL of DMF was added to a stirring solution of 3.25 g (20 mmol) of anhydrous $FeCl_3$ in 25 mL of DMF at room temperature, and the mixture was heated at 60 °C for 3 h. The reaction mixture was poured into 10% aqueous HCl and extracted with chloroform. The chloroform extract was washed with 10% aqueous HCl and with water and dried over anhydrous Na_2SO_4. After the chloroform solution was evaporated, the residue was subjected to column chromatography on silica gel (benzene eluent) to furnish 2.10 g (88% yield) of cyclopentadecane-1,3-dione (**4**) as a keto–enol tautomer mixture. **4**: IR (neat) 1700, 1600 cm^{-1} (broad); NMR ($CDCl_3$ with Me_4Si) δ 1.44–2.00 (broad s, 20 H), 2.32–2.62 (m, 4 H), 3.68 (s) + 5.67 (s) + 15.72 (broad s) (2 H); mass spectrum M^+ *m/e* 238.

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.71; H, 11.18.

***dl*-Muscone (7).** A mixture of 2.38 g (10 mmol) of cyclopentadecane-1,3-dione (**4**) and 5 mL of isopropenyl acetate was heated at reflux for 3 h with 100 mg of *p*-toluenesulfonic acid.[8] The reaction mixture was poured into ice-cold water and extracted with chloroform. The chloroform extract was washed with aqueous NaCl and dried over Na_2SO_4. After the chloroform solution was evaporated, the residue was subjected to column chromatography (silica gel–chloroform) to produce 2.75 g of 3-acetoxy-2-cyclopentadecenone (**5**): IR (neat) 1770, 1700, 1630 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 1.10–1.80 (broad s, 16 H), 2.25 (s, 3 H), 2.10–2.50 (broad m, 4 H), 5.85 (s, 1 H). Lithium dimethylcopper,[7] prepared from 415 mg (2.3 mmol) of cuprous iodide and 4.6 mmol of methyllithium in 10 mL of ether at 0 °C, was added dropwise to a stirring solution of 560 mg (2.0 mmol) of **5** in 10 mL of ether, which was kept at −78 °C. The reaction mixture was stirred for an additional 30 min at −78 °C, and worked up with aqueous NH_4Cl, followed by extraction with ether. The ether extract was concentrated and subjected to the conventional hydrogenation with Pd/C. *dl*-Muscone (**7**, 372 mg, 78% yield) was isolated by preparative TLC on silica gel (chloroform solvent) as a light yellow oil, which was identified by comparison of its spectral data with those of an authentic sample.[10]

Registry No.—**1**, 5024-21-5; **2**, 62078-79-9; **3**, 62078-80-2; **4**, 21173-90-0; **5**, 62078-81-3; **7**, 956-82-1; trimethylchlorosilane, 75-77-4.

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(10) The authors thank Drs. H. Nozaki and K. Utimoto of Kyoto University for the spectral data of *dl*-muscone.

Total Synthesis of β-Elemenone

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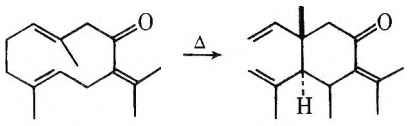
β-Elemenone (2) is a sesquiterpenoid isopropylidene cyclohexanone which has been isolated from Bulgarian zdravets oil[2] and *Rhododendron adamsii* Rehd.[3] The principal component of Bulgarian zdravet oil, germacrone 1,[4] undergoes



1 2

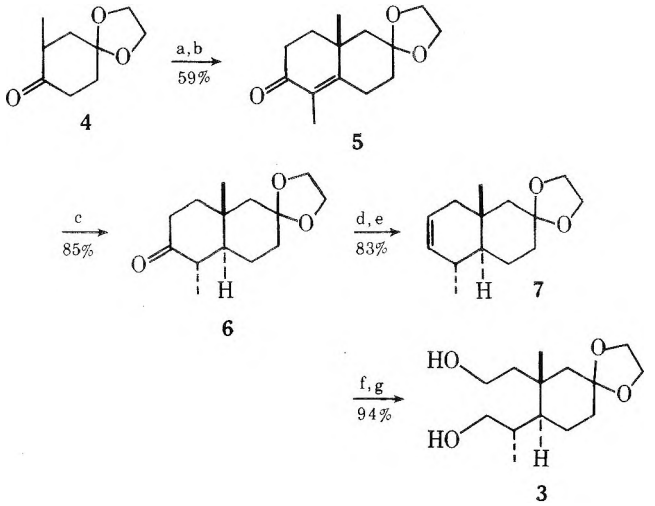
smooth thermal rearrangement to β-elemenone.[2,5,6] No recorded synthesis of β-elemenone has been described. This note details the total synthesis of racemic 2 which involves a facile method for the construction of the *trans*-1,2-divinylcyclohexane unit.

The key intermediate diol 3 was prepared from 2-methyl-4-ethylenedioxycyclohexanone (4) as outlined in Chart I. Intermediate 3 possesses appropriate functionality for the introduction of the two vinyl units as well as for construction of the isopropylidene unit. The annelated product 5 has been prepared on several previous occasions from compound 4 and various ethyl vinyl ketone equivalents including ethyl vinyl ketone.[7-10] In all cases reported the overall yield of isolated ring annelated material is less than 40%.

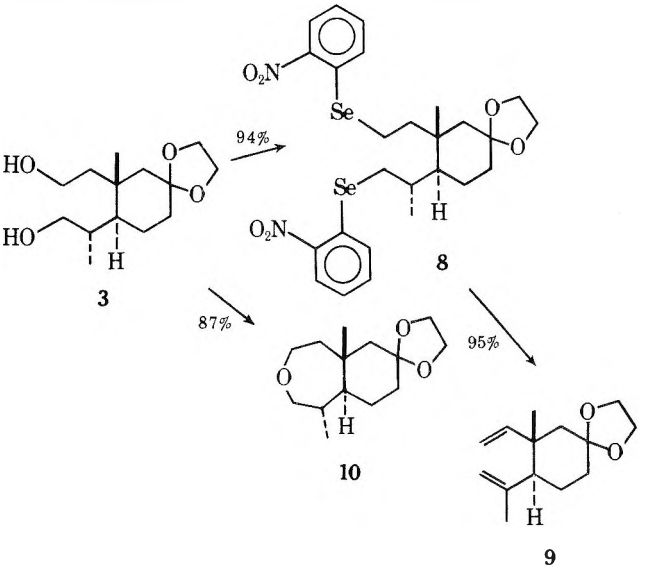
We have found that treatment of 4 with 1.3 equiv of sodium hydride in tetrahydrofuran and 1.8 equiv of 1-chloro-3-pentanone followed by treatment with methanolic potassium hydroxide gave reproducibly a 60% yield of 5 with only a trace amount of 4 remaining (see Experimental Section).

Generation of the trans ring fusion was carried out in a straightforward manner as indicated in Chart I. Introduction of the double bond in compound 6 was established by kinetic enolate formation followed by trapping of the enolate with diethyl chlorophosphate. The enol phosphate was reduced with lithium in ethylamine.[11] Ozonolysis of 7 with a sodium borohydride workup provided in very high yield intermediate diol 3, mp 61–62°.

Chart I. Synthesis of Intermediate Diol 3



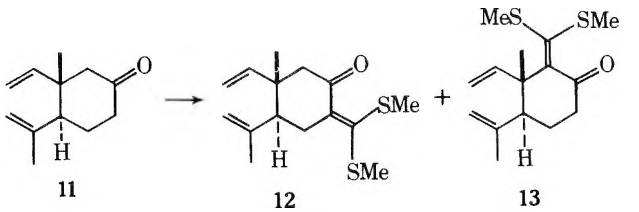
a, NaH, THF, $CH_3CH_2COCH_2CH_2Cl$; b, KOH, MeOH; c, Li, NH_3, *t*-BuOH, THF; d, LDA, THF, $(EtO)_2POCl$; e, Li, $EtNH_2$; f, O_3, MeOH; g, $NaBH_4$



3 8 10 9

Construction of the *trans*-1,2-divinylcyclohexane derivative 9 was carried out in a two-step process based on the method for the direct conversion of alcohols to alkyl aryl selenides.[12] Treatment of diol 3 with 2.4 equiv of *o*-nitrophenyl selenocyanate[13] in tetrahydrofuran containing 2.4 equiv of tri-*n*-butylphosphine at room temperature for 30 min gave a 94% yield of bisselenide 8 which was directly converted to diene 9 in very high yield upon treatment with 50% hydrogen peroxide in tetrahydrofuran.[14] Utilization of only 1.0 equiv of *o*-nitrophenyl selenocyanate and 1 equiv of tri-*n*-butylphosphine during an attempted conversion of 3 → 8 resulted in spontaneous formation of the seven-membered ring ether 10.

The conversion of compound 9 to β-elemenone is detailed below. Cleavage of ketal 9 under acidic conditions afforded ketone 11 which was converted to the α-dithiomethylene derivatives 12 and 13 in a ratio of 3:1 in disappointingly low yield.[15]



11 12 13

Reaction of 12 with 2 equiv of lithium dimethylcuprate at −78 °C produced β-elemenone in 90% yield. The NMR spec-

trum of synthetic β-elemenone displayed a sharp singlet at 1.03 ppm (3 H), broad singlets at 1.80 (6 H) and 2.00 ppm (3 H), a multiplet located at 2.22–2.71 ppm (5 H), and protons characteristic of the *trans*-1,2-divinylcyclohexane unit. The NMR and infrared spectra of synthetic **2** were identical with those of a sample of β-elemenone obtained by thermolysis (165 °C, 20 mm) of natural germacrone (**1**). We are indebted to Professor V. Herout (Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Science) for a generous gift of "zdravets oil" (*Geranium sp.*) from which we readily isolated germacrone.

Experimental Section

Melting points were determined on a Fisher-Johns hot stage melting point apparatus. All melting points and boiling points are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 247 grating infrared spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded at 60 MHz (Varian A-60D or T-60 spectrometer). Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (Me_4Si) (δ_{Me_4Si} 0.00 ppm) as an internal standard. Low-resolution mass spectra were recorded on an LKB-9000 instrument. High-resolution spectra were recorded on a Varian MAT CH5-DF instrument. Microanalyses were performed by Galbraith, Inc., Knoxville, Tenn.

Reactions were run under an atmosphere of nitrogen. "Dry" solvents were dried immediately before use. Tetrahydrofuran was distilled from lithium aluminum hydride. Ether was distilled from sodium metal.

6,6-Ethylenedioxy-1,10β-dimethyl-$\Delta^{1(9)}$-octal-2-one (5). 4,4-Ethylenedioxy-2-methylcyclohexanone[7] (8.31 g, 48.8 mmol) was added dropwise at room temperature to a suspension of sodium hydride (1.25 g, 63.4 mmol) in dry tetrahydrofuran (60 mL) under nitrogen. After refluxing for 2 h, the contents of the flask were cooled to room temperature and freshly distilled 1-chloropentan-3-one (8.19 g, 68.3 mmol) was added. The mixture was heated at 45 °C for 2 h followed by an additional 2.34 g of 1-chloropentan-3-one in 10 mL of tetrahydrofuran. Heating at 45 °C was continued for an additional 1 h. The reaction was quenched with 5% aqueous sodium carbonate solution and the reaction mixture was concentrated in vacuo. The product was isolated by ether extraction.[17] The residue was treated at 45 °C with ca. 7 g of solid potassium hydroxide in 150 mL of methanol. After 6 h, the methanol was evaporated under reduced pressure and the residue was taken up in ether and brine. The aqueous phase was thoroughly extracted with ether. The combined ethereal extracts were washed with water and brine, dried over anhydrous sodium sulfate, and concentrated in vacuo, yielding 8.9 g of residue which was chromatographed on 300 g of silica gel. Elution with ether–hexanes (2:1) yielded 6.80 g (59%) of **5**: mp 59–59.5 °C (lit.[7] 61–62 °C); bp 133–135 °C (0.2 mm) [lit.[7] 140–142 °C (0.3 mm)]; IR ($CHCl_3$) 1670, 1613 cm^{-1}; NMR (CCl_4) δ 1.32 (s, 3 H), 1.71 (s, 3 H), 3.90 (m, 4 H). Only a trace of compound **4** was recovered.

6,6-Ethylenedioxy-1α,10β-dimethyl-*trans*-2-decalone (6). To a solution of lithium (46 mg, 6.52 mmol) in 100 mL of liquid ammonia (distilled from sodium) was added dropwise a solution of octalone **5** (770 mg, 3.26 mmol) in 15 mL of dry tetrahydrofuran containing *tert*-butyl alcohol (213 mg, 2.60 mmol). The reaction mixture was stirred at reflux for 2 h followed by quenching with 1,3-butadiene. The liquid ammonia was evaporated and the product was isolated by ether extraction.[17] Evaporation of the solvent in vacuo left 762 mg of crude product which was chromatographed on 40 g of silica gel. Elution with ether–hexanes (1:3) gave 657 mg (85%) of pure decalone **6** as an oil: IR ($CHCl_3$) 1710 cm^{-1}; NMR (CCl_4) δ 0.95 (d, 3 H, J = 7 Hz), 1.20 (s, 3 H), 3.85 (m, 4 H); high-resolution mass spectrum m/e 238.1575 (calcd for $C_{14}H_{22}O_3$, 238.1569). An analytical sample was prepared by distillation [123–127 °C (bath temperature) (0.50 mmHg)].

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.59; H, 9.22.

6,6-Ethylenedioxy-1α,10β-dimethyl-Δ^2-*trans*-octalin (7). A solution of diisopropylamine (3.62 mg, 3.58 mmol) in 10 mL of dry tetrahydrofuran was treated with 1.79 mL (3.58 mmol) of a 2 M solution of *n*-butyllithium in hexane at 0 °C. After 30 min, a solution of decalone **6** (657 mg, 2.76 mmol) in 3 mL of dry tetrahydrofuran was added dropwise. After an additional 30 min 1.8 mL of tetramethylethylenediamine was added followed by 617 mg (3.58 mmol) of freshly distilled diethyl chlorophosphate in 1.0 mL of tetrahydrofuran. The resulting solution was stirred at room temperature for 2 h. The reaction was quenched by the addition of water and concentrated in vacuo. Isolation by ether extraction[17] gave 1.13 g of crude enol phosphate. Chromatography of the crude product on 46 g of silica gel (elution with ether–hexanes, 3:1) gave 973 mg (94%) of enol phosphate [IR ($CHCl_3$) 1680, 1270, 1040 cm^{-1}; NMR (CCl_4) δ 0.99 (s, 3 H), 1.10 (d, 3 H, J = 7 Hz), 1.25 (t, 6 H), 3.8–4.4 (m, 8 H), 5.40 (6 s, 1 H)] which was used directly in the next reaction.

Following the general procedure of Muchmore,[16] lithium (51 mg, 7.32 mmol) was added in small pieces to 100 mL of dry ethylamine. After ca. 1 h at reflux, a solution of enol phosphate (913 mg, 2.44 mmol) containing dry *tert*-butyl alcohol (600 mg, 7.32 mmol) in 20 mL of dry tetrahydrofuran was added dropwise. Stirring was continued for 30 min, during which time the blue color persisted. Excess lithium was consumed by careful addition of a saturated aqueous ammonium chloride solution. The ethylamine was evaporated and the product was isolated by ether extraction.[17] Chromatography of crude **7** (597 mg) on 10 g of silica gel (elution with ether–hexanes, 1:3) gave 474 mg (88%) of pure octalin **7** as an oil: IR ($CHCl_3$) 1650 cm^{-1}; NMR (CCl_4) δ 0.91 (s, 3 H), 0.98 (d, 3 H, J = 7 Hz), 3.82 (m, 4 H), 5.41 (6 s, 2 H); high-resolution mass spectrum m/e 222.1620 (calcd for $C_{14}H_{22}O_2$, 222.1618). An analytical sample was prepared by distillation [62–65 °C (bath temperature) (0.35 mmHg)].

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.86; H, 10.10.

Ozonolysis of Octalin 7. 6,6-Ethylenedioxy-1α,10β-dimethyl-Δ^2-*trans*-octalin (249 mg, 1.12 mmol) was dissolved in 40 mL of absolute methanol, cooled to −78 °C, and treated with 36 mL of a cooled (−78 °C) saturated solution of ozone (1.45 mmol) in methylene chloride. During a 1-h period, sodium borohydride (55 mg, 1.45 mmol) was added in four equal portions every 15 min at −78 °C. After warming to room temperature, the solvent was removed in vacuo and the residue was dissolved in ethyl acetate and washed with brine. The aqueous wash was extracted exhaustively with ethyl acetate. The combined organic washes were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude diol **3** (301 mg) was chromatographed on 18 g of silica gel. Elution with ether–hexanes (3:1) gave 272 mg (94%) of pure diol **3** as an oil: IR (CCl_4) 3650, 3325 cm^{-1}; NMR (CCl_4) δ 0.77 (d, 3 H, J = 7 Hz), 0.95 (s, 3 H); high-resolution mass spectrum m/e 240.1722 (calcd for $C_{14}H_{26}O_4 - H_2O$, 240.1726). An analytical sample was prepared by distillation [150–155 °C (bath temperature) (0.5 mmHg)]. Upon standing at 0 °C overnight, diol **3** crystallized, mp 61–62 °C.

Anal. Calcd for $C_{14}H_{26}O_4$: C, 65.09; H, 10.14. Found: C, 64.98; H, 10.16.

Bis Aryl Selenide Formation. A solution of 184 mg (0.713 mmol) of diol **3** and 388 mg (1.71 mmol) of o-nitrophenyl selenocyanate[13] in 6.0 mL of dry tetrahydrofuran under nitrogen was treated with tri-*n*-butylphosphine (379 mg, 1.71 mmol) at room temperature. After ca. 30 min the solvent was removed in vacuo and the residue (519 mg) was chromatographed on 30 g of silica gel. Elution with ether–hexanes (1:3) afforded 418 mg (94%) of crystalline bisselenide **8**: mp 54–56 °C; IR ($CHCl_3$) 1595, 1571, 1521, 1339, 1308 cm^{-1}; NMR (CCl_4) δ 2.81 (m, 4 H), 3.88 (bs, 4 H), 7.35 (m, 6 H), 8.18 (m, 2 H).

Anal. Calcd for $C_{26}H_{32}N_2O_6Se_2$: C, 49.85; H, 5.15; N, 4.47. Found: C, 50.03; H, 5.22; N, 4.44.

Preparation of *trans*-1,2-Divinylcyclohexane (9). A solution of 400 mg (0.64 mmol) of bisselenide **8** in 5.0 mL of tetrahydrofuran cooled to 0 °C was treated dropwise with 173 μL of 50% aqueous hydrogen peroxide (2.55 mmol). After addition was complete the reaction mixture was warmed to room temperature. After 3.5 h the solvent was removed under reduced pressure and the product was isolated by ether extraction.[17] The crude oil (271 mg) was chromatographed on 18 g of silica gel. Elution with ether–hexanes (1:3) provided 134 mg (95%) of pure **9** as an oil: IR ($CHCl_3$) 3090, 1640 cm^{-1}; NMR (CCl_4) δ 1.05 (s, 3 H), 1.69 (s, 3 H), 3.83 (m, 4 H), 4.55–5.08 (m, 4 H), 5.57–6.00 (q, 1 H); high-resolution mass spectrum m/e 222.1600 (calcd for $C_{14}H_{22}O_2$, 222.1618). An analytical sample was prepared by distillation [51–56 °C (bath temperature) (0.45 mmHg)].

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.51; H, 9.90.

***trans*-1,2-Divinylcyclohexanone (11).** A solution of 130 mg (5.85 mmol) of ketal **9** in 14.7 mL of tetrahydrofuran containing 0.30 mL of concentrated hydrochloric acid was stirred at room temperature for 8 h. The reaction was quenched by the addition of solid sodium bicarbonate and the solvent was removed under reduced pressure. Isolation of the product by ether extraction[17] gave 113 mg of crude ketone which was chromatographed on 8.0 g of silica gel. Elution with ether–hexanes (1:3) yielded 96 mg (92%) of pure ketone **11**: IR (CCl_4) 3090, 1720, 1641 cm^{-1}; NMR (CCl_4) δ 0.99 (s, 3 H), 1.78 (s, 3 H), 4.70–5.03 (m, 4 H), 5.62–6.10 (m, 1 H); high-resolution mass spectrum m/e 178.1360 (calcd for $C_{12}H_{18}O$, 178.1358).

β-Elemenone (2). To a solution of 253 mg (1.12 mmol) of 4-

methyl-2,6-di-*tert*-butylphenol in 3.0 mL of anhydrous ether (cooled to −10 °C) was added 560 μL of 2 M *n*-butyllithium in hexane. The observed precipitate dissolved upon warming to room temperature. To the homogeneous reaction mixture was added dropwise 95 mg (0.53 mmol) of ketone **11** in 1.0 mL of dry ether followed by addition of 214 mg (2.82 mmol) of carbon disulfide. After 14 h at room temperature, 196 mg (1.40 mmol) of methyl iodide was added and stirring was continued for an additional 5 h. The reaction mixture was quenched by the addition of brine and ether. The aqueous phase was extracted with ether. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue (391 mg) was chromatographed on 30 g of silica gel. Elution with ether–hexanes (1:4) gave 45 mg (30%) of pure α-dithiomethylene derivative **12**: IR ($CHCl_3$) 3090, 1690, 1665, 1641 cm^{-1}; NMR δ (CCl_4) 1.04 (s, 3 H), 1.80 (s, 3 H), 2.30 (s, 3 H), 2.38 (s, 3 H). Continued elution gave 14 mg of pure α-dithiomethylene derivative **13**.

To a stirred suspension of copper iodide (29.6 mg, 0.16 mmol) in 1.0 mL of anhydrous ether at 0 °C was added 132 μL (0.31 mmol) of a 2.37 M solution of methyllithium in ether. After cooling to −78 °C, 22 mg (0.078 mmol) of compound **12** in 1.0 mL of dry ether was added dropwise. The reaction mixture was stirred for 20 min at −78 °C followed by quenching with methanol. Isolation of product by ether extraction[17] afforded 17 mg of crude β-elemenone which was chromatographed in 5.0 g of silica gel. Elution with ether–pentane (1:5) gave 15.4 mg (90%) of β-elemenone: IR (CCl_4) 3080, 2960, 2930, 2902, 2855, 1680, 1635, 1618, 1442, 1430, 1408, 1370, 1300, 1280, 1271, 1258, 1239, 1210, 1198, 1125, 1050, 1018, 998, 910, 891 cm^{-1}; NMR (CCl_4) δ 1.03 (s, 3 H), 1.80 (s, 6 H), 2.00 (s, 3 H), 2.22–2.71 (m, 5 H), 4.74–5.16 (m, 4 H, terminal vinyl), 5.61–6.07 (m, 1 H); high-resolution mass spectrum *m/e* 218.1667 (calcd for $C_{15}H_{22}O$, 218.1670).

Preparation of Seven-Membered Ring Ether 10. A solution of 15.0 mg (0.058 mmol) of diol **3** in 1.0 mL of tetrahydrofuran containing 13.2 mg (0.058 mmol) of *o*-nitrophenyl selenocyanate was treated with 11.7 mg (0.058 mmol) of tri-*n*-butylphosphine at room temperature. After 30 min the solvent was removed in vacuo and the residue was chromatographed on 5 g of silica gel. Elution with ether–hexane (1:2) afforded 12.1 mg (87%) of pure ether **10**: IR ($CHCl_3$) 2950, 2890, 1460, 1389, 1365, 1335, 1300, 1265, 1220, 1165, 1145, 1120, 1100, 1085, 1070, 1064, 1022, 1015, 995, 955, 900 cm^{-1}; NMR (CCl_4) δ 0.95 (d, 3 H, *J* = 7 Hz), 1.01 (s, 3 H), 1.1–2.3 (m, 10 H), 3.3–3.7 (m, 4 H), 3.83 (m, 4 H).

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Registry No.—**2**, 30824-86-3; **3**, 62183-43-1; **4**, 54316-77-7; **5**, 13944-80-4; **6**, 13944-79-1; **6** enol phosphate, 62183-44-2; **7**, 62183-45-3; **8**, 62183-46-4; **9**, 62183-47-5; **10**, 62183-48-6; **11**, 30824-87-4; **12**, 62183-49-7; 1-chloropentan-3-one, 32830-97-0; o-nitrophenyl selenocyanate, 51694-22-5; 4-methyl-2,6-di-*tert*-butylphenol, 128-37-0; carbon disulfide, 75-15-0; methyl iodide, 74-88-4; diethyl chlorophosphate, 814-49-3.

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A General Method for the Preparation of α-Labeled Amino Acids[1]

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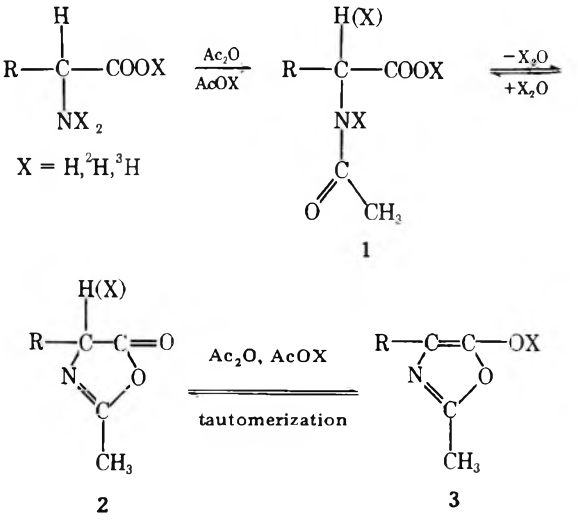
The usefulness of specifically deuterated amino acids for studying peptides and proteins is becoming more widely appreciated.[2-6] For example, with the deuterium labels providing unique nuclei for observation using modern biophysical techniques, information relevant to the conformation and dynamics of peptides and to the binding of peptide hormones to carrier proteins (or receptors) may be gathered.[7] One impediment for such studies has been the limited availability and/or high cost of specifically labeled amino acids.

Previous attempts to exchange the α proton of amino acids have met with limited success.[8-12] The most successful methods require high pressure and long reaction times,[13] or preparation, separation, and reduction of cobalt(III) complexes of amino acids.[14]

We report here a rapid, inexpensive, and generally applicable preparation of α amino acids starting from commercially available amino acids. The reaction is an adaptation of a method for racemization of amino acids which employs refluxing acetic acid and acetic anhydride to give racemic *N*-acetyl amino acids.[15] In our procedure, a mixture of excess acetic anhydride with D_2O is used to give a solution of Ac_2O in AcOD. Treatment of amino acids with this solution at reflux for a few minutes leads to acylation, racemization, *and* exchange at the α position. One possible mechanism for the reaction is given by the following equations [other mechanism(s) may also be used to account for the exchange].



From examination of the suggested mechanism, several points emerge. First, it is not necessary to use the more expensive stereopure L amino acids in this reaction since tautomerization proceeds through a planar intermediate. Second, this process is unlikely to affect the stereointegrity of asymmetric sites other than the α position thus simplifying the

Table I. Deuteration of Amino Acids at the α Position

Amino acid	α-Deuteration, % One exchange	Two exchanges	Registry no.
Isoleucine	77	>95[a]	62076-83-9
Leucine	83	91	62076-84-0
Methionine	79	>95[a]	62076-85-1
Valine	81	>95[a]	62076-86-2
Alanine	82	92	5046-58-2
Tyrosine	80	95	62076-87-3
S-Benzylcysteine	67	89	57866-79-2
Proline	73	86	62076-88-4

[a] No measurable α protons were detected by ^{1}H NMR.

problem of stereoisomer resolution. The resolution scheme for the four stereoisomers of isoleucine, for example, is quite lengthy. Third, this process directly yields *N*-acetyl-α-labeled amino acids which are the starting compounds for enzymatic resolution using hog renal acylase, carboxypeptidase, or other enzymes capable of selective cleavage of an acetyl group from one stereoisomer without a significant cleavage of the enantiomeric compound. Fourth, if the D isomer is not desired, it can be recycled. Fifth, the exchange efficiency is related to the proportional excess of available deuterons to protons. To achieve high levels of exchange, a high ^{2}H/^{1}H ratio is required. This condition can be approached in several ways: (a) a high molar excess of acetic acid-*d* relative to the amino acid can be used; (b) labile hydrogens of the amino acid can be subjected to prior exchange; (c) the exchange reaction can be repeated.

With the methods we have used thus far, one treatment generally leads to 70–80% exchange. A second treatment raises the level of exchange to 90–100% in most cases studied (Table I).

Experimental Section

Synthesis of *N*-Acetyl-DL-[α-^{2}H$_1$]alanine. The following procedure exemplifies the experimental procedure used. All-protio alanine (0.89 g, 0.01 mol) was shaken with 3.7 mL of D_2O to exchange labile protons. The mixture was frozen and lyophilized to dryness. Immediately, 21.7 mL of Ac_2O and 2.5 mL of D_2O were added to the resulting powder and the flask was placed in a 170 °C bath. The solution was refluxed for 2 min, then cooled (drying tube) and 2 mL of D_2O was added to destroy the remaining Ac_2O and convert any azlactone **2** back to the *N*-acetyl amino acid. The solvents were removed by rotary evaporation. Crystals appeared as the evaporation neared completion. The residue was recrystallized from ethyl acetate. The crystals were filtered, washed with ether, and dried in vacuo over KOH: yield 1.17 g (89%); mp 127–128 °C; NMR (Me_2SO-d_5) δ 1.55 (s, 3 H), 2.15 (s, 1.1 H), 2.80 (Me_2SO), 4.4–4.6 (α-CH, 0.18 H). After the reaction was repeated, 0.08 α hydrogens were detectable by proton nuclear magetic resonance spectroscopy, yield 1.06 g (80%). Similar procedures were used for other amino acids and the results are summarized in Table I.

There was exchange of deuterium into the acetyl methyl groups. This fact effectively decreases the ^{2}H/^{1}H ratio and is undoubtedly responsible for some, if not most, of the nondeuteration at the α carbon. Clearly, this method could also be used for the exchange of tritium into the α position.

Registry No.—DL-Isoleucine, 443-79-8; DL-leucine, 328-39-2; DL-methionine, 59-51-8; DL-valine, 516-06-3; DL-alanine, 302-72-7; DL-tyrosine, 556-03-6; DL-*S*-benzylcysteine, 5680-65-9; DL-proline, 609-36-9.

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Conformational Analysis. 127. Force Field Calculations on the Dodecahydrophenanthrenes[1,2]

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In an earlier paper the structures and relative stabilities of the isomeric octahydronaphthalenes were discussed.[3] It was felt that the relative energies of the various isomers could be accurately calculated, and simultaneous but independent experimental work showed that this was indeed so.[4] In the course of continuing studies on the isomers of perhydrophenanthrene,[5] various synthetic sequences were projected which involved a dodecahydrophenanthrene with a trans,syn,trans backbone as an intermediate. Because of the possibility of rearrangement, it was desirable to know something about the relative stabilities of some of these compounds. The previously used calculational methods (molecular mechanics) were expected to yield reliable predictions here, so the calculations were carried out (1973 force field[6]) and the results are reported herein.

There are 25 isomers of dodecahydrophenanthrene which were considered in this work. They are shown in Table I. The calculated heat of formation (H_f, gas, 25 °C) is −29.60 kcal/mol for the most stable compound (7). The values of $\Delta H_f°$ are given for each conformation. Also, the values of ΔH for each *compound* (conformational mixture) relative to the most stable isomer are shown, together with the relative entropies if nonzero, calculated by taking into account symmetry numbers and entropies of mixing. The relative free energies (80 °C) are also shown for isomers within 4 kcal/mol of the most stable one.

A few experimental investigations of the relative stabilities of some of the isomers of dodecahydrophenanthrene have appeared in the literature, together with suggestions regarding possible bond migrations in the course of a synthesis of a perhydrophenanthrene[7]. Christol and co-workers, in a series of papers,[8] carried out some equilibration studies, and isolated what they believed to be the isomers indicated, in the yields

Table I. Relative Enthalpies, Energies, Entropies, and Free Energies of the Conformations of the Dodecahydrophenanthrenes[a,b] 1–25

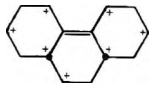
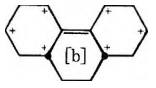
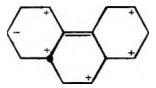
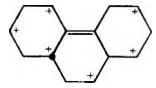
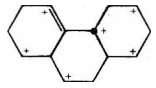
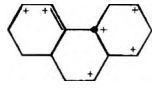
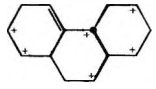
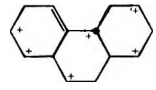
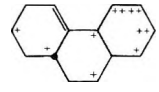
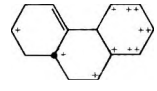
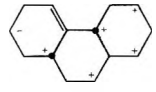
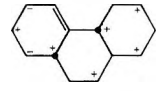
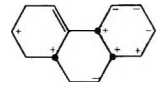
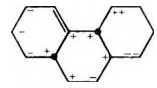
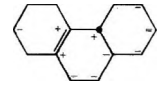
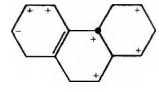
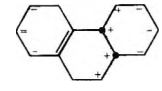
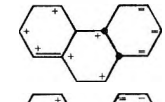
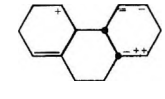
No.	Structure	Position of double bond	ΔH_f° (25 °C)	ΔH	ΔS	ΔG (80 °C)
1		4a,4b	3.17	3.17	−1.38	3.66
1	 [b]	4a,4b	13.21			
2		4a,4b	5.82	3.12	−0.43	3.27
2		4a,4b	3.81			
2		4a,4b	2.94			
3		4,4a	7.23	7.18		
3		4,4a	7.14			
3		4,4a	14.49			
3		4,4a	12.43			
4		4,4a	2.98	2.98		2.98
4		4,4a	9.23			
5		4,4a	3.04	3.07	+1.37	2.59
5		4,4a	3.09			
6		4,4a	7.02	7.07		
6		4,4a	9.18			
7		4,10a	6.27	0.00	0	0.00
7		4,10a	0.00			
8		4,10a	1.61	1.28	+1.19	0.86
8		4,10a	1.13			
9		1,10a	3.97	4.03		
9		1,10a	7.52			

Table I
(*Continued*)

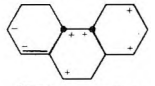
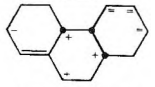
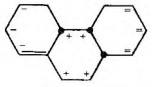
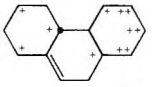
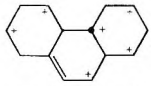
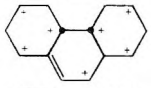
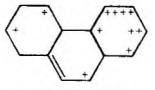
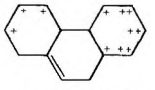
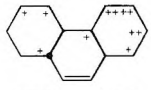
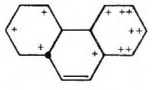
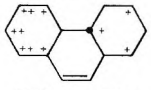
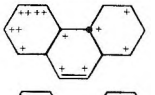
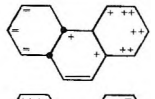
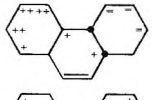
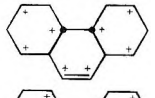
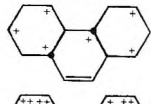
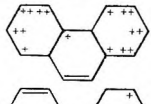
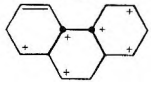
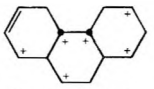
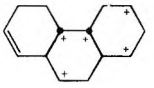
No.	Structure	Position of double bond	$\Delta H_f°$ (25 °C)	ΔH	ΔS	ΔG (80 °C)
10		1,10a	1.64	1.64	0	1.64
11		1,10a	9.13	7.00		
11		1,10a	6.98			
12		1,10a	5.37	5.37		
12		1,10a	11.93			
13		10,10a	3.34	3.31	+1.37	2.83
13		10,10a	3.24			
14		10,10a	1.36	1.36	0	1.36
15		10,10a	2.42	2.42	0	2.42
16		10,10a	4.98	4.99		
16		10,10a	8.15			
17		9,10	5.28	5.28		
17		9,10	14.50			
18		9,10	5.00	5.00		
18		9,10	12.98			
19		9,10	6.31	6.41		
19		9,10	7.87			
20		9,10	11.38	11.38		
21		9,10	4.00	4.00		
22		9,10	9.96	9.96		
23		3,4	11.94	11.94		

Table I
(*Continued*)

No.	Structure	Position of double bond	ΔH_f° (25 °C)	ΔH	ΔS	ΔG (80 °C)
24		2,3	8.49	8.49		
25		1,2	11.25	11.25		

[a] The values for ΔH_f° are the relative (to 7) values for the individual conformations. The values for ΔS allow for symmetry and mixing, and together with ΔG, these are for *compounds* rather than *conformations*. All for the gas phase. [b] The symbol (+) [or (−)] means that the carbon indicated is above (or below) the general place of the molecule. The symbols (++) and (− −) mean the same thing to a greater degree.

shown: **8**, 40%; **7**, 30%; **3**, 30%. They obtained the same mixture in several different ways, and hence concluded that it represented equilibrium. Their identification of the isomers was by gas phase chromatography, and structure determination with the aid of infrared, NMR (proton only), and Raman sepctroscopy.

Our calculations are in moderate agreement with the experimental work of the French workers. We agree that isomers **7** and **8** are the most stable, but find that isomer **3** is quite unstable, and therefore not likely to contribute significantly to the equilibrium mixture. We believe that isomer **10** or isomer **14**, or possibly a mixture of the two, was the third component which they obtained in the mixture. An unambiguous distinction between isomers **10**, **14**, and **3** does not seem possible on the basis of only infrared, Raman spectra, and ^1H NMR.

The starting coordinates were generated in each case from Fieser models by projection onto graph paper. About 3–6 min of computer time (IBM 360/65) was required for each calculation.

Registry No.—**1**, 16041-60-4; **2**, 17002-05-0; **3**, 20480-70-0; **4**, 62076-17-9; **5**, 62075-58-5; **6**, 62075-59-6; **7**, 20480-69-7; **8**, 20480-68-6; **9**, 62046-20-2; **10**, 62046-21-3; **11**, 62406-22-4; **12**, 62046-23-5; **13**, 62046-24-6; **14**, 39142-79-5; **15**, 62046-25-7; **16**, 62046-26-8; **17**, 62046-27-9; **18**, 62046-28-0; **19**, 62046-29-1; **20**, 62046-30-4; **21**, 62046-31-5; **22**, 62046-32-6; **23**, 62046-33-7; **24**, 62046-34-8; **25**, 62046-35-9.

References and Notes

(1) Paper 126: J. C. Tai and N. L. Allinger, *J. Am. Chem. Soc.*, in press.
(2) Supported in part by the Max Kade Foundation, New York, N.Y., and in part by the National Science Foundation (Grant MPS74-08071).
(3) N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *J. Am. Chem. Soc.*, **90**, 5773 (1968).
(4) A. Weitkamp, cited in ref 3.
(5) N. L. Allinger, B. J. Gorden, I. J. Tyminski, and M. Wuesthoff, *J. Org. Chem.*, **36**, 739 (1971).
(6) N. L. Allinger, *Adv. Phys. Org. Chem.*, **14**, 1 (1976). The program (MMI) is available from the Quantum Chemistry Program Exchange, No. QCPE 318, University of Indiana, Bloomington, Ind.
(7) U. Burkert and H. Hönig, unpublished.
(8) (a) H. Christol, Y. Pietrasanta and J. L. Vernet, *Ann. Chim. (Paris)*, **3**, 361 (1968); (b) *ibid.*, **3**, 145 (1968) (c) H. Christol, F. Pietrasanta, Y. Pietrasanta, and J. C. Rousselou, *Bull. Soc. Chim. Fr.*, 2770 (1972).

Phthalide Components of Celery Essential Oil

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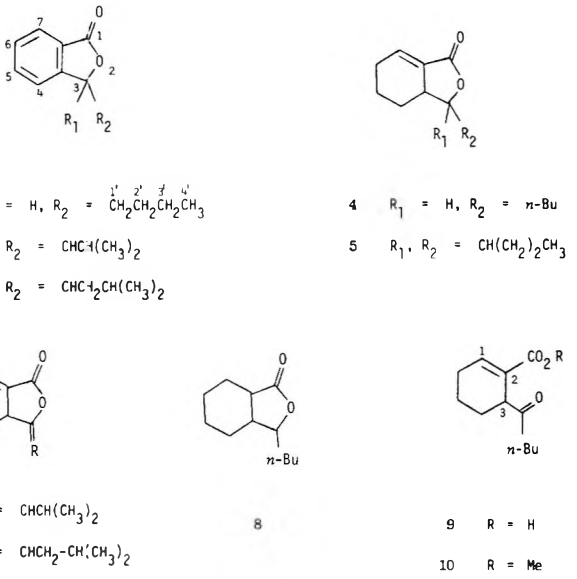
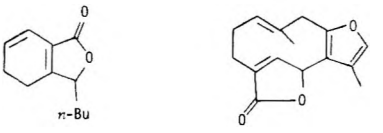
The characteristic odor of celery essential oil is due to a series of phthalide derivatives, of which 3-*n*-butyl phthalide (**1**) and sedanolide (**4**)[1,2] are reported to be the major odor components. Several other phthalides (**2**, **3**, **6**–**8**)[2–4] occur in



trace quantities along with an additional major component which on base hydrolysis yields sedanonic acid (**9**). The suggested identity of this secondary component, sedanonic anhydride (**5**), was proposed by Ciamician and Silber[1] based on their classical work with celery constituents. More recent reports continue to suggest that sedanonic anhydride is a major odor component of celery and other oils.[5–7]

Our work with certain biologically active components of celery oil[8] has resulted in the isolation of the two major phthalide compounds: the well-characterized 3-*n*-butyl phthalide (**1**) and a second material which yields sedanonic acid on treatment with aqueous base. We wish to report the results of our work, which indicate that this secondary material is not sedanonic anhydride, but an unreported compound, 3-*n*-butyl 4,5-dihydrophthalide (sedanenolide) (**11**).



11 **12**

Chromatographic separation of the essential oil components of celery seed led to the isolation of 3-*n*-butyl phthalide (**1**) and sedanenolide in approximately equal quantities. Sedanenolide (**11**), $C_{12}H_{13}O_2$ (high-resolution mass spectrum), $[\alpha]^{24}D$ −43.2°, shows absorption at λ_{max} 280 nm (ϵ 3790) in agreement with the cross-conjugated 3,4-dihydrophthalide system.[9] The

IR spectrum shows intense absorption at 1750 cm^{-1} in agreement with the α,β-unsaturated, γ,δ-saturated, γ-lactone. The ^1H NMR spectrum displays a one-proton doublet at 6.12 ppm (J = 10 Hz) and a one-proton multiplet at 5.85 ($W_{1/2}$ = 8 Hz) for the vinyl protons, H-7 and H-6, respectively,[10] and a one-proton multiplet at 4.86 ($W_{1/2}$ = 8 Hz) for H-3.

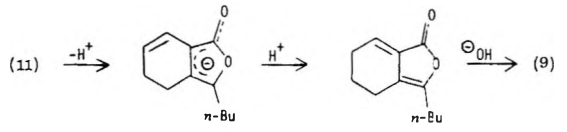
The ^{13}C NMR spectrum of sedanenolide is in accord with the proposed structure and played a key role in positional assignment of double bonds. Of primary importance in this regard is the appearance in the off-resonance decoupled spectrum of a doublet at 82.6 ppm, indicating saturation at C-3. Double bond assignments of the type indicated in compounds **13** and **5** are thus ruled out. Also appearing are two doublets (128.4 and 116.8) and a singlet (124.5) consistent with disubstituted and tetrasubstituted double bonds composed of C-6 and C-7, and C-1a and C-3a, respectively. In addition, signals appear for the side chain (C-1′ thru C-4′) as a series of four multiplets in the range 13.8–22.4, for C-4 and C-5 as two triplets (31.9 and 26.7, respectively), and for C-1 as a singlet (161.5).

Catalytic hydrogenation of sedanenolide in acetic acid over platinum oxide led to the formation of the known 3-*n*-butyl hexahydrophthalide (**8**) (IR, NMR, MS, and mp).

Treatment of sedanenolide with aqueous base gives, in quantitative yield, sedanonic acid (**9**) (IR, UV, NMR, MS, and mp),[11] which was readily converted to the corresponding methyl ester **10** (IR, UV, MS, NMR) by treatment with diazomethane. Similar facile keto ester formation from a substituted Δ^2-butenolide has been observed by Takeda et al.[12] in their work with linderalactone (**12**).

A reasonable mechanism for formation of sedanonic acid from sedanenolide (Scheme I) requires an initial proton ab-

Scheme I



(13)

straction from C-3 with formation of the delocalized furanoid system, followed by double bond rearrangement and hydrolysis.

It is of interest to note that no evidence was obtained in the present investigation for the presence of sedanolide in celery essential oil. Barton and DeVries[11] have also made this observation and they have suggested that 3-*n*-butyl phthalide has been confused with sedanolide in the relatively recent literature. Several reports have also appeared of the occurrence of sedanonic acid or sedanonic anhydride in various plant extracts.[4,5] These reports describe characterizations based on treatment of crude extracts with aqueous base or phthalazone formation. These procedures would not distinguish between sedanonic anhydride and sedanenolide. The natural product may very well be the latter compound in these cases.

Experimental Section

Melting points were taken in capillaries and are uncorrected. IR sepctra were measured in chloroform on a Perkin-Elmer 137 spectrometer; UV spectra were measured in ethanol using Bausch and Lomb Spectronic 505 and Cary Model 14 spectrometers; ^1H NMR spectra were taken in CCl_4 (unless otherwise indicated) on a Varian T-60 spectrometer; ^{13}C NMR spectra were determined in $DCCl_3$ at 25.144 MHz in the Fourier mode using a Nicolet TT-23 spectrometer with Brucker 40 console in conjunction with a 8K memory computer; chemical shifts are reported in δ units from internal Me_4Si, and when followed by parentheses give multiplicity of signal, coupling constant if applicable, and assignment. Spin multiplicity is given by s = singlet, d = doublet, t = triplet, m = multiplet. Mass spectra were obtained on a CEC 103 (low resolution) or CEC 21-110B (high resolution] instrument. Optical rotations were measured on solutions in 95% EtOH; column chromatography was performed on Merck silica gel 60 (>230 mesh). Thin-layer chromatography was carried out on silica gel precoated 60 F-254 chromatoplates (5 × 10 cm, 0.25-mm thick, EM Laboratories, Inc.).

Isolation of Phthalides from Celery Seed. Steam distillation at atmospheric pressure of ground celery seed (1 kg) produced 27 L of aqueous distillate, which was extracted consecutively with petroleum ether (bp 30–60 °C, 18 L), ethyl ether (18 L), and chloroform (18 L). Evaporation of the organic extracts in vacuo gave a combined yield of 16.8 g of essential oil. This material was placed on a silica gel column and nine fractions were eluted with 4.5 L of hexane–diethyl ether (1:1, v/v). A tenth fraction was eluted with 500 mL of methanol. Solvents were removed in vacuo and the oily residues were assayed for sedative activity as described by Brodie.[13] Significant activity resided only in the phthalide-containing fractions. 3-*n*-Butyl phthalide and sedanenolide were isolated from fractions 5 and 6 by gas chromatography under the following conditions: aluminum column (20 ft × ⅜ in.), packed with 15% S.E. 30 on dimethylchlorosilane (DMCS)-treated 60/80 mesh gas Chromosorb W, helium flow rate of 100 mL/min; and column, injector, and detector temperatures, 200, 218, and 235 °C, respectively. 3-*n*-Butyl phthalide and sedanenolide had retention times of 57 and 75 min, respectively, under these conditions.

3-*n*-Butyl phthalide (**1**) was obtained as a pale yellow oil with a distinct odor of celery oil: UV absorptions at 228, 275, and 282 nm (ϵ 8190, 1480, and 1480, respectively); IR band at 1750 cm^{-1} (γ-lactone); NMR signals at δ 7.23–7.84 (m, H-4, 5, 6, 7) and 5.41 (m, H-3), in accord with published data.[11]

Sedanenolide (**11**) is a colorless oil with a distinct celery odor: $[\alpha]^{24}_D$ −43.2°; IR bands at 1750 (γ-lactone), 1650, 1460, 1430, 1310, 1270, 1040, 960, and 915 cm^{-1}; UV spectrum λ_{max} 280 nm (ϵ 3790). The high-resolution mass spectrum displayed the molecular ion peak (22.9%); other major peaks were at *m/e* (composition, %) 163 ($C_{11}H_{15}O$, 3.6), 135 ($C_8H_7O_2$, 5.3), 108 (C_7H_8O, 21.7), 107 (C_7H_7O, 100.0), 85 (C_5H_9O, 9.7), 79 (C_6H_7, 24.3), 77 (C_6H_5, 24.2), and 57 (C_4H_9, 14.4).

Anal. Calcd for $C_{12}H_{16}O_2$: mol wt, 192.1150. Found: mol wt, 192.1158 (MS).

3-n-Butyl Hexahydrophthalide (**8**). A solution of sedanenolide (20 mg) in glacial acetic acid (5 mL) was hydrogenated over 50 mg of PtO_2 at atmospheric pressure for 48 h and filtered. The residue obtained after evaporation of solvent was purified by gas chromatography under the conditions described for the parent compound. The reduced product (rentention time, 35 min) was obtained as a low melting solid (mp 39–41 °C, lit,[11] 48–49 °C): IR bands at 1765 (γ-lactone), 1440, 1180, 1165, 1125, 980, and 735 cm^{-1}; NMR signals at 4.12 (m, $W_{1/2}$ = 10 Hz, H-3), and 2.61 (m, $W_{1/2}$ = 12 Hz, H-7a); UV spectrum showed only end absorption. The high-resolution mass spectrum exhibited the molecular ion (4.3%); other major peaks were at *m/e* 180 ($C_{12}H_{20}O$, 4.3), 165 ($C_{11}H_{17}O$, 3.1), 152 ($C_{11}H_{20}$, 18.2), 139 ($C_8H_{11}O_2$, 37.6), 111 ($C_7H_{11}O$, 9.2), and 109 (C_7H_9O, 34.8).

Anal. Calcd for $C_{12}H_{20}O_2$: mol wt, 196.1463. Found: mol wt, 196.1450 (MS).

Sedanonic Acid (**9**). Sedanenolide (50 mg) was treated with aqueous potassium hydroxide and sodium carbonate solutions as described by Barton and DeVries[11] for isolation of sedanonic acid from celery oil. Crystallization of the acidic reaction product from benzene/hexane afforded sedanonic acid (38 mg) as colorless needles: mp 109–110 °C (lit.,[11] 110–111 °C); IR bands at 2500–3400 (–OH), 1710 (acyclic ketone), 1695 (α,β-unsaturated carboxyl), 1650 (conjugated double bond), 1530, 1420, and 1260 cm^{-1}; NMR ($DCCl_3$) signals at 7.34 (t, J = 4 Hz, H-1) and 3.62 (m, $W_{1/2}$ = 10 Hz, H-3). The high-resolution mass spectrum revealed a molecular ion peak (1.3%); other major peaks were at *m/e* (composition, %) 125 ($C_7H_9O_2$, 2.7), 108 (C_7H_8O, 59.3), 97 (C_6H_9O, 3.0), 85 (C_5H_9O, 57.2), 79 (C_6H_7, 21.6), and 57 (C_4H_9, 100.0).

Anal. Calcd for $C_{12}H_{18}O_3$: mol wt, 210.1256. Found: mol wt, 210.1243 (MS).

Sedanonic Acid Methyl Ester (**10**). Methylation of 20 mg of **9** with excess diazomethane in the usual way and purification of the crude product by preparative TLC (silica gel, solvent chloroform) yielded 15 mg of **10** as a colorless oil: IR bands at 1710 (α,β-unsaturated ester and acyclic ketone), 1430, 1250, and 1080 cm^{-1}; UV spectrum λ_{max} 215 nm (ϵ 15 300); NMR signals at 7.02 (m, $W_{1/2}$ = 5 Hz, H-1) and 3.64 (s, OMe). The high-resolution mass spectrum afforded the molecular ion peak 4.7% and other major peaks at *m/e* 192 ($C_{12}H_{16}O_2$, 6.1), 140 ($C_8H_{12}O_2$, 22.9), 108 (C_7H_8O, 15.5), 86 (C_4H_9O, 7.5), 85 (C_5H_9O, 100.0), 79 (C_6H_7, 22.8), and 57 (C_4H_9, 85.3).

Anal. Calcd for $C_{13}H_{20}O_3$: mol wt, 224.1412. Found: mol wt, 224.1392 (MS).

Registry No.—1, 6066-49-5; 8, 3553-34-2; 9, 6697-07-0; 10, 62006-38-6; 11, 62006-39-7.

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Some 1-Pentacyanobutadienyl Derivatives[1]

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In 1972 reactions of polycyanovinyl halides with metal carbonyl anions were first reported[3] to give good yields of stable polycyanovinyl transition metal derivatives.[4] Subsequent work[5,6] showed that further reactions of these polycyanovinyl transition metal derivatives gave a variety of unusual and interesting cyanocarbon transition metal complexes including compounds containing terminal[7,8] and bridging[3,4] dicyanovinylidene ligands, dicyanoketeneimmonium derivatives,[9] novel types of chelates,[9] and new polycyano olefin complexes.[10]

This extensive new area of transition metal chemistry created by the discovery of polycyanovinyl transition metal derivatives made of interest the preparation and reactions of similar transition metal polycyanobutadienyl derivatives. This suggested an investigation of reactions of halopolycyanobutadienes with metal carbonyl anions. However, since halopolycyanobutadienes were completely unknown at that time, it was first necessary to develop methods for their preparation. This paper describes the methods for the preparation of 1-halopentacyanobutadienes that we first developed in 1972 as well as their reactions with certain metal carbonyl anions to give pentacyanobutadienyl transition metal derivatives.

Experimental Section

Infrared spectra were determined on a Perkin-Elmer Model 621 spectrometer with grating optics. Mass spectra were determined using a Perkin-Elmer Hitachi RMU-6 mass spectrometer. Relative intensities are given in parentheses with the indicated relative intensities for the ions containing chlorine and bromine being the sums of the ions containing the two major isotopes (i.e., ^{35}Cl and ^{37}Cl for chlorine and ^{79}Br and ^{81}Br for bromine). Melting points are taken in capillaries and are uncorrected.

Tetracyanoethylene was purchased from Kay-Fries Chemicals Inc., New York, N.Y., and converted to tetraethylammonium pentacyanobutadien-1-olate via tetracyanoethane[11] and disodium hexacyanobutenediide[12] by the published procedure.[13] Metal carbonyl derivatives were obtained by procedures similar to those used in previous work.[4]

Preparation of 1-Chloropentacyanobutadiene. A solution of 10.0 g (30.8 mmol) of tetraethylammonium pentacyanobutadien-1-olate in 150 mL of redistilled 1,2-dimethoxyethane was added to a solution of 7.7 g (5.2 mL, 60.8 mmol) of redistilled oxalyl chloride in 50 mL of redistilled 1,2-dimethoxyethane. After stirring for 34 h at room temperature, the reaction mixture was filtered to remove a tan precipitate. Solvent was then removed at ~25 °C (40 mm). The residue was extracted with dichloromethane. Excess diethyl ether was added to the filtered dichloromethane extract to precipitate 3.22 g of unreacted tetraethylammonium pentacyanobutadien-1-olate (32% recovery), identified by its infrared spectrum. After removal of this precipitate by filtration followed by evaporation of the filtrate at ~25 °C (40 mm), sublimation of the residue at 110–125 °C (0.2 mm) gave 1.91 g (29% conversion, 42% yield) of white, crystalline 1-chloropentacyanobutadiene: mp 195 °C dec; infrared spectrum (KBr) 2245 (w), 1540 (m), 1524 (m), 1399 (vw), 1378 (vw), 1357 (m), 1315 (sh), 1277 (w), 1234 (m), 1226 (m), 1208 (w, sh), 1028 (w), 1000 (m), 978 (w), 924 (vw), 900 (m), 806 (vw), 778 (m), 771 (w, sh), 654 (vw), 623 cm^{-1} (vw); ultraviolet spectrum (CH_3CN) 329 nm (ϵ 4700), 315 (6400), 264 (9200), 253 (11 400); mass spectrum $C_9N_5Cl^+$ (100), $C_8N_4Cl^+$ (6), $C_9N_5^+$ (13), $C_8N_4^+$ (9), $C_7N_3^+$ (15), $C_5N_3^+$ (7), $C_6N_2^+$ (16), C_3NCl^+ (15), $C_4N_2^+$ (33), C_4N^+ (10), C_3N^+ (7), C_2N^+ (9).

In repeat experiments the yields of 1-chloropentacyanobutadiene were erratic.

Anal. Calcd for C_9ClN_5: C, 50.5; H, 0.0; N, 32.8. Found: C, 49.4, 51.2; H, 0.3, 0.8; N, 33.1; 32.6.

Preparation of 1-Bromopentacyanobutadiene. A. From $[(C_2H_5)_4N][C_4(CN)_5O]$ and Oxalyl Bromide. A solution of 10.0 g (308 mmol) of tetraethylammonium pentacyanobutadien-1-olate in 100 mL of redistilled 1,2-dimethoxyethane was added to a solution of 7.2 g (3.0 mL, 33.3 mmol) of oxalyl bromide in 150 mL of 1,2-dimethoxyethane. After stirring for 22 h at room temperature solvent was removed at 40 °C (40 mm). The residue was extracted with two 250-mL portions of benzene. Evaporation of the filtered benzene extracts at ~40 °C (40 mm) gave a pale brown residue. Fractional sublimation of this residue first gave 0.33 g of an unidentified substance at 110–125 °C (0.2 mm) which was not investigated further since its infrared spectrum showed the absence of cyano groups. After removal of this substance, further vacuum sublimation at 130–135 °C (0.2 mm) gave 0.56 g (7% conversion, 12% yield) of 1-bromopentacyanobutadiene, identified by its infrared spectrum (see below). The residue remaining from the benzene extraction was crystallized from a mixture of dichloromethane and diethyl ether to give 4.1 g (41% recovery) of unreacted tetraethylammonium pentacyanobutadien-1-olate.

B. From $Na_2C_4(CN)_6$ and Bromine. A mixture of 10.1 g (~40 mmol) of disodium *trans*-hexacyanobutenediide [dried at 110 °C (0.1 mm) for 20 h], 4.0 mL (11.7 g, 73.1 mmol as Br_2) of bromine, and 80 mL of hexane was stirred for 25 h at room temperature. The reaction mixture was then evaporated to dryness at 40 °C (40 mm). Excess bromine was removed by pumping at 25 °C (0.1 mm) for 12 h. The dark brown residue was extracted with two 150-mL portions of benzene followed by one portion of 1,2-dichloroethane. Evaporation of the combined extracts at ~40 °C (40 mm) followed by vacuum sublimation at 135 °C (0.2 mm) gave 0.9 g (9% yield) of 1-bromopentacyanobutadiene: mp 228 °C dec; infrared spectrum (KBr) 2251 (w), 1549 (m), 1531 (m), 1401 (w), 1375 (m), 1348 (vw), 1276 (w), 1265 (m), 1220 (m), 1211 (vw), 1199 (vw), 1030 (vw), 1021 (w), 1002 (vw), 925 (vw), 911 (w), 872 (vw), 809 (vw), 784 (m), 777 cm^{-1} (w); ultraviolet spectrum (CH_3CN) 333 nm (ϵ 3700), 313 (4400), 265 (9600), 253 (9700); mass spectrum $C_9N_5Br^+$ (100), $C_9N_5^+$ (95), $C_8N_4^+$ (5), $C_7N_3^+$ (40), $C_5N_3^+$ (19), $C_6N_2^+$ (20), $C_4N_2^+$ (42), C_4N^+ (13), C_3N^+ (7), C_2N^+ 12).

Anal. Calcd for C_9BrN_5: C, 41.8; H, 0.0; N, 27.1; Br, 31.0. Found: C, 41.9; H, 0.3; N, 27.1; Br, 30.6.

Preparation of 1-Ethoxypentacyanobutadiene. A mixture of 0.30 g (1.4 mmol) of 1-chloropentacyanobutadiene, 10 mL of absolute ethanol, and 50 mL of tetrahydrofuran was boiled under reflux for 24 h. Removal of solvent at ~40 °C (40 mm) followed by crystallization from a mixture of dichloromethane and hexane gave a total of 0.30 g (96% yield) of 1-ethoxypentacyanobutadiene. Sublimation of the crude product at 110 °C (0.15 mm) gave the analytical sample as white crystals: mp 130–132 °C; infrared ν(CN) 2245 (w), ν(C=C) 1570 (m) and 1535 cm^{-1} (m); ^1H NMR spectrum CH_2 at τ 5.28 (quartet, J = 7 Hz), CH_3 at τ 8.44 (triplet, J = 7 Hz); ultraviolet spectrum (CH_3CN) 347 nm (ϵ 7500), 337 (6600), 270 (10 200).

Anal. Calcd for $C_{11}H_5N_5O$: C, 59.2; H, 2.2; N, 31.4. Found: C, 59.7; H, 2.4; N, 30.4.

Reaction of 1-Bromopentacyanobutadiene with $NaMn(CO)_5$. A solution of $NaMn(CO)_5$ was prepared by stirring a solution of 1.0 g (2.55 mmol) of $Mn_2(CO)_{10}$ in 50 mL of redistilled tetrahydrofuran with an amalgam of 0.2 g (8.7 mg-atoms) of sodium metal in 5 mL of mercury for 1.5 h. This solution was treated at −78 °C with a solution of 0.9 g (3.5 mmol) of 1-bromopentacyanobutadiene in 100 mL of redistilled tetrahydrofuran. After the resulting green mixture was stirred for 1 h at room temperature, solvent was removed at 25 °C (40 mm). The residue was extracted with dichloromethane. Addition of hexane to the filtered dichloromethane extracts followed by slow solvent removal at ~25 °C (40 mm) and addition of hexane gave 0.27 g (21% yield) of yellow $(NC)_2C{=}C(CN)C(CN){=}C(CN)Mn(CO)_5$. The analytical sample was obtained by chromatography of the filtrate on Florisil in dichloromethane solution followed by recrystallization from mixtures of dichloromethane and hexane to give a yellow solid: mp 140 °C dec; infrared spectrum ν(CO) frequencies at 2142 (s), 2090 (m), and 2048 cm^{-1} (vs) in CH_2Cl_2; ν(CN) frequencies at 2246 (w) and 2236 cm^{-1} (w) in KBr; and ν(C=C) frequencies at 1525 (s) and 1505 cm^{-1} (m) in KBr.

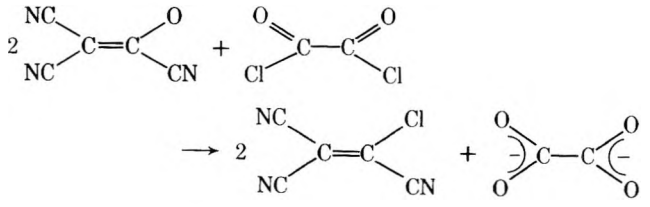
Anal. Calcd for $C_{14}MnN_5O_5$: C, 45.0; H, 0.0; N, 18.8; O, 21.4. Found: C, 45.0; H, 0.0; N, 18.4; O, 22.0.

Reaction of 1-Bromopentacyanobutadiene with $NaW(CO)_3C_5H_5$. A solution of $NaW(CO)_3C_5H_5$ was prepared by boiling under reflux a mixture of 1.41 g (4 mmol) of $W(CO)_6$ and 5 mmol of sodium cyclopentadienide (from NaH and cyclopentadiene) in 1,2-dimethoxyethane solution. This solution was treated at −78 °C with 1.03 g (4 mmol) of 1-bromopentacyanobutadiene. After stirring for 2 h at room temperature, the solvent was removed at ~40 °C (40 mm). A concentrated solution of the purple residue in dichloromethane was chromatographed on a Florisil column. Red-violet ($[C_5H_5W(CO)_3]_2$), orange ($C_5H_5W(CO)_3Br$), and magenta (unidentified) bands were first successively eluted from the chromatogram with mixtures of dichloromethane and hexane. Further elution of the next yellow-brown band with pure dichloromethane followed by evaporation of the eluate and two successive crystallizations from mixtures of dichloromethane and hexane gave 0.05 g (2.5% yield) of yellow $(NC)_2C{=}C(CN)C(CN){=}C(CN)W(CO)_3C_5H_5$: mp 185–190 °C dec; infrared spectrum ν(CH) frequency at 3121 cm^{-1} (w) in KBr; ν(CN) frequencies at 2245 (w) and 2230 cm^{-1} (w) in KBr; ν(CO) frequencies at 2050 (s) and 1955 cm^{-1} (vs) in CH_2Cl_2; ν(C=C) frequencies at 1523 (m) and 1500 cm^{-1} (m) in KBr; ^1H NMR spectrum in $(CD_3)_2CO$, τ (C_5H_5) 3.85.

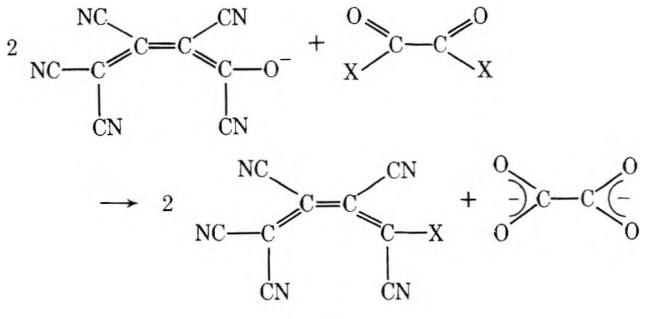
Anal. Calcd for $C_{17}H_5N_5O_3W$: C, 39.9; H, 1.0; N, 13.7; O, 9.4. Found: C, 40.3; H, 1.4; N, 12.9; O, 10.1.

Results and Discussion

The reaction of tetramethylammonium tricyanoethenolate with oxalyl chloride in 1,2-dimethoxyethane has been reported[14] to provide a convenient synthesis of tricyanovinyl chloride according to the following scheme:



Our syntheses of 1-halopentacyanobutadienes use the completely analogous reactions of tetraethylammonium pentacyanobutadien-1-olate with oxalyl halides in 1,2-dimethoxyethane according to the following schemes (X = Cl or Br):



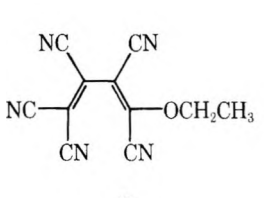
I

The yields of the 1-halopentacyanobutadienes from these reactions were somewhat erratic for reasons that are not completely clear. Alternative reagents for conversion of the tetraethylammonium pentacyanobutadiene-1-olate to 1-chloropentacyanobutadiene (I, X = Cl) are $POCl_3$ in 1,2-dimethoxyethane and thionyl chloride in dichloromethane, but neither of these reagents appears to offer any advantages over oxalyl chloride.

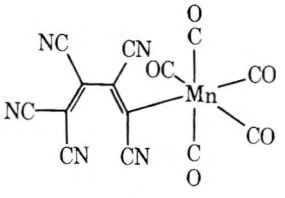
During the course of some work on hexacyanobutadiene, an alternative synthesis of 1-bromopentacyanobutadiene (I, X = Br) was discovered. The reaction of disodium hexacyanobutenediide with bromine vapor is reported[12] to result in oxidation to give hexacyanobutadiene. However, in this work the reaction of disodium hexacyanobutenediide with excess bromine in hexane solution was found to proceed differently resulting in replacement of one cyano group with bromine to give 1-bromopentacyanobutadiene. Speculation on the mechanism of this interesting reaction appears premature.

The spectroscopic properties of the 1-halopentacyanobutadienes (I, X = Cl and Br) are in accord with the proposed structures. The infrared spectra exhibit the expected ν(CN) frequencies at 2248 ± 3 cm^{-1} as well as symmetric and antisymmetric ν(C=C) frequencies at 1545 ± 5 and 1528 ± 4 cm^{-1}, respectively. The mass spectra exhibit the expected molecular ions. These molecular ions $C_9N_5X^+$ fragment most readily by halogen loss to give $C_9N_5^+$ followed by successive CN losses to give $C_8N_4^+$, $C_7N_3^+$, and $C_6N_2^+$. The last ion may be derived from 1,4-dicyanobutadiyne, NCC≡CC≡CCN. Another important ion is $C_4N_2^+$ possibly derived from dicyanoacetylene. In the chloro derivative I (X = Cl) cyano loss from the molecular ion to give $C_8N_4Cl^+$ apparently can compete with the more usual chlorine loss to give $C_9N_5^+$, whereas the analogous $C_8N_4Br^+$ was not found in the corresponding bromo derivative I (X = Br) apparently because of the lower strength of carbon–bromine bonds relative to carbon–chlorine bonds.

The halogen atoms in the 1-halopentacyanobutadienes were found to be relatively reactive toward nucleophiles similar to the halogen atoms in polycyanovinyl halides. Thus treatment of 1-chloropentacyanobutadiene (I, X = Cl) with ethanol readily leads to replacement of the chlorine with an ethoxy group to form 1-ethoxypentacyanobutadiene (II). The compound II was also isolated when diethyl ether was used to crystallize the crude product from tetraethylammonium pentacyanobutadien-1-olate and oxalyl chloride.



II



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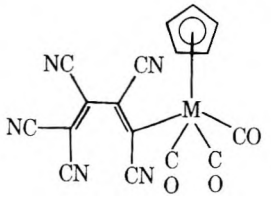

IV

The halogen atoms in the 1-halopentacyanobutadienes (I) were also found to be reactive toward metal carbonyl anions to give pentacyanobutadienyl transition metal carbonyl derivatives. Thus the reaction of 1-bromopentacyanobutadiene with $NaMn(CO)_5$ gives the manganese pentacarbonyl derivative $(NC)_2C{=}C(CN)C(CN){=}C(CN)Mn(CO)_5$ (III) identi-

fied by elemental analyses and a pattern of infrared ν(CO) frequencies similar to those found in the previously reported[4] polycyanovinylmanganese pentacarbonyl derivatives. A similar reaction of 1-bromopentacyanobutadiene with $NaW(CO)_3C_5H_5$ gives a complex mixture from which the corresponding pentacyanobutadienyl derivative $(NC)_2C{=}C(CN)C(CN){=}C(CN)W(CO)_3C_5H_5$ (IV, M = W) can be isolated in low yield by chromatography. This pentacyanobutadienyl derivative was identified by elemental analyses, the expected pattern of infrared ν(CO) frequencies for an $RW(CO)_3C_5H_5$ derivative, and the expected single C_5H_5 ^1H NMR resonance. A similar attempt to prepare the molybdenum analogue IV (M= Mo) gave a complex mixture from which a pure product could not be separated.

The infrared ν(C=C) frequencies of the pentacyanobutadienyl transition metal derivatives III and IV (M = W) appear at 1524 ± 1 and 1503 ± 3 cm^{-1} which are about 25 cm^{-1} lower than the ν(C=C) frequencies found in the corresponding 1-halopentacyanobutadienes I (X = Cl and Br). This decrease in the ν(C=C) frequencies of a cyanoolefin upon forming a σ bond to a metal carbonyl unit is a consequence of partial donation of electrons from the filled metal d orbitals into the antibonding orbitals of the carbon–carbon double bond. The magnitude of this effect (~25 cm^{-1}) in the pentacyanobutadienyl transition metal derivatives III and IV (M = W) is less than that of the corresponding effect (90–100 cm^{-1}) in the previously reported[4] polycyanovinyl transition metal derivatives since only one of the two carbon–carbon double bonds of the pentacyanobutadienyl system is adjacent to the transition metal system. The infrared spectra of pentacyanobutadienyl transition metal derivatives III and IV (M = W) exhibit two ν(CN) frequencies at 2245 ± 1 and 2233 ± 3 cm^{-1} in contrast to the 1-halopentacyanobutadienes I (X = Cl and Br) which exhibit only a single ν(CN) frequency at 2248 ± 1 cm^{-1}. The lower of the ν(CN) frequencies in the metal complexes III and IV (M = W) can arise largely from the cyano group bonded to the same carbon as the transition metal. Again this lowering of the ν(CN) frequency by ~10 cm^{-1} can arise from partial donation of the transition metal d electrons into the antibonding orbitals of the carbon–nitrogen triple bond.

A characteristic property of cyano olefins[15] and hexacyanobutadiene[12] is the formation of charge transfer complexes with aromatic hydrocarbons. The 1-halopentacyanobutadienes (I, X = Cl and Br) form red solid charge-transfer complexes with hexamethylbenzene in contrast to the reported[12] black solid charge transfer complex formed from hexacyanobutadiene and hexamethylbenzene. 1-Ethoxypentacyanobutadiene forms a yellow solid charge-transfer complex with hexamethylbenzene. Qualitative inspection of the colors of these hexamethylbenzene charge transfer complexes suggests the following observations: (1) Replacement of a cyano group with a halogen weakens the charge transfer complexes because part of the planar delocalized system is lost. (2) Replacement of a cyano group with an ethoxy group weakens the charge transfer complexes more than a halogen atom because of the nonplanarity of the ethoxy groups.

Acknowledgment. We are indebted to the Office of Naval Research for partial support of this work.

Registry No.—I (X = Cl), 62139-51-9; I (X = Br), 62139-52-0; II, 62139-53-1; III, 62227-95-6; IV, 62227-96-7; tetraethylammonium pentacyanobutadien-1-olate, 62139-55-3; oxalyl chloride, 79-37-8; oxalyl bromide, 15219-34-8; disodium *trans*-hexacyanobutenediide, 28804-86-6; $NaMn(CO)_5$, 13859-41-1; $NaW(CO)_3C_5H_5$, 12107-36-7.

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(2) Postdoctoral research associate, 1971–1972.
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Quaternary Ammonium Halides as Powerful Lanthanide Shift Donors

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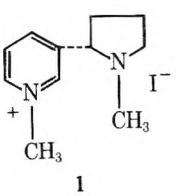
Lanthanide shift reagents (LSR) have been of considerable use in a wide variety of structural problems, ranging from the determination of relative configurations to the assessment of enantiomeric purity.[1] The simplicity of this nuclear magnetic resonance technique belies the complexity of the mechanisms[2] responsible for observed shifts. This complexity has stimulated investigations into the interactions of the shift reagent and the substrate, especially for substances having two or more sites[3] capable of complexation.

We now report our observation that proton resonances of quaternary ammonium halides are more strongly shifted by $Eu(fod)_3$ than the corresponding resonances of related tertiary amine functionalities.[12] This is a striking finding in that amines have been considered to be the strongest donors among all the previously examined functional groups.[3]

N-Methylnicotinium iodide (1), of interest as a chemical[4]



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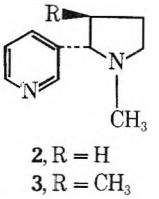


2, R = H
3, R = CH_3

and biological[5] analogue of nicotine, was examined in $CDCl_3$ solution with $Eu(fod)_3$ (Figure 1). Two sites of complexation can be a priori suggested for 1: at the pyrrolidine nitrogen's lone pair electrons and at the quaternary ammonium iodide functionality. The induced shift gradients clearly indicate that significantly larger shifts are observed for the pyridine ring protons than for the pyrrolidine ring protons. The relative order of lanthanide induced shift (LIS) observed (C_6H > $^+NCH_3$ > C_5H > C_2H ≫ $N'CH_3$) implies that the Eu is located near the quaternary center.

We propose that the quaternary ammonium iodide acts as a LIS donor by $Eu(fod)_3$ complexation with the counterion of the quaternized nitrogen, I^-; the resulting $Eu(fod)_3$–I^- complex is in turn associated with the positively charged

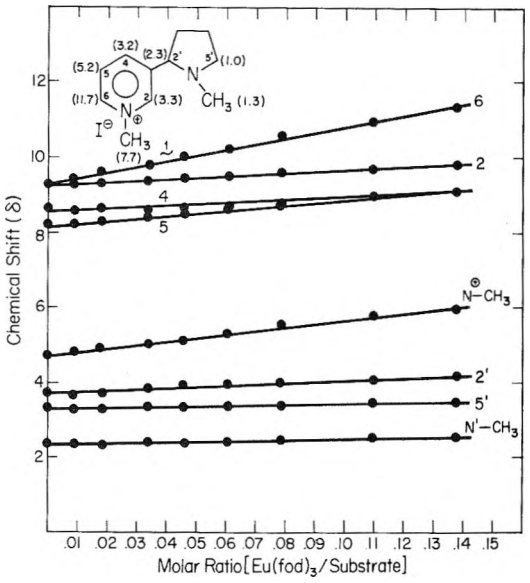


Figure 1. Lanthanide shift study of *N*-methylnicotinium iodide (**1**) with $Eu(fod)_3$. The relative LIS are shown in parentheses adjacent to the corresponding proton position.

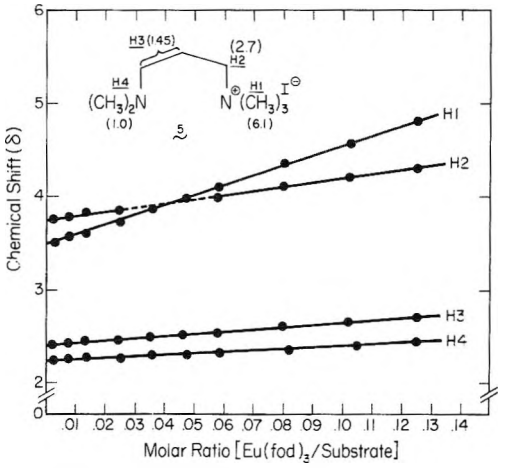


Figure 2. Lanthanide shift study of dimethylaminotrimethylpropylammonium iodide (**5**) with $Eu(fod)_3$.

moiety.[6] Chloroform, being a nonpolar solvent, probably enhances the LIS by forcing the $Eu(fod)_3$–I^- complex close to the positive charge distribution.[8]

$Eu(fod)_3$ is a Lewis acid, and competitive LIS studies have shown relationships between donor power and functional group basicity (directly proportional)[1] and steric hindrance to complexation (inversely proportional).[9] Indeed, recent LIS studies of nicotine (**2**)[10a] and *trans*-3′-methylnicotine (**3**)[10b] have shown significantly greater shifts for the pyridyl ring protons than the pyrrolidine ring protons for these compounds, and steric inhibition to complexation at the more basic pyrrolidine nitrogen was cited as causal. Similarly, one might expect that the pyrrolidine nitrogen of **1** would be sterically blocked.

An alternative explanation of our LIS results would involve pyrrolidine nitrogen complexation and an unusual LIS angle dependency. In order (1) to establish that complexation occurs with the iodide counterion, and (2) to more accurately compare the donor power of quaternary ammonium halides with uncharged tertiary amines, two additional experiments were performed.

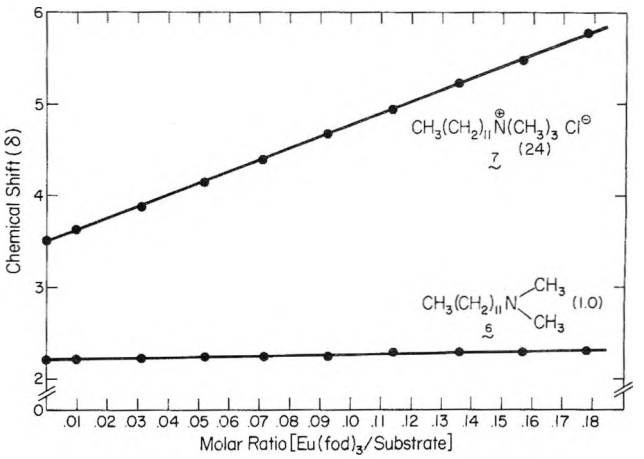
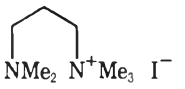


Figure 3. Competitive lanthanide shift study of dimethyldodecylamine (**6**) and trimethyldodecylammonium iodide (**7**) with $Eu(fod)_3$. The resonances of the $N\text{-}CH_3$ groups are plotted as a function of LSR/substrate.

Firstly, quaternary salt **5**, the monomethiodide of *N,N,N′,N′*-tetramethyl-1,3-propanediamine (**4**), was exam-



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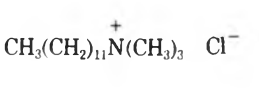

7

ined in the presence of $Eu(fod)_3$. As shown in Figure 2, significantly greater LIS were observed for protons closer to the quaternary nitrogen than to protons closer to the tertiary amine. To completely eliminate ambiguities due to LIS involving difunctional molecules, a second type of competitive complexing was examined. A 1:1 mixture of *N,N*-dimethyldodecylamine (**6**) and *N,N,N*-trimethyldodecylammonium chloride (**7**) in $CDCl_3$ was treated with $Eu(fod)_3$. As shown in Figure 3, the *N*-methyl groups in the quaternary salt **7** underwent a LIS almost 25 times greater than the LIS of the *N*-methyl groups in the tertiary amine **6**. These two experiments clearly establish that the quaternary ammonium halide moiety is a more powerful LIS donor than the corresponding tertiary amines.[12]

A closer examination of the relative LIS of the nicotinoids **1**–**3** reveals an interesting result. For **2** and **3**, the shifts of the pyridyl ring protons are somewhat symmetrical; i.e., the LIS of C_2H and C_6H are very similar.[10] It is likely that the LSR complexes with the pyridine lone pair electrons of **2** and **3** along the C_4–N axis; however, for **1**, C_6H has the largest shift gradient and the order of LIS suggests complexation on (or close to) the C_6–C_3 axis para to the pyrrolidine ring. The atomic bulk of the iodide counterion in **1** and consequently the bulk of the $Eu(fod)_3$–I^- must meet severe steric repulsions due to the *N*-methylpyrrolidine ring in any attempt for symmetrical complexation with the substituted pyridine ring. In addition, charge is delocalized throughout the heterocyclic ring, and, in part, onto the pyrrolidine ring. We have shown[4] that through-space interactions between the pyrrolidine nitrogen and the pyridine ring occur in **1**, and this interaction, coupled with the delocalization phenomenon and the steric hindrance considerations, serves in favor of nonsymmetrical complexation.

The use of organic counterions, e.g., $CH_3CO_2^-$ or $C_6H_5CO_2^-$, will allow one to monitor the LIS of both the cation and the anion in these quaternary nitrogen salts. This information, coupled with the McConnell–Robertson relationship,[1] may allow the evaluation of ion–ion phenomena in nonpolar solution. However, the relative contributions of

contact and pseudocontact shifts at these relative concentrations and experimental conditions must be first determined.[11,12]

Experimental Section

All NMR spectra were recorded on either a Varian Associates A-60A or XL-100 spectrometer and are referenced to internal tetramethylsilane. *N*-Methylnicotinium iodide was prepared by iodomethylation of nicotine in acetic acid as previously described.[4] Dimethyldodecylamine and trimethyldodecylammonium chloride were obtained from Lachat Chemicals, Inc., MeQuon, Wis., and dried under vacuum and stored over P_2O_5 until used. $Eu(fod)_3$ was freshly sublimed immediately before use. All transfers of LSR were made under dry nitrogen.

3-Dimethylaminotrimethylpropylammonium Iodide (5). To a solution of 10.0 g (77 mmol) of *N,N,N′,N′*-tetramethyl-1,3-propanediamine in 150 mL of benzene was added all at once 5.5 g (38 mmol) of iodomethane (caution: cancer suspect agent). A precipitate immediately formed. After 25 h, the precipitate was filtered, washed with additional benzene, and dried under high vacuum giving 10.1 g (98% based on iodomethane) of **5**, mp 173.5–174 °C.

Anal. Calcd for $C_8H_{21}N_2I$: C, 35.30; H, 7.78; N, 10.30; I, 46.63. Found: C, 35.13; H, 7.68; N, 10.36; I, 46.42.

Representative Procedure of LIS Study. A solution of known concentration of quaternary salt was prepared in an oven-dried NMR tube. To this solution were added known volumes of a $Eu(fod)_3$ solution prepared to known molarity. NMR spectra were recorded after each addition. The relative concentration of $Eu(fod)_3$:substrate was kept below 0.2:1. Replicate experiments were performed.

Acknowledgment. Discussions with Drs. T. Phil Pitner, A. Kassman, and J. F. Whidby are acknowledged with pleasure.

Registry No.—**1**, 21446-46-8; **4**, 62126-65-2; **5**, 110-95-2; **6**, 112-18-5; **7**, 112-00-5; iodomethane, 74-88-4.

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(6) Walker and co-workers[7] have recently reported LIS studies on penta- and hexanitratolanthanate complexes of a number of pyridinium cations, e.g., $[R_4N]_2Ln(NO_3)_5$ and $[R_4N]_3Ln(NO_3)_6$. In these studies, the lanthanide shift "reagent" is in fact the anion of the quaternary ammonium salt.

(7) (a) M. Saleem Quereshi and I. M. Walker, *Inorg. Chem.*, **13**, 2896 (1974); (b) I. M. Walker and D. H. Wheeden, *ibid.*, **12**, 772 (1973); see also, G. A. Elgavish and J. Reuben, *J. Am. Chem. Soc.*, **99**, 1762 (1977).

(8) The shifts observed in these studies may be viewed as a counterion modification effect. Schiementz [*Tetrahedron*, **29**, 741 (1974), and earlier papers in this series] has shown that the anion $B(C_6H_5)_4^-$ can act as an effective shift reagent for quaternary ammonium cations in, e.g., R_4N^+ $B(C_6H_5)_4^-$ salts.

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(11) Following the completion of this portion of our work, K. B. Lipkowitz reported (Ph.D. Thesis, Montana State University, 1975, pp 171–178, Xerox University Microfilms No. 76-13,307) a LIS study of a sulfonium iodide. Two modes of lanthanide complexation are suggested, either with the remaining lone pair on sulfur or the halide counterion.

(12) **Note Added in Proof.** A competitive shift study between *N*-methyldodecylamine and **7** led to results nearly identical with those shown in Figure **3**, i.e., significantly greater LIS were observed for the *N*-methyl and *N*-methylene protons of the quaternary salt than for the corresponding protons of the free base. A similar competitive study between dodecylamine and **7** resulted in nonlinear LIS, indicating the probable need for association constant determinations in these systems.

Thermolysis of *N*-Acyl Substituted 2-Allylthioimidazolines. Evidence for a [3,3] Sigmatropic Rearrangement

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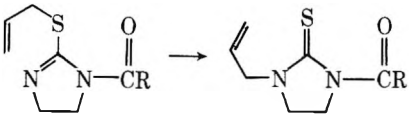
Thermal allylic rearrangements have been a subject of continuing synthetic[1] and mechanistic[2] interest. In relation to a current project dealing with the mechanism of biotin catalysis,[3] *N*-acetyl-2-allylthioimidazoline (**1a**) and *N*-carbomethoxy-2-allylthioimidazoline (**1b**) were prepared as potential model substrates. In light of the molecular framework of **1a** and **1b** it also became of interest to investigate the thermal properties of each of these compounds.

Pyrolysis of **1a** (145 °C, 72 h) gave the rearranged imidazolidinethione (**2a**) as the only product in 75% yield. Conversion of **1a** → **2a** could be monitored by the characteristic

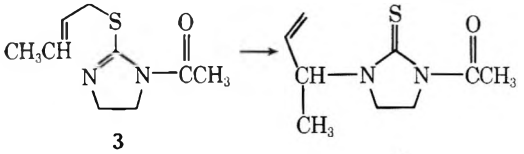


1a, R = CH_3 **2a**, R = CH_3
b, R = OCH_3 **b**, R = OCH_3

downfield NMR shift of the acetyl methyl protons from δ 2.20 to δ 2.80.[4]

Mechanistically, the thermal allylic rearrangement of **1a** can be formulated in terms of a number of different dissociative-recombination and concerted reaction pathways. Additional insight into the mechanism operative in this system comes from the thermolysis of compound **3**. *N*-Acetyl-2-crotylthioimidazoline (**3**) was readily prepared by the treatment of *N*-acetylimidazolidinethione[5] with a commercial mixture of 1-bromo-2-butene (80%) and 3-bromo-1-butene (20%) and triethylamine. Despite the possibility of forming a number of different positional isomers, a 91% yield of **3** (a mixture of *E* and *Z* isomers) was obtained.

Thermolysis of **3** under comparable reaction conditions (145 °C, 30 h) gave a 90% yield of *N*-acetyl-*N′*-(3′-butenyl)imidazolidinethione (**4**) as the only isolated product. Support for



3 **4**

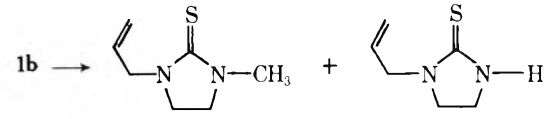
the indicated substitution pattern in the butenyl side chain comes from three complementary NMR observations. First, the lone methine proton resonance was identified as part of the complex multiplet at δ 5.10–6.04 by two successive proton decoupling experiments. Double irradiation of the protons at δ 1.23–1.30 in compound **4** simplified the multiplet at δ 5.10–6.04. Correspondingly, when the multiplet at δ 5.10–6.04 was doubly irradiated, the doublet at δ 1.23–1.30 collapsed into a singlet. Second, a comparison of the NMR spectrum of **2a** with that of **4** showed that the resonance associated with the allylic methylene protons (δ 4.22–4.40) in the former compound was absent in the spectrum of compound **4**. Third, an upfield shift of the high-field methyl proton resonance from δ 1.60–1.82 in **3** to δ 1.23–1.30 in **4** was noted. The resonance at ca. δ 1.60 is a diagnostic peak for vinylic methyl protons,[6] and the absence of this resonance in the spectrum of **4** is a further evidence of structure. The thermal rearrangement can

be conveniently monitored by NMR by observing the characteristic downfield shift of the acetyl methyl protons[4] as well as the upfield shift of the methyl doublet associated with the butenyl side chain. In a preliminary kinetic study, this rearrangement showed first-order behavior in benzene over 2 half-lives ($k_1 = 8.3 \pm 0.1 \times 10^{-6}$ s^{-1} at 141 ± 0.5 °C).

The high yield noted for the conversion of **3** → **4**, the absence of any other positional isomers, and the first-order kinetic behavior of the reaction argue that the thermolysis of **3** as well as **1a** proceeds by a [3,3] sigmatropic pathway. The reaction, therefore, can be considered as an additional example of a thio-Claisen rearrangement.[2,7] It is of interest to note that the [3,3] sigmatropic route is more favorable than either a dissociative-recombination pathway or a thermal Chapman-type four-center rearrangement for these compounds. These results parallel those previously observed for the thermal rearrangements of *O*-allyl imidates.[8]

When, however, compound **1b** was subjected to similar thermolysis conditions (170 °C, 72 h) the isomeric product (**2b**) was not formed, but instead *N*-methyl-*N'*-allylimidazolidinethione (**5**) and *N*-allylimidazolidinethione[9] (**6**) were isolated in 65 and 25% yields, respectively.

There are several intermolecular as well as intramolecular mechanisms that can account for the formation of both **5** and **6**. Precedent does exist for the loss of carbon dioxide in carbamates. Recently, Loozen, Drouen, and Piepers have shown that thermolysis of *N*-alkoxycarbonylimidazoles yielded the corresponding N-alkylated imidazoles,[10] and have suggested a four-center Chapman-type rearrangement for these reactions.[11] We are currently investigating the mechanism of this reaction.[14]



5 6

Experimental Section

General. Melting points were determined with a Thomas-Hoover melting point apparatus. Infrared spectra (IR) were run on Perkin-Elmer Model 700 and 237B spectrometers and calibrated against the 1601-cm^{-1} band of polystyrene. Proton nuclear magnetic resonance spectra were recorded on Varian Associates Model T-60 and EM-390 instruments. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were determined on a Varian Associates Model XL-100-15 spectrometer. The XL-100 was equipped with a Nicolet Technology Corp. TT-100 data system. Chemical shifts are expressed in parts per million relative to Me_4Si. Mass spectra (MS) data were obtained at an ionizing voltage of 70 eV on a Hitachi Perkin-Elmer Model RMU-6H mass spectrometer. High-resolution mass spectra were performed by Dr. R. Grigsby at the Department of Biochemistry and Biophysics, Texas A & M University, on a CEC21-110B double focusing magnetic sector spectrometer at 70 eV. Exact masses were determined by peak matching. Elemental analyses were obtained at Spang Microanalytical Laboratories, Ann Arbor, Mich.

The solvents and reactants were of the best commercial grade available and were used without further purification. All reactions were run under nitrogen, and all glassware oven dried before use.

Thermolysis of *N*-Acetyl-2-allylthioimidazoline (1a). Preparation of *N*-Acetyl-*N'*-allylimidazolidinethione (2a). Compound **1a**[4] (0.40 g, 0.002 mol) was sealed in a glass tube and heated at 145 ± 2 °C for 72 h. The reaction product was then triturated overnight with hexane (25 mL), the hexane layer filtered, and the filtrate allowed to stand at 0 °C for 24 h. The hexane layer was refiltered and evaporated in vacuo, and the resultant oil vacuum distilled to give 0.30 g (75%) of **2a**: bp 160 °C (0.4 mm); IR (neat, NaCl) 1680, 1510 cm^{-1}; NMR ($CDCl_3$) δ 2.80 (s, 3 H), 3.40–4.14 (m, 4 H), 4.22–4.40 (d, J = 4 Hz, 2 H), 5.10–5.40 (m, 2 H), 5.50–6.10 (m, 1 H); MS *m/e* (rel intensity) 184 (60), 169 (100), 141 (51), 127 (88), 70 (77), 43 (81); mol wt 184.0672 (calcd for $C_8H_{12}N_2OS$, 184.0670).

Thermolysis of *N*-Carbomethoxy-2-allylthioimidazoline (1b). The preceding reaction and workup was repeated using 0.40 g (0.002 mol) of **1b**.[4] The bath temperature was maintained at 170 ± 2 °C for 72 h. Distillation of the resultant oil gave 0.26 g (65%) of **5**: bp 160 °C (0.25 mm); IR (neat) 1700, 1510 cm^{-1}; NMR ($CDCl_3$) δ 3.11 (s, 3 H), 3.40–3.55 (m, 4 H), 4.15–4.33 (d, J = 4 Hz, 2 H), 5.00–5.40 (m, 2 H), 5.41–6.20 (m, 1 H); MS *m/e* (rel intensity) 156 (94), 141 (100), 113 (72), 69 (39); mol wt 156.0726 (calcd for $C_7H_{12}N_2S$, 156.0721).

Anal. Calcd for $C_7H_{12}N_2S$: C, 53.81; H, 7.74; N, 17.93. Found: C, 53.88; H, 7.80; N, 17.84.

The white solid recovered from the second filtration was recrystallized from hexane to give 0.07 g (25%) of **6**:[9] mp 81–82.5 °C; IR (KBr) 1510 cm^{-1}; NMR ($CDCl_3$) δ 3.45–3.65 (m, 4 H), 4.12–4.25 (d, J = 4 Hz, 2 H), 5.00–5.35 (m, 2 H), 5.61–6.08 (m, 2 H); MS *m/e* (rel intensity) 142 (100), 127 (87), 100 (9), 70 (48).

Preparation of *N*-Acetyl-2-crotylthioimidazoline (3). To a stirred CH_2Cl_2 solution (125 mL) containing *N*-acetylimidazolidinethione[5] (2.88 g, 0.02 mol) and triethylamine (4.04 g, 0.04 mol), 4.1 mL (0.04 mol) of a 80:20 mixture of 1-bromo-2-butene and 3-bromo-1-butene was slowly added. The solution was refluxed (16 days), then consecutively washed with aqueous 5% $NaHCO_3$ (2 × 50 mL) and H_2O (50 mL), and dried (Na_2SO_4). The CH_2Cl_2 layer was evaporated in vacuo, the residue triturated with hexane (250 mL), and the hexane layer concentrated to give 3.60 g (91%) of **3**: mp 81–82.5 °C; IR (KBr) 1680, 1590 cm^{-1}; NMR ($CDCl_3$) δ 1.60–1.82 (d, J = 4 Hz, 3 H), 2.20 (s, 3 H), 3.50–3.76 (m, 2 H), 3.95 (s, 4 H), 5.50–5.75 (m, 2 H); MS *m/e* (rel intensity) 198 (52), 183 (100), 155 (81), 141 (61), 123 (55), 102 (26), 70 (12); mol wt 198.0820 (calcd for $C_9H_{14}N_2OS$, 198.0827).

Thermolysis of *N*-Acetyl-2-crotylthioimidazoline (3). Preparation of *N*-Acetyl-*N'*-(3'-butenyl)imidazolidinethione (4). Thermolysis and workup of 3 (0.04 g, 0.002 mol) under similar reaction conditions (145 ± 2 °C, 30 h) used for the preparation of **2a** gave 0.36 g (90%) of **4** after vacuum distillation, bp 130 °C (0.4 mm). The product was further purified by chromatography (silica gel, 70–230 mesh, 1.5 × 76 cm column) using a 5:95% mixture of Et_2O–CH_2Cl_2 as the eluent. Fractions 9–12 (10-mL fractions) after concentration gave 0.32 g of **4** (80%): IR (neat, NaCl) 1680 cm^{-1}; NMR ($CDCl_3$) δ 1.23–1.30 (d, J = 8 Hz, 3 H), 2.83 (s, 3 H), 3.25–4.13 (m, 4 H), 5.10–6.04 (m, 4 H). Double irradiation of the protons at δ 1.23–1.30 simplified the multiplet at δ 5.10–6.04. Correspondingly, when the multiplet at δ 5.10–6.04 was doubly irradiated, the doublet at δ 1.23–1.30 collapsed to a singlet. ^{13}C NMR ($CDCl_3$) 15.0, 26.6, 40.5, 43.6, 52.6, 117.2, 135.5, 171.9 ppm; MS *m/e* (rel intensity) 198 (100), 183 (84), 155 (87), 141 (82); mol wt 198.0833 (calcd for $C_9H_{14}N_2OS$, 198.0827).

Themolysis of *N*-Acetyl-2-crotylthioimidazoline (3). General Kinetic Method. The kinetics were performed by immersing a sealed NMR tube (Wilmad No. 501-PS) containing an 0.56 M solution of 3 in benzene-d_6 in a vapor bath of refluxing xylene (141 ± 0.5 °C) for specific time intervals. The reactions were quenched by removing the tube from the bath. Runs were carried out in duplicate and followed through over 2 half-lives.

Acknowledgment. We would like to thank the National Institutes of Health for their support of our work and the National Science Foundation for a matching instrumental grant for the purchase of the Varian XL-100-15 NMR spectrometer and Nicolet TT-100 data system.

Registry No.—**1a**, 61076-81-1; **1b**, 61076-84-4; **2a**, 62139-89-3; *E*-**3**, 62182-95-0; *Z*-**3**, 62182-96-1; **4**, 62139-90-6; **5**, 62139-91-7; **6**, 24521-43-5; *N*-acetylimidazolidinethione, 5391-52-6; 1-bromo-2-butene, 4784-77-4; 3-bromo-1-butene, 22037-73-6.

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(7) At the suggestion of a referee we have examined whether this reaction

(3 → 4) is subject to nucleophilic catalysis. In a recent study on the mechanism of the thio-Claisen rearrangement of allylic phenyl sulfides, Kwart and Schwartz[2a] have carefully demonstrated that these rearrangements were susceptible to catalysis by tertiary amines and a number of anionic bases. Addition of 1.1 equiv of pyridine to a 0.56 M benzene solution of **3**, however, did not affect the rate of conversion to imidazolidinethione **4** ($k_1 = 8.2 \pm 0.3 \times 10^{-6}$ s^{-1} at 141 ± 0.5 °C).

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(11) The Chapman rearrangement was originally restricted to the thermal conversion of aryl *N*-arylbenzimidates to *N*-aroyldiphenylamines.[12] The molecular constraints of this definition and the mechanistic deviations noted for the corresponding alkyl analogues of benzimidates suggests that alternative processes (i.e., intermolecular, radical) should also be considered for these reactions.[12,13]
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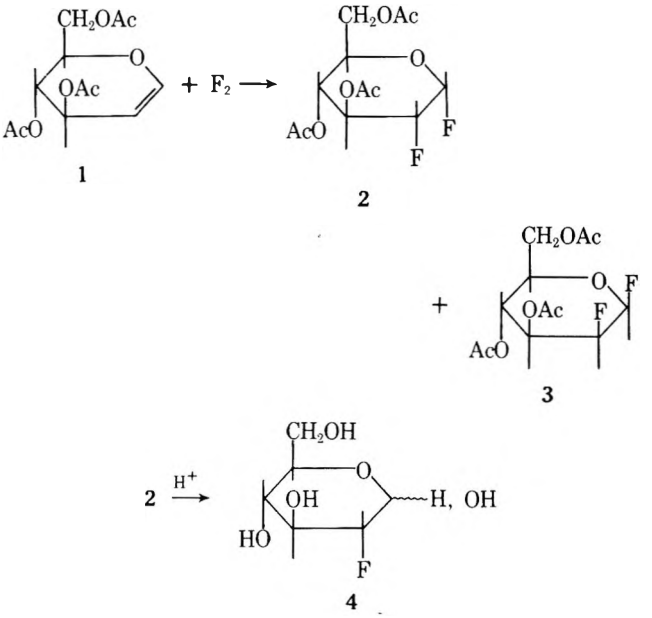
(13) For a discussion on the mechanism of the decarboxylation of *N*-carbalkoxypyrazoles see J. J. Wilczynski and H. W. Johnson, *J. Org. Chem.*, **39**, 1909 (1974), and references cited therein.
(14) Analogously, pyrolysis of *N*-carbomethoxy-*N*-methylimidazolidinethione[4] under similar reaction conditions (170 °C, 72 h) gave *N,N'*-dimethylimidazolidinethione (55%) and *N*-methylimidazolidinethione (45%) by NMR.

Scheme I



Fluorination with F_2. A Convenient Synthesis of 2-Deoxy-2-fluoro-D-glucose[1a]

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For many years molecular fluorine (F_2) was considered to be of limited value in organic synthetic applications owing to its extreme chemical reactivity as well as difficulty in handling.[2] More recently, however, the use of fluorine diluted with an inert gas has led to some remarkably selective and controllable transformations such as electrophilic additions to double bonds[3,4] and regioselective fluorine substitution at saturated carbon.[5]

In our work on the development of a labeled tracer to serve as a probe for local glucose metabolism in man,[6] we required a convenient synthesis of 2-deoxy-2-fluoro-D-glucose (2-FDG) that was adaptable to labeling with readily available chemical forms of fluorine-18 (^{18}F)[7] such as ^{18}F-labeled F_2.

Previous synthetic routes to 2-FDG involve fluoride displacement on an anhydro sugar[8,9] and electrophilic fluorination with trifluoromethyl hypofluorite (CF_3OF).[10] Since both of these routes required starting materials that were not readily available and neither could be readily adapted to labeling with ^{18}F, we investigated direct fluorination with F_2.

We report here the direct conversion of 3,4,6-tri-*O*-acetyl-D-glucal (**1**) to 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α-D-glucopyranosyl fluoride (**2**) and 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-β-D-mannopyranosyl fluoride (**3**) by reaction with F_2 (Scheme I). Hydrolysis of **2** and **3** to 2-FDG and 2-deoxy-2-fluoro-D-mannose has previously been described.[10]

Since this method can be used to prepare **2** and **3** in yields of 35 and 26%, respectively, direct fluorination followed by hydrolysis is a convenient synthetic alternative route to deoxyfluoro sugars.

Experimental Section

Melting points are not corrected. NMR spectra were taken with a JEOL JNM-MH-100 spectrometer using tetramethylsilane as an internal standard.

Handling Fluorine. F_2 is extremely reactive and highly toxic. Those who work with it should be familiar with the potential hazards associated with the storage and use of compressed fluorine and the proper techniques for the safe manipulation of small quantities of F_2 in the laboratory. A detailed description of the reactivity of F_2 as it applies to its safe use in the laboratory has appeared in the literature.[11] Systems for the remote handling of cylinders of compressed F_2 along with technical bulletins are commercially available.[12]

In this synthesis F_2 was passed through a sodium fluoride trap to remove HF, then diluted with argon in a nickel cylinder. Reaction vessels and related equipment exposed to F_2 were dried prior to use and were constructed of glass, Teflon, Kel-F, or passivated nickel or Monel. Although F_2 is a strong oxidant and we have experienced no difficulty when it is diluted with an inert gas prior to use in organic synthesis, we recommend adherence to these safety precautions to protect the chemist from explosion and exposure to F_2.

Reaction of 3,4,6-Tri-*O*-acetyl-D-glucal (1) with Fluorine. A solution of **1** (272.4 mg, 1.0 mmol) in $CFCl_3$ (10 mL, dried over 4 Å molecular sieves) was cooled to −78 °C. F_2 (3 mmol) diluted with argon (1:40) was passed into the solution (4–5 mL/min) for 2 h. The reaction mixture was allowed to warm to room temperature and the excess F_2 and $CFCl_3$ were removed using a stream of He. The residue was dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$. The $NaHCO_3$ layer was extracted with CH_2Cl_2 and the combined organic extracts were dried (Na_2SO_4) and concentrated to give 288 mg of a viscous oil. GLC analysis of the oil [XE60 nitrile (20%), 6 ft × 0.25 in. column, 250 °C, 86 mL/min] showed peaks at 1.1, 2.9, 3.8, 4.6, 5.3, 6.4, and 9.1 min in an area ratio of 1.4:0.5:0.8:0.5:22.6:0.5:1.0. The three peaks at 1.1, 5.3, and 9.1 min correspond to **1**, 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α-D-glucopyranosyl fluoride (**2**),[13] and 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-β-D-mannopyranosyl fluoride (**3**).[13] Compounds **2** and **3** were separated by column chromatography on 2 × 20 cm silicic acid (100 mesh) column and eluted with *n*-hexane, ether, methylene chloride, and methanol, yielding 123 mg (39.7%) of **2** and 80 mg (25.8%) of **3**.[14] Further purification of **2** on a second column gave 108 mg (34.8%) of colorless crystals which were recrystallized from hexane–ether (1:1): mp 69–70 °C (lit.[10] mp 91–92 °C); NMR spectrum ($CDCl_3$) was identical with that of an authentic sample of **2**[13] and showed three singlets at δ 2.1 (9 H, $CH_3C{=}O$), a multiplet at 4.1–4.4 (3 H, H_5 and H_6) which is overlapping with another multiplet centered at 4.6 (1 H, H_2, multiplet, $J_{H_1H_2} = 2.9$, $J_{H_2H_3} = 9.5$, $J_{H_2F_1} = 23.8$, $J_{H_2F_2} = 46$ Hz), a quasi-triplet at 5.16 (1 H, H_4, $J = 9.5$ Hz), a multiplet at 5.25–5.8 (1 H, H_3) which is overlapping with a doublet of doublets centered at 5.9 (1 H, H_1, $J_{H_1H_2} = 2.9$, $J_{H_1F_1} = 51$ Hz). Compound **3** had mp 114–115 °C (lit.[10] mp 113–114 °C); NMR spectrum ($CDCl_3$) was identical with that of an authentic sample of **3**[13] and showed three singlets at δ 2.1 (9 H, $CH_3C{=}O$), a doublet at 4.3 (2 H, H_6, $J = 7.5$ Hz), multiplets at 3.8–4.0 (1 H, H_5), 4.3–4.8 (1 H, H_2, $J_{H_2F_1} = 7.6$, $J_{H_2F_2} = 34$ Hz), 5.1–5.5 (1 H, H_3) which is overlapping with a doublet of doublets (1 H, H_1, $J_{H_1F_2} = 12.8$, $J_{H_1F_1} = 48$ Hz). Coupling constants for **2** and **3** are in agreement with previously reported values.[10]

2-Deoxy-2-fluoro-D-glucose (4). The glucosyl fluoride **2** (108 mg, 0.35 mmol) was hydrolyzed according to the method of Adamson and

co-workers,[10] to give 37 mg (58.4%) of **4** which had the same R_f (0.67) on TLC [cellulose, isobutyric acid–ammonia–water (66:1:33)], on high-pressure liquid chromatography [Waters μBondapak carbohydrate column, 30 cm × 4 mm, CH_3CN–H_2O (85:15), 1.5 mL/min, retention time 6 min, refractive index detector] as an authentic sample of **4**.[13] The NMR spectrum was also identical with that of an authentic sample of **4**.

Registry No.—**1**, 2873-29-2; **2**, 24679-90-1; **3**, 24679-92-3; **4**, 23094-77-1; fluorine, 7782-41-4.

References and Notes

(1) (a) Research carried out at Brookhaven National Laboratory under contract with the U.S. Energy Research and Development Administration and supported by its Division of Physical Research and Division of Biomedical and Environmental Research and also by the National Institutes of Health (USPHS Grant 2 R01 GM-16, 248-16 S1, and USPHS Grant 1-P07—RR00657-01A1). (b) National Institute of Radiological Sciences, Anagawa, Chiba-City, Japan.
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(6) M. Reivich et al., manuscript in preparation.
(7) Fluorine-18 is a short-lived radioactive isotope of fluorine ($t_{1/2}$ = 110 min). It decays by positron annihilation resulting in the production of two 511-keV photons which can be detected outside the body barrier. Therefore it is a useful label of biologically important molecules since it can be used to probe their metabolic fate in living systems including man.
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(11) R. Landau and R. Rosen, *Ind. Eng. Chem.*, **39**, 281 (1947).
(12) Matheson Gas Products, Report No. G-115B and Technical Bulletin, "Fluorine".
(13) Authentic samples of **2**, **3**, and **4** were prepared according to the method of Adamson et al.[10] The authors are grateful to Dr. R. H. Hesse for an authentic sample of **4** which served as a spectral and chromatographic standard.
(14) The relative areas of **2** and **3** on GLC do not reflect their isolated yields because **3** undergoes decomposition on GLC.

1,4-Transannular Nitrogen to Carbon Rearrangement Following Intramolecular Carbenoid Insertion. Formation of 6-*trans*-Styryl-3-azabicyclo[3.1.0]hexane

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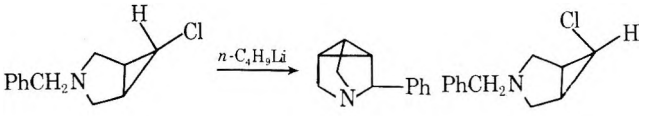
We are reporting a novel nitrogen to carbon transannular rearrangement following a carbenoid insertion reaction. Previously, we reported the formation of 3-phenyl-4-azatricyclo[2.2.1.0^{2,6}]heptane (**2**) from 3-benzyl-6-*exo*-chloro-3-

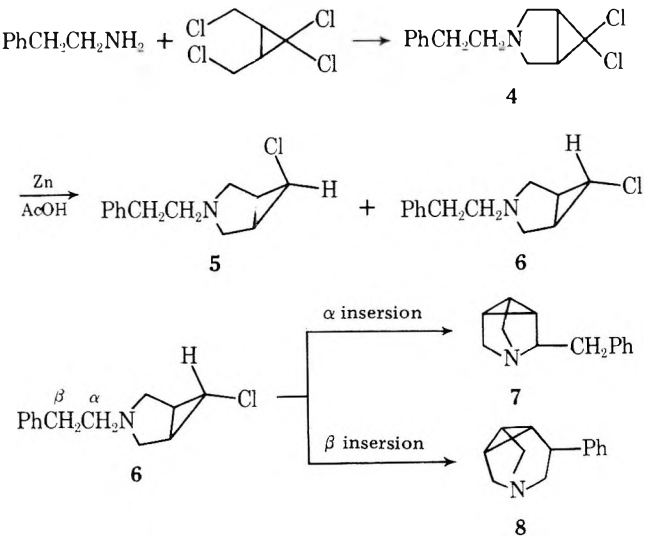


1 **2** **3**

azabicyclo[3.1.0]hexane (**1**) by a proposed intramolecular carbenoid carbon–hydrogen insertion.[2] In addition, it was shown that the epimeric *endo*-chlorocyclopropane (**3**) did not undergo the intramolecular insertion reaction.

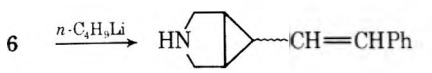
To further explore the scope of this reaction, 6-*exo*-chloro-3-phenethyl-3-azabicyclo[3.1.0]hexane (**6**) was prepared[3] utilizing the procedure previously reported (Scheme I). It was anticipated that reaction of **6** with butyllithium

Scheme I



would yield 3-benzyl-4-azatricyclo[2.2.1.0^{2,6}]heptane (**7**) or 3-phenyl-5-azatricyclo[3.2.1.0^{2,7}]octane (**8**) by intramolecular carbenoid insertions into either the α or β C–H bonds, respectively. Addition of phenethylamine to 1,1-dichloro-*cis*-2,3-bis(chloromethyl)cyclopropane yielded 6,6-dichloro-3-phenethyl-3-azabicyclo[3.1.0]hexane (**4**). Reduction of **4** with zinc dust in glacial acetic acid[4] yielded the epimeric *endo*- and *exo*-monochloro isomers **5** and **6**. The exo isomer **6** was the major product (63% yield), whereas **5** was isolated in 5% yield.

When the reaction was carried out by addition of butyllithium solution to an ethereal solution of the exo isomer **6** at room temperature, a solid product having a molecular weight of 185 was isolated in low yield after extensive column chromatography. Spectral data were not consistent with structures **7** or **8**. On the basis of its ^{1}H NMR, IR, and UV spectral characteristics, the substance was determined to be 6-*trans*-styryl-3-azabicyclo[3.1.0]hexane (**9**). The ^{1}H NMR spectrum



9

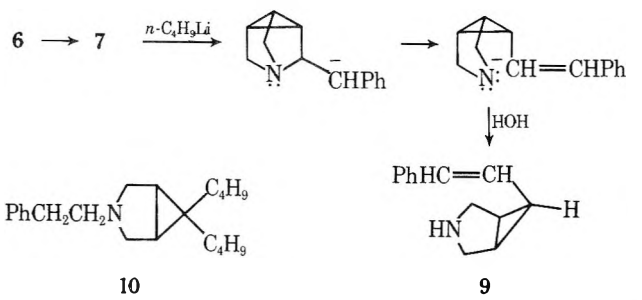
of **9** was characterized by a singlet at δ 1.72 (N–H) which disappeared on addition of D_2O and by olefinic proton absorptions at δ 5.87 (1 H, d of d, $^3J_{vic}$ = 8 Hz, $^3J_{olefinic}$ = 16 Hz) and δ 6.45 (1 H, d, $^3J_{olefinic}$ = 16 Hz). The large value of the olefinic proton coupling constant suggests trans couplings.[5] A multiplet at δ 1.45 (3 H) in the spectrum of **9** indicated that the cyclopropyl ring remained intact. Irradiation at δ 1.45 caused the doublet of doublets at δ 5.78 to collapse to a simple doublet. A singlet at δ 3.03 (4 H) was attributed to the four protons on the carbons adjacent to the nitrogen, in contrast to the ^{1}H NMR spectrum of **2** which was characterized by two sets of unequally coupled doublets of δ 2.28 and δ 2.70 for the protons adjacent to the nitrogen due to the shielding effect of the benzene ring.

The UV maximum of **9** occurred at 248 nm (ϵ 22 900). This comparatively large value for the extinction coefficient indicated the presence of a strong chromophore which was not seen in previous products and strongly supports the presence of the styryl group. *trans*-β-Methylstyrene, for example, has an absorption maximum of 251 nm (ϵ 17 000).[6] In the infrared

spectrum, absorptions were observed at 3400 and 2330 cm^{-1} which were attributed to free and associated N–H stretching vibrations, respectively. There were also absorptions at 1637 and 1590 cm^{-1} assigned to the double bond conjugated with an aromatic ring. A weak absorption at 1298 cm^{-1} and a strong one at 960 cm^{-1} support the presence of a trans-substituted double bond.[7]

It appears reasonable that **9** may be formed by hydrogen abstraction and ring opening of the proposed tricyclic compound **7** upon reaction with excess butyllithium present in the reaction mixture (Scheme II). The spectral evidence available

Scheme II



10 9

does not permit unequivocal determination of the geometry about carbon 6, but it seems likely that the *trans*-styryl group is endo to the bicyclic ring system providing isomerization has not occurred. The fact that insertion occurs into the C–H bond α to the nitrogen rather than at the β carbon is consistent with the results of Baird and Kaura.[8]

No evidence by ^1H NMR or mass spectral analysis was found for the formation of **9** on reaction of the dichloro compound **4** or the *endo*-chloro isomer **5** with *n*-butyllithium. In the case of **4**, mass-spectral analysis of the reaction mixture indicated the presence of a product, probably **10**, having a mass corresponding to the replacement of the chlorine atoms by two butyl groups. Unreacted starting material accounted for the bulk of the material recovered from the reaction of the endo isomer **5** with *n*-butyllithium. However, a peak at *m/e* 152 did indicate the presence of some material formed by replacement of the chlorine of **5** by a butyl group.

The fact that the *exo*-chloro isomers **1** and **6** yield an intramolecular insertion product or substance resulting from this process, whereas the epimeric *endo*-chloro isomers **3** and **5** do not react or yield butyl derivatives, is consistent with results obtained by Taylor and co-workers[9] and by Goldstein and Dolbier.[10]

Work is currently in progress to determine the mechanism of this interesting rearrangement and to further elucidate the factors influencing and controlling the carbenoid insertion reactions.

Experimental Section

All compounds used as starting materials in the synthetic procedures were obtained either from commercial sources or by known procedures. Reagent grade solvents were used in reactions. Commercial grade solvents were used for column chromatography and extraction procedures. High-resolution proton NMR spectra were recorded on a Varian Model A-60 high-resolution spectrometer. Spin-decoupling experiments were performed on a Varian T-60 equipped with a frequency decoupler. The ^1H NMR spectra were obtained in deuteriochloroform solutions using tetramethylsilane as an internal standard. The ^1H NMR spectra of amine salts were obtained in deuterium oxide (D_2O) solutions using sodium 3-trimethylsilylpropionate-2,2,3,3-d_4 (TSP) as an internal standard. Mass spectra were obtained with a Perkin-Elmer Model RMU-6H mass spectrometer (ionizing voltage 70 eV, inlet temperature 200 °C). Infrared spectra were recorded on a Perkin-Elmer Model 621 infrared spectrophotometer. Liquid samples were run as films between salt (NaCl) plates. Solid samples were run as KBr pellets. Ultraviolet spectra were recorded on a Cary Model 15 spectrophotometer using methanol as the solvent. A Varian Aerograph Model A-700 equipped with a column of 0.2% OV-1 on glass beads (6 ft × 0.25 in.) was used for gas chromatographic analyses. Silica gel G precoated uniplates (250 μm thickness, 2.5 × 10 cm) from Analtech, Inc., were used for thin-layer chromatographic (TLC) analyses. A short-wavelength ultraviolet lamp (2537 Å) or iodine vapor was used for visualization of zones. For column chromatography, either 60–100-mesh Florisil (Floridin Co.) or 70–230-mesh silica gel 50 (E. Merck) was used. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Compounds which were isolated and purified were analyzed for carbon, hydrogen, and nitrogen content using a Perkin-Elmer Model 240 elemental analyzer, and analyses are within ±0.3% of the theoretical values. Pertinent spectral data are given on those compounds which were isolated and characterized. Unless indicated, spectral data for amines are for the free bases.

1,1-Dichloro-*cis*-2,3-bis(chloromethyl)cyclopropane. A sodium hydroxide solution (390-mL 50% aqueous solution, 7.5 mol) was added dropwise over a period of 4 h to a stirred solution of 1,4-dichloro-*cis*-2-butene (62.5 g, 0.5 mol), chloroform (600 mL, 7.5 mol), and cetyltrimethylammonium bromide (1.0 g, 2.75 mmol). The reaction mixture was stirred at ambient temperature for about 60 h and then poured into 2 L of water. The chloroform layer was separated, washed with water, dried over magnesium sulfate, and concentrated at reduced pressure. The residual oil was vacuum distilled through a 12 × 80 mm column packed with glass helices. The fraction distilling at 123–126 °C (22 Torr) was collected. In a typical reaction, 46.1 g (44.5%) of product was obtained: ^1H NMR ($CDCl_3$) δ 2.22 (2 H, m), 3.67 (4 H, m); IR (film) 1255 cm^{-1} ($-CH_2Cl$); UV λ_{max} (methanol) 239 nm (ϵ 87.5).

Anal. Calcd for $C_5H_6Cl_4$: C, 28.89; H, 2.91; Cl, 68.20. Found: C, 28.57; H, 2.90.

6,6-Dichloro-3-phenethyl-3-azabicyclo[3.1.0]hexane (4). Phenethylamine (6.1 g, 0.05 mol), 1,1-dichloro-*cis*-2,3-bis(chloromethyl)cyclopropane (10.4 g, 0.05 mol), sodium bicarbonate (12.6 g, 0.15 mol), and *n*-butyl alcohol (100 mL) were stirred together and heated at reflux for 36 h. The mixture was cooled and filtered, and the filtrate was concentrated at reduced pressure. The residual oil was chromatographed on a column of Florisil (100 g) using petroleum ether (30–60 °C), benzene, and acetone mixtures to elute the product. The oily product was converted to the hydrochloride salt. Recrystallization from isopropyl alcohol–isopropyl ether gave 4.5 g (35%) of gray-white solid, mp 193–194.5 °C: ^1H NMR ($CHCl_3$) δ 2.25 (2 H, m), 2.70 (4 H, s), 2.86 (2 H, d), 3.15 (2, d of m), 7.25 (5, s); IR (film) 2800 (s, tertiary alkylamine), 1015 cm^{-1} (cyclopropane ring deformation); UV (HCl salt) λ_{max} (methanol) 257 nm (ϵ 179).

Anal. Calcd for $C_{13}H_{16}NCl_3$: C, 53.36; H, 5.51; N, 4.79. Found: C, 53.29; H, 5.50; N, 4.92.

6-Chloro-3-phenethyl-3-azabicyclo[3.1.0]hexane, Endo Isomer 5 and Exo Isomer 6. Zinc dust (14.3 g, 0.22 mol) was added in small portions to a stirred refluxing solution of 6,6-dichloro-3-phenethyl-3-azabicyclo[3.1.0]hexane (4) (11.0 g, 0.043 mol) in glacial acetic acid (100 mL). Sufficient time was allowed between additions of zinc dust for the foaming to subside. The reaction mixture was stirred at reflux for 18 h and then allowed to cool. The acetic acid solution was decanted from the inorganic material and concentrated at reduced pressure to yield a residue which was treated with 100 mL of 3 N NaOH solution and extracted twice with 100-mL portions of ethyl ether. The ether extract was washed with water, dried over magnesium sulfate, and concentrated to give 8.0 g of crude product which was chromatographed on Florisil using increasing portions of acetone in benzene to elute the components. The first component eluted was shown to be the exo isomer **6** (6.0 g, 63% yield). A second minor component was not isolated or identified. The third component eluted was shown to be the endo isomer **5** (0.5 g, 5.2% yield).

A small portion of each isomer was converted to the hydrochloride salt and recrystallized from isopropyl alcohol–isopropyl ether for elemental analysis.

(a) 6-*exo*-Chloro-3-phenethyl-3-azabicyclo[3.1.0]hexane (**6**): ^1H NMR ($CDCl_3$) δ 1.70 (2 H, m), 2.37 (2 H, d of m), 2.67 (4 H, s), 3.15 (2 H, d), 3.23 (1 H, s), 7.25 (5 H, s); IR (film) 2790 (s, tertiary alkylamine), 1000 cm^{-1} (m, cyclopropane ring deformation); UV (HCl salt) λ_{max} (methanol) 257 nm (ϵ 184); mp (HCl salt) 201.5–202.5 °C.

Anal. Calcd for $C_{13}H_{17}NCl_2$: C, 60.48; H, 6.64; N, 5.43. Found: C, 60.40; H, 6.64; N, 5.42.

(b) 6-*endo*-Chloro-3-phenethyl-3-azabicyclo[3.1.0]hexane (**5**): ^1H NMR ($CDCl_3$) δ 1.80 (2 H, m), 2.71 (4 H, s), 2.80 (2 H, d), 3.15 (2 H, d of m), 3.40 (1 H, t), 7.25 (5 H, s); IR (film) 2790 (s, tertiary alkylamine), 1005 cm^{-1} (w, cyclopropane ring deformation); UV (HCl salt) λ_{max} (methanol) 257 nm (ϵ 180); mp (HCl salt) 190–191 °C.

Anal. Calcd for $C_{13}H_{17}NCl_2$: C, 60.48; H, 6.64; N, 5.43. Found: C, 60.46; H, 6.59; N, 5.45.

6-*trans*-Styryl-3-azabicyclo[3.1.0]hexane (9). A butyllithium solution (18.9 mL of 2.4 M hexane solution, 0.045 mol) was added dropwise to a stirred solution of 6-*exo*-chloro-3-phenethyl-3-azabicyclo[3.1.0]hexane (**6**) (5.0 g, 0.023 mol) in 100 mL of ethyl ether under a nitrogen atmosphere. During addition the reaction became exothermic and mild reflux occurred. The reaction mixture gradually became dark red-brown. Stirring was continued for 16 h and water (50 mL) was then carefully added dropwise to hydrolyze the reaction mixture. The ether solution was separated, dried over magnesium sulfate, and concentrated at reduced pressure to give 4.6 g of oil which was shown by TLC to contain several components. This oil was subjected to molecular distillation at 150 °C (0.01 Torr). On standing, partial crystallization occurred in the distillate. Trituration of the distillate in petroleum ether (30–60 °C) gave an amorphous solid which was collected by filtration. Trituration of this solid with isopropyl ether gave a white solid which was collected by filtration. TLC of this solid shows a single spot (R_f 0.5, 20% methanol in chloroform). The filtrates were combined and evaporated to dryness, and the oily residue was triturated with ethyl ether to give an additional quantity of the white solid. The combined solids were molecularly distilled twice at 150 °C (0.01 Torr) to give about 300 mg (7%) of a white crystalline solid: ^{1}H NMR ($CDCl_3$) δ 1.50 (3 H, m), 1.72 (1 H, s, replaceable by D_2O), 3.03 (4 H, s), 5.87 (1 H, d of d), 6.45 (1 H, d), 7.32 (5 H, s); IR (KBr pellet) 3400, 3230 (m, NH str), 1030 cm^{-1} (w, cyclopropane ring deformation); UV λ_{max} (methanol) 259 nm (ϵ 22 900); mp 82–84 °C.

Anal. Calcd for $C_{13}H_{15}N$: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.09; H, 8.12; N, 7.54.

Reaction of 6,6-Dichloro-3-phenethyl-3-azabicyclo[3.1.0]hexane (4) with *n*-Butyllithium. In a nitrogen atmosphere, an *n*-butyllithium solution (2.4 mL of 2.4 M hexane solution, 0.006 mmol) was added dropwise to a stirred solution of 6,6-dichloro-3-phenethyl-3-azabicyclo[3.1.0]hexane (**4**) (0.5 g, 0.002 mol) in an anhydrous ether (15 mL) at 0 °C. After the addition was completed, the mixture was stirred for 15 h at room temperature. Water was added and the ether layer was separated, washed once with water, dried, and concentrated at reduced pressure to give a brown oil. Mass-spectral analysis showed the presence of a product having a mass corresponding to replacement of the chlorine atoms by butyl groups.

Reaction of 6-*endo*-Chloro-3-phenethyl-3-azabicyclo[3.1.0]hexane (5) with *n*-Butyllithium. A solution of 6-*endo*-chloro-3-phenethyl-3-azabicyclo[3.1.0]hexane hydrochloride (**5**) (0.12 g, 0.00047 mol) in 3 mL of water was made basic to litmus by addition of 6 N NaOH solution. This mixture was extracted four times with 5-mL portions of ether. The combined extracts were dried over anhydrous sodium sulfate. Under nitrogen, an *n*-butyllithium solution (0.6 mL, 0.014 mol, 1.6 M hexane solution) was added dropwise with stirring to the dried ether solution of **5** and the mixture was stirred at ambient temperature for 16 h. Water was added and the ether layer was separated, dried ($MgSO_4$), and concentrated at reduced pressure to yield a small quantity of oil which was shown by ^{1}H NMR analysis to be unreacted **5**. Mass-spectral analysis showed, in addition to the parent and fragment ions of the starting material **5**, a peak at *m/e* 152 which could be a fragment arising from a product in which the chlorine was replaced by a butyl group.

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Registry No.—**4**, 62154-20-5; **4** HCl, 62182-98-3; **5**, 62210-63-3; **5** HCl, 62154-16-9; **6**, 62210-64-4; **6** HCl, 62249-34-7; **9**, 62154-17-0; **10**, 62154-18-1; 1,1-dichloro-*cis*-2,3-bis(chloromethyl)cyclopropane, 56505-31-8; 1,4-dichloro-*cis*-2-butene, 1476-11-5; phenethylamine, 64-04-0; *endo*-6-butyl-3-phenethyl-3-azabicyclo[3.1.0]hexane, 62154-19-2.

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A ^{13}C Nuclear Magnetic Resonance Study of *N*-Acetyldaunorubicinol[1]

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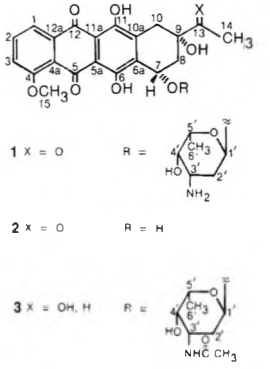
Daunorubicin is an anthracycline antibiotic and is represented by structure **1**. It consists of the tetracyclic quinoid aglycone daunorubicinone **2** in a glycosidic linkage to the



amino sugar daunosamine.[3] Daunorubicin has both well-demonstrated cytotoxic activity[4] and interesting antitumor properties.[5]

In our continuing effort to improve its therapeutic properties and to decrease the undesirable cardiac toxicity of daunorubicin, modification by biotransformation of this antibiotic has been undertaken at the Frederick Cancer Research Center.

To understand the changes that occurred during biotransformation, it was thought that ^{13}C NMR spectroscopy might prove useful in structure elucidation. The ^{13}C NMR spectra of daunorubicin and daunorubicinone were studied, and assignments to all carbons were made (Table I). Using the above-mentioned data it was shown that one of our biotransformed molecules is *N*-acetyldaunorubicinol, represented by structure **3**.

Off-acquisition gated noise decoupling and single-frequency experiments on **2** and chemical shifts reported in the literature[6–9] allowed us to distinguish C-14 (24.5 ppm, q, $^1J_{CH}$ = 130 Hz), C-15 (56.6 ppm, q, $^1J_{CH}$ = 155 Hz), C-8 (35.3 ppm, t, $^1J_{CH}$ = 120 Hz), C-10 (33.1 ppm, t, $^1J_{CH}$ = 120 Hz), C-1 (119.6 ppm, d, $^1J_{CH}$ = 160 Hz), C-2 (135.3 ppm, d, $^1J_{CH}$ = 160 Hz), C-3 (118.3 ppm, d, $^1J_{CH}$ = 160 Hz), and C-7 (61.9 ppm, d, $^1J_{CH}$ = 160 Hz). Single-frequency decoupling experiments on all of the protons of **2** also confirmed the above assignments. The rest of the carbons show only small multiple bond C–H coupling or are singlets. The assignment of carbons 5, 12, 5a, 11a, 6a, 10a, 12a, and 4a was based on published results.[6,10]

Single-frequency decoupling experiments on protons of C-7 and of the amino sugar, together with chemical shifts on model

Table I. ^{13}C Chemical Shift Assignments[a]

C	1	2	3	C	1	2	3
1	119.5	119.6	119.5	12a	134.0	134.0	134.0
2	135.3	135.3	135.3	4a	120.2	122.2	120.5
3	118.2	118.3	118.1	5a	110.5	110.3	111.0
4	160.8	160.9	160.7	11a	110.7	110.4	111.5
5	186.0	186.0	186.0	10a	133.9	133.5	135.5
6	155.0	155.0	155.0	6a	133.6	133.3	135.0
7	69.0	61.9	69.0	15	56.6	56.6	56.5
8	34.8	34.3	34.7	1′	100.7		100.2
9	78.8	78.5	73.5	2′	32.3		29.9
10	33.4	33.1	32.4	3′	46.2		45.4
11	156.4	156.0	156.0	4′	70.5		70.2
12	186.0	186.0	186.0	5′	66.0		66.0
13	211.6	211.6	71.6	6′	17.0		16.9
14	24.7	24.5	16.6	$NHC(=O)CH_3$			169.0
				$NHC(=O)\mathbf{C}H_3$			24.0

[a] In parts per million (δ), obtained from (0.03 M) $CDCl_3$ solutions containing Me_4Si as internal standard.

compounds,[9] permit us to assign all the carbons in the amino sugar in **1**.

Using the assignments of **1** and **2**, we were able to attribute all the carbons in our biotransformed molecule, *N*-acetyldaunorubicinol (**3**). The assignments are summarized in Table I. As expected, the ^{13}C NMR of **3** is similar to that of **1**, except at C-13 where the carbonyl (211.6 ppm) was reduced to the alcohol (71.6 ppm); carbons 9 and 14, which are adjacent to C-13, were slightly shifted upfield; two new peaks, which belong to the *N*-acetyl, appeared at 169.0 [$HNC(=O)CH_3$] and 24.0 ppm [$HNC(=O)\mathbf{C}H_3$]. Thus ^{13}C NMR confirmed that the structure of one of the biotransformed molecules is **3**. Structure assignments have been made previously for this biotransformed molecule.[11]

The 4–10 ppm differences in chemical shift for carbons 5, 6, 11, 12, and 13 between daunorubicinone and that of the recently reported data[10] on daunorubicin tetraacetate could be attributed to the absence of hydrogen bonding in the latter. In addition, there is disagreement in the assignment of carbons 8 and 10, but single-frequency experiments clearly place C-10 upfield from C-8. However, the above assignments are in good agreement with recently published results[12] with the expected minor shift differences. These differences are due to the fact that Mondelli[12] et al. used Me_2SO as solvent whereas $CDCl_3$ was used in the present study.

Registry No.—**1**, 20830-81-3; **2**, 21794-55-8; **3**, 62133-95-3.

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Communications

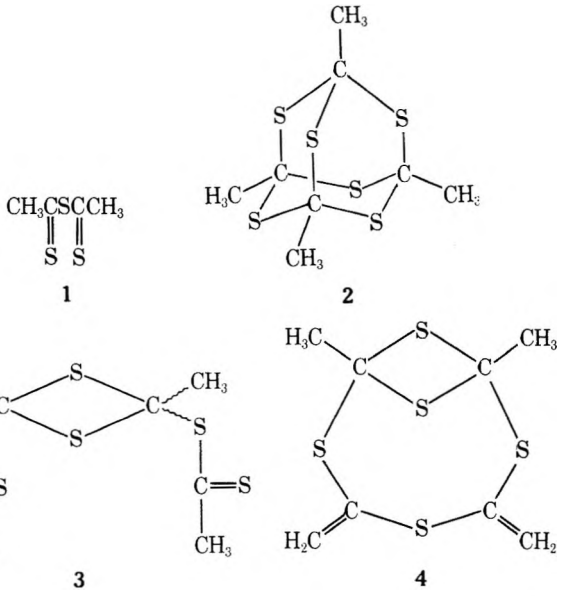
Reaction between Dithioacetic Acid and Dicyclohexylcarbodiimide—Structure of Products. Crystal and Molecular Structure of *trans*-2,4-Dimethyl-2,4-bis(thioacetylthio)-1,3-dithietane

Summary: The reaction between dithioacetic acid and dicyclohexylcarbodiimide gives the unstable bis(thioacetyl) sulfide (**1**) which dimerizes to the hexathiaadamantane (**2**) and both isomers of 2,4-dimethyl-2,4-bis(thioacethylthio)-1,3-dithietane (**3**); **4** is a minor product.

Sir: The reaction between monothioacetic acid and dicyclohexylcarbodiimide (DCC) has recently been shown to give dicyclohexylthiourea and bisacetyl sulfide—a symmetrical monothioanhydride.[1] The analogous reaction with dithioacetic acid should produce the hitherto unknown bis(thioacetyl) sulfide (**1**). In this context it is worthy of note that 1,3,5,7-tetramethyl-2,4,6,8,9,10-hexathiaadamantane (**2**)[2-4] may be considered as a dimeric form of **1**. Although this view is in accord with the mass spectral fragmentation of **2**,[4] there is no direct experimental evidence supporting **1** → **2** conversion.

We have now treated DCC with 2 mol of dithioacetic acid in acetonitrile or ether at temperatures between −20 and 20 °C. In addition to the expected dicyclohexylthiourea (~90% yield), a complicated mixture of products derived from dithioacid was obtained. By preparative TLC using a CCl_4/hexane/benzene (20:6:1) we have isolated three products, **2**, **3**, and **4**.

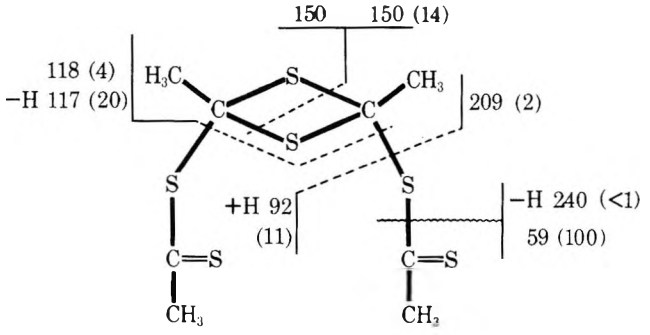
The first compound (R_f 0.06–0.13) has been identified as



1 2 3 4

hexathiaadamantane **2** by NMR[5] [^{1}H NMR 2.1 ppm (s, CH_3); ^{13}C NMR 29.2 (CH_3), 58.5 ppm (>C<)], mass spectra[4] (*m/e* 300), and comparison with an authentic sample of **2**.[2] It is formed in ~40% yield in acetonitrile at room temperature. However, in ether at −20 °C **2** is formed in a trace amounts only.

The second isolated product (R_f 0.3–0.42) with a broad melting point, 120–135 °C, when crystallized from ethanol or hexane gave yellow crystals, $C_8H_{12}S_6$, mp 145–147 °C. The spectral data agree with structure **3** which is a new dimeric form of **1**. The ^{1}H NMR spectrum shows two singlets of equal intensity at 2.27 and 2.8 ppm. The ^{13}C NMR spectrum showed four signals at 34.4 and 38.0 ($J_{^{13}C-^1H}$ = 137 ± 2 Hz) corresponding to the methyl carbons, at 60.6 belonging to the dithietane ring carbon, and at 229.5 ppm (C=S). The IR spectrum showed thiocarbonyl absorption at 1180 cm^{-1}. The mass spectrum of **3** is very similar to that of **2**.



3, M$^+$ 300 (<1)

Since dithietane **3** may exist in two geometrical forms and the ^{1}H and ^{13}C NMR spectra of the product having mp 120–135 °C showed two distinct sets of the above-discussed signals, it was obvious that a mixture of both isomers was obtained. This mixture is formed as a major product in 50–65% yield when the reaction between dithioacetic acid and DCC is carried out in ether. The spectral differences permitted an easy estimation of isomeric ratio as 1:1 and permitted assignment of the spectral data to the second isomer [^{1}H NMR 2.3 and 2.8 ppm (2 s, CH_3); ^{13}C NMR 35 and 38 (CH_3), 61 (ring carbon), 230 ppm (C=S)]. An attempt to isolate the more soluble isomer of **3** from the hexane mother liquor gave a sample of 75% diastereomeric purity.

To obtain further information concerning the geometry of the less soluble, diastereomerically pure dithietane **3**, mp 145–147 °C, we determined its structure by x-ray analysis.[6]

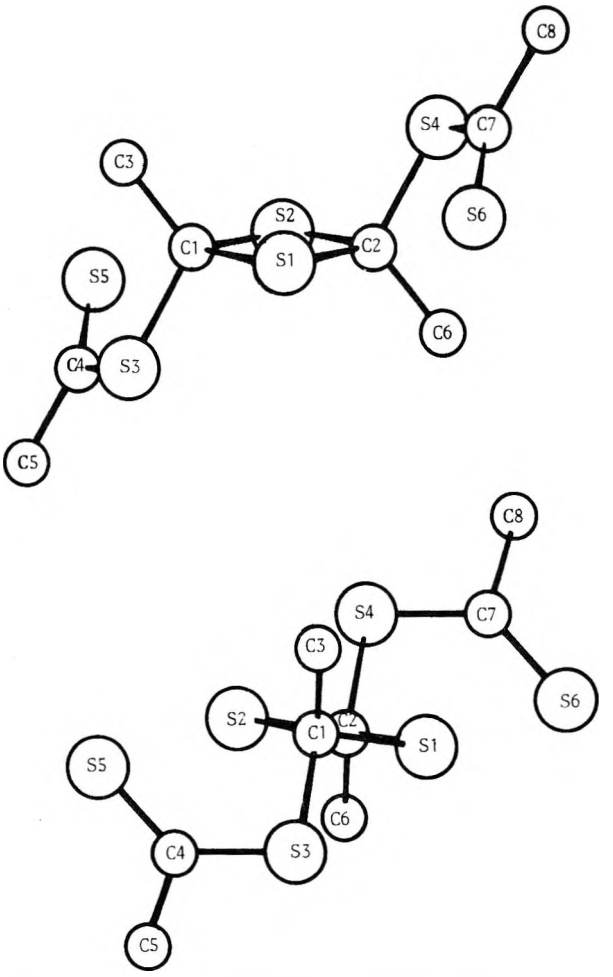


Figure 1. A view of *trans*-2,4-dimethyl-2,4-bis(thioacetylthio)-1,3-dithietane (**3**) along the S(1)–S(2) (upper) and C(1)–C(2) (bottom) axis.

Crystal Data. $C_8H_{12}S_6$, M = 300; orthorhombic, a = 11.15 (7), b = 5.945 (17), c = 19.91 (5) Å, U = 1319.6 Å^3, Z = 4, d_{measd} = 1.506 g cm^{-3}, d_{calcd} = 1.51 g cm^{-3}; space group *Pna*2; 1399 reflections with $I < 3\sigma(I)$ have refined to R = 0.0289. The geometry of the molecule is shown in Figure 1. Bond lengths and angles are listed in Table I and II.[7] Crystallographic analysis revealed the trans geometry of the isomer investigated. From the drawings and coordinates the molecule can be seen to be almost perfectly centrosymmetric. An exception is the greater length of the C(1)–S(1)[8] compared to the remaining ring C–S distances. This appears to be genuine as an idealized centrosymmetric set of coordinates returned to the values given on further refinement. A consequence of the approximate center of symmetry is the planarity of the four-membered ring. Thus, dihedral angles between the two pairs of planes—S(1), C(1), S(2) and S(1), C(2), S(2); and C(1), S(1), C(2) and C(1), S(2), C(2)—are 0.85 and 0.79°, respectively.

Table I. Bond Lengths

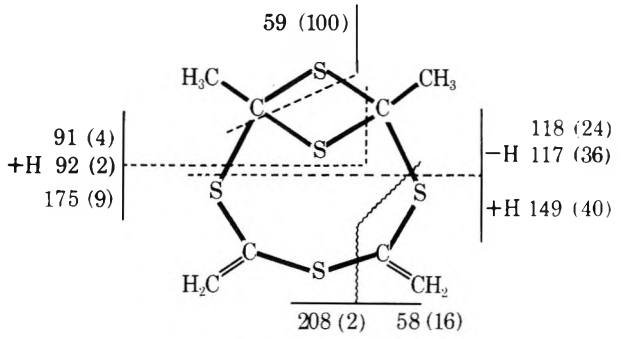
Bond	Length, Å (esd)	Bond	Length, Å (esd)
C(1)–S(1)	1.851 (4)	C(2)–S(1)	1.815 (4)
C(1)–S(2)	1.816 (4)	C(2)–S(2)	1.819 (4)
C(1)–S(3)	1.815 (4)	C(2)–S(4)	1.835 (4)
C(1)–C(3)	1.501 (6)	C(2)–C(6)	1.512 (6)
C(4)–S(3)	1.705 (5)	C(7)–S(4)	1.722 (5)
C(4)–S(5)	1.631 (5)	C(7)–S(6)	1.609 (5)
C(4)–C(5)	1.495 (8)	C(7)–C(8)	1.540 (8)

Table II. Bond Angles

Bonds	Angle, degree (esd)	Bonds	Angle, degree (esd)
C(1)–S(1)–C(2)	85.4 (2)	C(1)–S(2)–C(2)	86.3 (2)
S(1)–C(1)–S(2)	93.6 (2)	S(1)–C(2)–S(2)	94.7 (2)
S(1)–C(1)–S(3)	106.4 (2)	S(1)–C(2)–S(4)	111.8 (2)
S(1)–C(1)–C(3)	112.8 (3)	S(1)–C(2)–C(6)	116.7 (3)
S(2)–C(1)–S(3)	112.7 (2)	S(2)–C(2)–S(4)	106.8 (2)
S(2)–C(1)–C(3)	116.5 (3)	S(2)–C(2)–C(6)	115.1 (3)
S(3)–C(1)–C(3)	112.9 (3)	S(4)–C(2)–C(6)	110.6 (3)
C(1)–S(3)–C(4)	104.9 (2)	C(2)–S(4)–C(7)	105.2 (2)
S(3)–C(4)–S(5)	125.4 (3)	S(4)–C(7)–S(6)	125.6 (3)
S(3)–C(4)–C(5)	111.9 (4)	S(4)–C(7)–C(8)	109.9 (4)
S(5)–C(4)–C(5)	122.5 (4)	S(6)–C(7)–C(8)	124.5 (4)

It is interesting to note that the nonbonded S···S and C···C distances of the four-atom ring of trans-**3** are 2.672 and 2.488 Å, respectively.

As mentioned above TLC revealed the presence of a third minor product (R_f 0.19–0.29). Although we did not succeed in purifying it to an analytical purity all of the spectral data point to the structure of 1,7-dimethyl-3,5-dimethylene-2,4,6,8,9-pentathiabicyclo[5.1.1]nonane (**4**). The mass spectrum showed molecular peak at *m/e* 266 and the number of the sulfur atoms present in the molecule was easily recognized



4. M^+ 266 (6)

from the pattern of isotopic peaks due to ^{34}S. The ^1H NMR spectrum showed two singlets at 2.08 and 5.84 ppm with the intensity ratio 3:2 which have been ascribed to the methyl and methylene protons, respectively. In ^{13}C NMR four signals appeared at 29 ($J_{^{13}C-^1H}$ = 137 Hz), 55.6, 126 ($J_{^{13}C-^1H}$ = 164 Hz), and 133.6 ppm attributed to the methyl, quaternary, methylene, and thiomethylene carbon, respectively.

In summary, one may conclude that the reaction of dithioacetic acid with DCC results in the formation of trithioanhydride (**1**) which owing to its instability undergoes ready dimerization to give **2** and the mixture of *trans*-**3** and *cis*-**3**. The latter eliminates H_2S giving rise to **4**. Further experiments to stabilize the monomeric structure of aliphatic trithioanhydrides by steric hindrance are in progress.[9]

Acknowledgment. We thank Dr. D. J. H. Smith, the University of Leicester, for his interest in the present work.

Supplementary Material Available. A typical experimental procedure, Figure 2, showing the ^1H NMR spectrum of the crude reaction product, and the atomic coordinate and thermal parameter tables (5 pages). Ordering information is given on any current masthead page.

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(7) Atomic coordinates and atomic thermal parameters will appear in Tables 3 and 4 following this article in the microfilm edition of this volume.
(8) This fact coincides well with our observation that *trans*-**3** is not configurationally stable and undergoes slow transformation into a mixture of *cis*- and *trans*-**3** on storage at room temperature or on heating. The mechanism of epimerization of dithietane **3** is currently under investigation.
(9) After completion of this work Kato et al.[10] reported the reaction of DCC with some para-substituted dithiobenzoic acids which gave relatively stable bis(thioaroyl) sulfides.
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Oxidation with Light and Electrochemistry. An Apparently Selective Radical Forming Reaction

Summary: Catalytic amounts of various quinones have been irradiated in the presence of a substrate and a graphite anode charged at the potential of the quinone–hydroquinone couple. The photochemical reaction yields hydroquinone (or quinhydrone) and an oxidized substrate. The hydroquinone is converted back to quinone electrochemically. With toluene and similar materials as substrates, the products are bibenzyls in clean high-yield reactions. With 2-propanol, the product is acetone.

Sir: Although photochemical oxidations have been known for a long time,[1] their preparative use has been limited since photochemical reactions in themselves do not involve any change in oxidation state. Thus, some sort of disproportionation (i.e., the benzophenone reactions[1]) must be involved, or an external oxidizing agent such as air, iodine, or more recently Cu(II)[2] must be used. Frequently these secondary oxidizing agents are not very specific. We have devised a method in which the oxidizing "agent" is a suitably charged graphite anode.[3]

The specific reactions involved are the photochemical reactions of quinones with alkylbenzenes to yield dehydrodimers (e.g., bibenzyl from toluene)[4] and the reaction of quinones with alcohols to yield carbonyl products.[5] Poor yields are reported in both cases. Since the quinone is regenerated electrochemically, it serves as a catalyst only and can be used in small amounts. There are two advantages in the system. First, the electrochemical potentials needed to regenerate quinone are quite low[6] and are therefore fairly specific. Second, the hydroquinone which is reported[7] to retard the photochemical reaction is rapidly removed.

In our system, reactions 1–4 appear to take place.[7] A similar system has been described for analytical work by Zolotova,

Table I. Preparative Photoelectrochemical Oxidations [a]

Substrate	Product[b]	Oxidn time, h	Initial current, mA	Product isold, mmol	Current yield,[c] %
Toluene	Bibenzyl	20	35	3.5	90
p-Xylene	1,2-Di-*p*-xylylethane	24	76	10	60
Ethylbenzene	2,3-Diphenylbutane (meso and *RR–SS*)	20	17	2.9	~100
2-Propanol	Acetone	6	80	6.3	75[d]

[a] The yields based upon catalyst were from 300 to 1000%. [b] The hydrocarbon products were isolated in a pure form, and their properties agreed with literature values. [c] Current yield is calculated as product formed per coulomb of electricity passed (two electrons per mole of product). The starting material was present in excess. [d] Acetone was isolated as a 2,4-dinitrophenylhydrazone.

Shelepin, and Vasil'ev[8] with the same equations for 1, 2, and 3. No products were reported. The preparative data are summarized in Table I.

$$Q \xrightarrow{h\gamma} Q^* \quad (1)$$

$$Q^* + 2RH \rightarrow 2R\cdot + QH_2 \quad (2)$$

$$QH_2 - 2e - 2H^+ \rightarrow Q \quad (3)$$

$$2R\cdot \rightarrow RR \quad (4)$$

The cell used was essentially a 450-W Hanovia source enclosed in a Pyrex cooling sleeve placed in a tall glass cell containing a graphite felt[9] anode (75 cm^2) and a similar graphite cathode (22 cm^2 placed in a small sack made of Du Pont Nafion membrane).[10] A standard calomel reference electrode was placed close to the anode, and the potential was controlled at the anodic peak of the quinone (as deduced from a cyclic voltammogram; generally about +0.6 V with a PAR Model 170 electrochemical system).[11] Several quinones were investigated: anthraquinone, anthraquinone-2-sulfonic acid, and anthraquinone-2,6-disulfonic acid. The data in Table I were obtained using anthraquinone-2-sulfonic acid. The reaction mixture consisted of 800 mL of CH_3CN–H_2O (4:1), containing $LiClO_4$ (0.1 M) and 0.2–2 g of quinone. The cell was deoxygenated with N_2, and the reaction was carried out under N_2. About 20 mL of substrate was added. Yields are based upon the current observed to flow through the cell.

All of the reactions, 1–4, are known to occur under various conditions. However, the combined system as described in this paper offers at least one unique feature. The benzyl radicals formed from arylalkanes are produced in an environment containing *no* oxidizing agent strong enough to oxidize them to carbonium ions.[12] Thus, they dimerize, and the reaction appears to be without by-products. When the reaction is carried out in the presence of air or oxygen, the products are, as expected, benzoic acids. In the oxidation of 2-propanol, the initially formed ketyl radical $CH_3\dot{C}OHCH_3$ is apparently more easily oxidized than the benzyl radical and is converted to acetone, either electrochemically or by another molecule of quinone.

The reaction is being further explored.

Acknowledgments. This work was sponsored in part by Grant GP-7601 from the National Science Foundation. The authors are further indebted to the Du Pont Co. for a gift of Nafion 425 membrane and to LaTrobe University, Melbourne, Australia, where initial experiments were carried out.

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(10) Nafion 425 membrane is a polyfluorinated ion-exchange membrane produced by Plastics department of the E. I. du Pont de Nemours and Co., Wilmington, Del.
(11) Princeton Applied Research, Princeton, N.J.
(12) The potential normally required to produce a benzyl radical by electrochemical means alone is +2.3 V. The potential estimated for the oxidation of the benzyl radical is "below +1.2 V". See V. D. Parker and B. E. Burger, *Tetrahedron Lett.*, 2411 (1968). Our oxidations were generally carried out at about +0.6 V.

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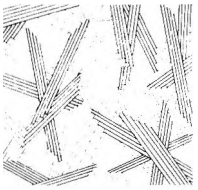

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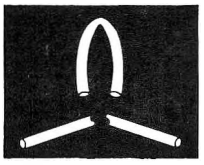

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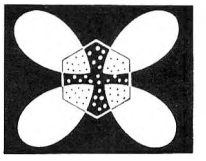

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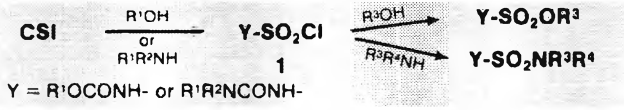
Chlorosulfonyl Isocyanate

Chlorosulfonyl isocyanate (CSI) is probably the most chemically reactive isocyanate known, yet it itself is stable at temperatures up to 300°C. It was first reported by Graf[1] 25

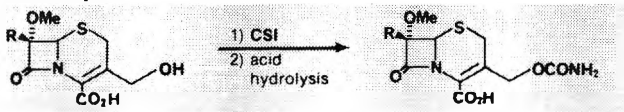
$ClSO_2NCO$ **(CSI)**

years ago and has been the subject of several reviews.[2] This exciting reagent has enabled a variety of useful and often novel transformations, some of which are described below.

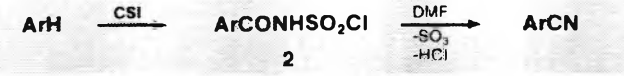
CSI undergoes the expected nucleophilic additions by alcohols and amines to produce the respective *N*-chlorosulfonyl carbamates and ureas (**1**), which may be subsequently functionalized.



The reactivity of **CSI** with alcohols is so great that alcohols can be derivatized in the presence of other functional groups. Work by Christensen[3] on synthetic cephalosporins provides an example.

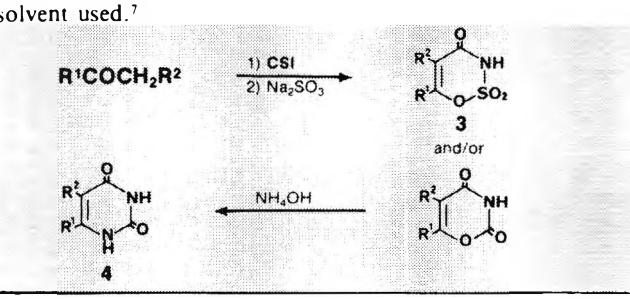


Aromatic compounds that readily undergo electrophilic substitution (*e.g.*, anthracene and 1,3-dimethoxybenzene) react with **CSI** to produce the *N*-chlorosulfonyl carboxamides **2**, which can be subsequently converted to the corresponding *nitriles* in 70-90% overall yields by treatment with DMF.[4]

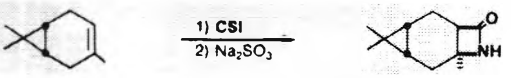


A related sequence converts carboxylic acids[4] and enolizable ketones[5] to nitriles in 60-90% overall yields.

A variation of the latter method provides either the potential "third generation" sweeteners[6] **3** or substituted uracils **4**, depending on the nature of the ketone substituents and the solvent used.[7]

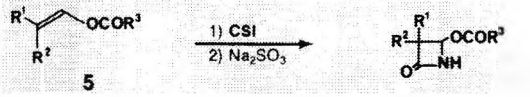


The ability of **CSI** to undergo cycloaddition to multiple bonds adds another dimension to its usefulness. The most extensively studied case is the net [2 + 2] cycloaddition of **CSI** to olefins, leading to β-lactams in moderate to high yields.[8] These additions are highly regio- and stereospecific, as the following example[9] illustrates:



The use of sodium sulfite is a mild, convenient and apparently general method[10] for reducing the initially formed *N*-chlorosulfonyl β-lactams to the corresponding N-unsubstituted compounds.

Heterosubstituted β-lactams, comprising the fundamental nucleus of the penicillin and cephalosporin antibiotics, may be prepared by the reaction of **CSI** with vinyl esters (**5**).[11] The acyloxy substituent of the resulting lactam is readily displaced by a variety of nucleophiles (*e.g.*, RCO_2^-, RSO_2^-, N_3^-, RO^-, and RS^-) in good to excellent yields, leaving the 4-membered ring intact.



In view of the *cis* addition of **CSI** to olefins and the facile hydrolytic cleavage of β-lactams, this versatile reagent also provides a convenient route to *erythro*- and *threo*-β-aminoacids.[12]

Use of the uniparticulate electrophilic character of **CSI** as a *mechanistic probe* has been amply demonstrated by Paquette in his studies of molecules such as bullvalene[13] and barrelene.[14]

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