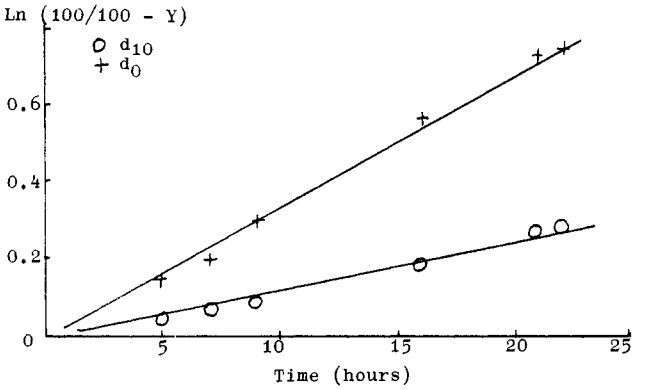

Figure 5. Reaction of 1,4-dihydronaphthalene with anthracene.

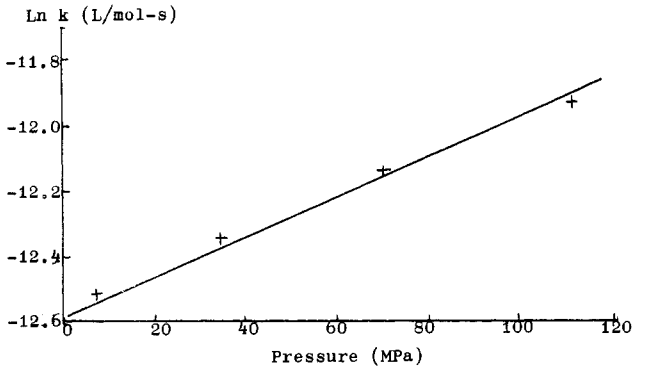

Figure 6. Pressure effect on disproportionation of 1,2-dihydronaphthalene.

3.35×10^{-6} s^{-1} for the d_{10} compound. Comparison of the rate constants and correction for isotopic purity gave KIE values presented in Table II.

Reaction of 1,4-Dihydronaphthalene with Anthracene. This reaction was also carried out under pseudo-first-order conditions. The molar ratio of 1,4-dihydronaphthalene to anthracene was 7:1. The reaction temperature was 220 °C. The conversion of anthracene to 9,10-dihydroanthracene was followed by GC, and the pseudo first-order rate constants were evaluated as described above (Figure 5). After correction for isotopic purity, we found KIE = 2.9 for perdeuterio-1,4-dihydronaphthalene.

Reaction of Anthracene with Cyclohexanol. The reaction rates were measured for the protium compound, $C_6H_{11}OD$, and cyclohexanol-d_{12}. The molar ratio of cyclohexanol to anthracene was 5:1, and the reaction temperature was 350 °C. The conversion of anthracene to 9,10-dihydroanthracene was followed by GC. The average second-order rate constants were 11×10^{-7} L/(mol s), 8.5×10^{-7} L/(mol s), and 3.2×10^{-7} L/(mol s) for $C_6H_{11}OH$, $C_6H_{11}OD$, and $C_6D_{11}OD$, respectively. Products of deuterium exchange (deuterated anthracene, H-containing perdeuteriocyclohexanol) were detected by GC/MS (a Hewlett-Packard 5790 MS detector with 5890A capillary GC) studies. GC/MS (a Hewlett-Packard 5790 MS detector with 5890A capillary GC) studies.

Table VIII. Rate Data for Activation Volume Measurements

Disporportionation of 1,2-Dihydronaphthalene				
P, MPa	6.9	34.5	69.0	110.3
10^6K, L/(mol s)	3.58	4.26	5.35	6.47
Dimethyl Maleate and 1,2-Dihydronaphthalene				
P, MPa	34.5	69.0	103.4	
10^6K, s^{-1}	8.1	10.1	13.2	
Anthracene and 1,4-Dihydronaphthalene				
P, MPa	34.5	69.0	103.4	
10^6k, s^{-1}	10.3	12.9	15.4	
Anthracene and 1,4-Cyclohexadiene				
P, MPa	34.5	69.0	103.4	
10^6K, s^{-1}	8.6	11.7	14.9	
Thymoquinone and 1,4-Cyclohexadiene				
P, MPa	6.9	34.5	69.7	
10^5k, s^{-1}	2.5	3.8	5.6	

Activation Volume Measurements. Glass syringes with the metal tip removed and the bottom converted to a test tube end were used as the reaction cells. After a reaction mixture was placed into the barrel, the plunger was inserted under reduced pressure. The cell was inserted into a high-pressure reactor, which was then filled with pressurizing fluid and placed in the thermostat (the high-pressure equipment and heating device have been previously described[14]). The pressure in the system was controlled by pumping or releasing the fluid as required. After the selected reaction time, the reactor was cooled and reaction mixture removed from the cell and analyzed by GC. The activaton volumes, ΔV^*, were obtained from plots of ln k vs. P according to the equation: $\Delta V^* = -RT(\partial \ln k/\partial P)_T$. Figure 6 presents such a plot for the disproportionation of 1,2-dihydronaphthalene. The reaction temperatures and final vlaues of ΔV^* are presented in Table III. The rate data are presented in Table VIII. Except for disproportionation of 1,2-dihydronaphthalene, all reactions were carried out under pseudo-first-order conditions. The fraction of hydrogenated product was followed by GC (with exception of the reaction of cyclohexa-1,4-diene with thymoquinone, where formation of benzene was measured).

Error. On the basis of repeatability we estimate that the relative error involved in reported values of KIE and ΔV^* is ±10%. There was no noteworthy variation in repeatability from one reaction to another.

Registry No. Tetralin, 119-64-2; 1,2-dihydronaphthalene, 447-53-0; bibenzyl, 103-29-7; thymoquinone, 490-91-5; anthraquinone, 84-65-1; indene, 95-13-6; nitrosobenzene, 586-96-9; 2-nitroso-1-naphthol, 132-53-6; dimethyl maleate, 624-48-6; anthracene, 120-12-7; 1,4-cyclohexadiene, 628-41-1; deuterium, 7782-39-0; cyclohexanol, 108-93-0.

Synthesis and Interconversion of Oxepanes and Bicyclo[3.2.1]octanes

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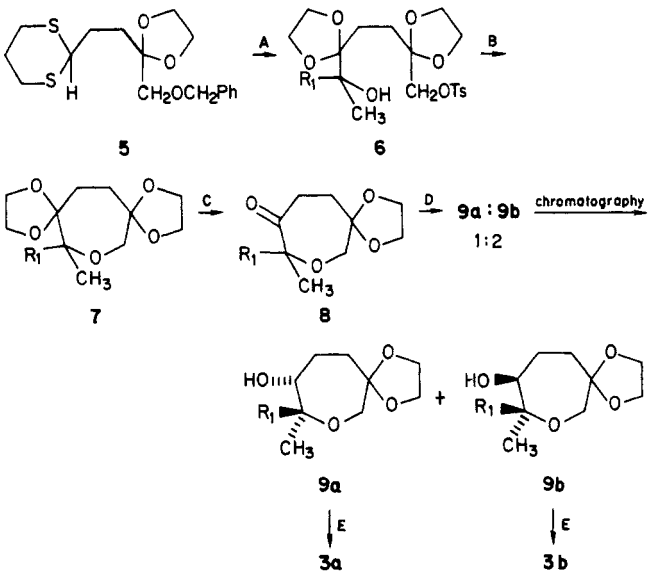
Received October 30, 1984

Methods for the synthesis of 2,2-dialkyl-substituted oxepanes (**3a–d**) and the corresponding 4,4-dialkyldioxabicyclo[3.2.1]octanes (**4a–d**) are described. The interconversion of the oxepane and dioxabicyclo[3.2.1]octane systems, particularly through the methoxyimino derivatives, is discussed. The use of each of the above oxepanes and bicyclic analogues as substrates for Wittig reactions to generate zoapatanol analogues is also described.

Recent papers from these laboratories have described the isolation, structure proof, and total synthesis of the novel oxepane diterpenoid zoapatanol (**1**) and the total synthesis of its dioxabicyclo[3.2.1]octane analogue **2**.[1,2]

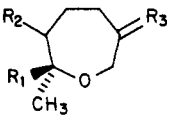
0022-3263/85/1950-2216$01.50/0

Scheme I[a]

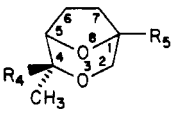


[a] (A) five steps, (a) BuLi, $RCOCH_3$, (b) Na/NH_3, Et_2O, (c) TsCl, Pyr, (d) $HgCl_2$, $CaCO_3$, (e) $HOCH_2CH_2OH$, TsOH; (B) NaH, Me_2SO; (C) 70% $HClO_4$, Et_2O; (D) $NaBH_4$; (E) (a) CH_3COCl, (b) HCl, acetone.

The unique structures of **1** and **2** have attracted the attention of synthetic chemists, and total synthesis of each have recently been reported from other laboratories.[3,4]



1, R_1=$(CH_2)_3CH(CH_3)COCH_2CH{=}C(CH_3)_2$; R_2=α-OH; R_3=(*E*)—$CHCH_2OH$
3a, R_1=*n*-C_3H_7; R_2=α-OAc; R_3=O
b, R_1=*n*-C_3H_7; R_2=β-OAc; R_3=O
c, R_1=*n*-C_5H_{11}; R_2=α-OAc; R_3=O
d, R_1=*n*-C_5H_{11}; R_2=β-OAc; R_3=O
14, R_1=*n*-C_3H_7; R_2=α-OAc; R_3=$CHCO_2Et$

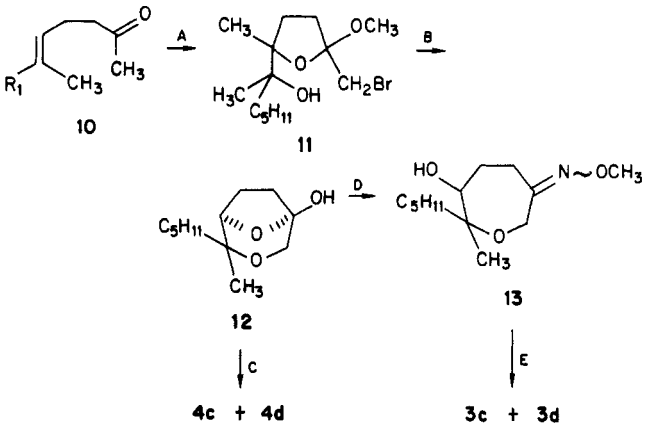


2, R_4=$(CH_2)_3CH(CH_3)CH(OH)CH_2CH{=}C(CH_3)_2$; R_5=CH_2CO_2H; 1,5-α-bridge
4a, R_4=*n*-C_3H_7; R_5=OH; 1,5-α-bridge
b, R_4=*n*-C_3H_7; R_5=OH; 1,5-β-bridge
c, R_4=*n*-C_5H_{11}; R_5=OH; 1,5-α-bridge
d, R_4=*n*-C_5H_{11}; R_5=OH; 1,5-β-bridge
15, R_4=*n*-C_5H_{11}; R_5=CH_2CO_2H; 1,5-α-bridge

In this paper, we describe methods for the synthesis of dialkyloxepanes **3** via diketal tosylate **6** and dioxabicyclooctanes **4** from **10** and the subsequent interconversion of **3** and **4**. Wittig or modified Wittig reactions can then be carried out on either the oxepanes **3** or the bicyclic series **4** to give acetic acid derivatives.

Since both epimeric ketones **3a** and **3b** (R_1 = *n*-propyl) were required for biological evaluation, our initial oxepane

Scheme II[a]



[a] (A) five steps, (a) LDA, Me_3SiCl, (b) NBS, (c) MCPBA, (d) HCl, acetone, (e) $HC(OMe)_3$, MeOH, H_2SO_4; (B) (a) KOH, Me_2SO, (b) HCl, acetone; (C) chromatography; (D) KOAc, MeOH, $NH_2OMe{\cdot}HCl$; (E) (a) Ac_2O, Pyr, (b) HCl, acetone.

synthesis utilized the diketal **7** as a common intermediate. The synthesis of **7** (Scheme I) was carried out via base closure of monotosylate **6**, which in turn was synthesized in five steps from dithiane **5**.[5,6] The dithiane has proved to be a versatile intermediate since addition reactions with appropriately functionalized methyl ketones[7] lead to oxepanes with a side chain at C-2 which can be elaborated to zoapatanol. The key step in the sequence was the selective hydrolysis of diketal **7** with 70% $HClO_4/Et_2O$ at 35 °C to give the 3-ketooxepane **8** and less than 5% (TLC and NMR) of the corresponding 6-ketooxepane. On the other hand, carrying out the $HClO_4$ hydrolysis at 0 °C rather than at 35 °C or employing 10% HCl/acetone at room temperature gives the 6-ketooxepane as the major product and compound **8** as a minor product. The bis(ketal) **7** is recovered unchanged upon treatment with $HClO_4/Et_2O$ at −78 °C. The epimeric alcohols **9a** and **9b** (1:2 ratio) which resulted from $NaBH_4$ reduction of **8** were separated by column chromatography. Acylation followed by acid treatment gave the desired 6-keto acetates **3a** and **3b**. It was also possible to carry the mixture of alcohols from the reduction through the same sequence and separate the 6-keto acetates via chromatography. Structural assignments for the epimeric oxepanes were determined by comparison with well-established zoapatanol analogues.

The ketooxepanes **3** are also accessible via the corresponding dioxabicyclo[3.2.1]octanes **4** by conversion to the 6-(methoxyimino)oxepanes followed by hydrolysis to the desired ketone. This sequence is depicted in Scheme II for the C-2 pentyl analogue. The unsaturated methyl ketone **10** (3:2 *E*:*Z*) was converted by a five-step sequence to bromo ketal **11**.[8] Ring closure and hydrolysis gave the dioxabicyclo[3.2.1]octanes **12**, which after chromatography gave hemiketals **4c** and **4d** [3:2 ratio, GC/MS (EI)].

Although we have amply demonstrated the feasibility of ring closure of 3,6-disubstituted oxepanes to the dioxabicyclo[3.2.1]octane system,[9] it was not immediately ob-

(1) Hajos, Z. G.; Wachter, M. P.; Werblood, H. M.; Adams, R. E. *J. Org. Chem.* **1984**, *49*, 2600.
(2) Kanojia, R. M.; Wachter, M. P.; Levine, S. D.; Adams, R. E.; Chen, R. H. K.; Chin, E.; Cotter, M. L.; Hirsch, A. F.; Huetteman, R.; Kane, V. V.; Ostrowski, P.; Shaw, C. J.; Mateos, J. L.; Noriega, L.; Guzman, A.; Mijarez, A.; Tovar, L.; Shefter, E. *J. Org. Chem.* **1982**, *47*, 1310 and references cited therein.
(3) Nicolaou, K. C.; Claremon, D. A.; Barnett, W. E. *J. Am. Chem. Soc.* **1980**, *102*, 6611.
(4) Walba, D. M.; Stoudt, G. S. *J. Org. Chem.* **1983**, *48*, 5405.
(5) Wachter, M. P. U.S. Patent 4 256 644, Mar 17, 1981.
(6) Nagasawa, N.; Kumanshiro, I.; Takenishi, T. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 1732.
(7) Wachter, M. P.; Adams, R. E. *Synth. Commun.* **1980**, *10*, 111.
(8) The pure *E* isomer of **10** containing a functionalized alkyl side chain has been elaborated to zoapatanol: Hajos, Z. G.; Wachter, M. P. U.S. Patent 4 237 055, Dec 2, 1980.
(9) Levine, S. D.; Adams, R. E.; Chen, R.; Cotter, M. L.; Hirsch, A. F.; Kane, V. V.; Kanojia, R. M.; Shaw, C.; Wachter, M. P.; Chin, E.; Huettemann, R.; Ostrowski, P.; Mateos, J. L.; Noriega, L.; Guzman, A.; Mijarez, A.; Tovar, L. *J. Am. Chem. Soc.* **1979**, *101*, 3404.

vious that the reverse reaction could be as readily achieved due to the potential involvement of Bredt's rule.

The ring-opening process is the bicyclic keto hemiacetal equivalent of carbohydrate monocyclic hemiacetal opening. We initially investigated ring opening through the intermediacy of dithioacetals[10] but abandoned this approach when only inseparable mixtures were obtained. However, ring opening of **12** was achieved through the use of methoxyamine hydrochloride, provided that it was buffered in advance with potassium acetate; otherwise the corresponding bicyclic methoxy amine is the major product. Thus, methoxyimino compound **13**, as a diastereomeric mixture, was obtained from **12** and converted to the acetoxy ketones **3c** and **3d** via simple acylation and acidic hydrolysis.

The interconversion of the oxepane and dioxabicyclooctane systems is further illustrated when the ketal hydrolysis of either of the acetates derived from **9a** or **9b** was carried out with aqueous HCl at room temperature for an extended period rather than with concentrated HCl in anhydrous acetone at 45 °C for 3 h as was the case for the synthesis of **3a** and **3b**. Although **3a** and **3b** were the major reaction products, the corresponding dioxabicyclooctanes **4a** and **4b** were also present in the reaction mixture (~20%) and were isolable via chromatography.

Both the oxepanes and dioxabicyclooctanes can serve as substrates for subsequent Wittig reactions to introduce the two-carbon fragment that is present in compound **1** at C-6 and in compound **2** at C-1. For example, treatment of **3a** with ethyl (diethoxyphosphinyl)acetate/NaH/benzene[11] gave the α,β-unsaturated ester **14** in 78% yield. Likewise, treatment of the epimeric C-2 pentyl dioxabicyclooctane **4d** with (carbethoxymethylene)triphenylphosphorane in refluxing xylene followed by base hydrolysis gave acid **15** in 50% overall yield.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. The IR spectra were recorded on a Beckman IR-8 spectrophotometer. ^{1}H NMR spectra were measured in the indicated solvent with tetramethylsilane as the internal standard on a Varian T-60A spectrometer. The values are expressed in parts per million (δ). EI and CI mass spectra were obtained on a Finnigan 1015D quadrupole mass spectrometer coupled to a Finnigan 9500 gas chromatograph.

2,2:5,5-Bis(ethylenedioxy)-6-hydroxy-6-methyl-1-(tosyloxy)nonane (6). 1-(Benzyloxy)-2,2-(ethylenedioxy)-4-(1,3-dithian-2-yl)butane[8] (**5**, 98.75 g) was treated in distilled THF (2.5 L) with *n*-BuLi (125 mL, 2.5 M in hexane) at −70 °C and allowed to stir below −25 °C for 2 h. The solution was cooled to −70 °C, methyl propyl ketone (28.75 g) was added, and the resulting solution was stirred below 0 °C for 16 h, concentrated to 250 mL in vacuo, and partitioned between Et_2O (500 mL) and brine (500 mL). The aqueous phase was extracted with Et_2O (900 mL), and the combined Et_2O extracts were washed with brine (900 mL), filtered through phase-separating paper, and dried (Na_2SO_4). The solvent was removed in vacuo to give a dark yellow oil (109.6 g), which was purified via silica gel chromatography using $CHCl_3$/hexane as the eluent to give 1-(benzyloxy)-2,2-(ethylenedioxy)-6-hydroxy-6-methyl-5,5-(1,3-propylenedithio)nonane (44 g). A 250-mg portion was further purified on Quantagram LPQ1F plates (EtOAc) to give an analytical sample (225 mg). NMR ($CDCl_3$) 7.21 (s, 5 H, aromatic H), 4.53 (s, 2 H, $ArCH_2O$), 3.98 (s, 4 H, OCH_2CH_2O), 3.31 (s, 2 H, 1-CH_2O), 2.8 (m, 4 H, $SCH_2 \times 2$), 1.32 (s, 3 H, 6-CH_3), 0.93 (t, 3 H, 9-CH_3).

Anal. Calcd for $C_{22}H_{34}O_4S_2$: C, 61.97; H, 7.98. Found: C, 62.15; H, 7.99.

1-(Benzyloxy)-2,2-(ethylenedioxy)-6-hydroxy-6-methyl-5,5-(1,3-propylenedithio)nonane (34.7 g) was added in Et_2O (500 mL) to distilled liquid NH_3 (700 mL). Sodium (5.65 g) was added in portions over a 15-min period and the reaction mixture stirred vigorously for 3 h. NH_4Cl (15.6 g) was added and the NH_3 allowed to evaporate overnight. Et_2O and brine were added, and after the mixture was stirred for 45 min the Et_2O layer was removed. The aqueous phase was extracted with Et_2O (1.8 L), and the combined Et_2O extracts were washed with brine, filtered through phase-separating paper, and dried (Na_2SO_4). The solvent was removed in vacuo to give a pale yellow oil (30.3 g). A 300-mg portion of the oil was purified on Quantagram PQ1F plates (EtOAc) to give 1,6-dihydroxy-2,2-(ethylenedioxy)-6-methyl-5,5-(1,3-propylenedithio)nonane (245 mg). NMR ($CDCl_3$) 4.0 (s, 4 H, OCH_2CH_2O), 3.5 (s, 2 H, 1-CH_2O), 2.8 (m, 4 H, $SCH_2 \times 2$), 1.35 (s, 3 H, 6-CH_3), 1.1 (t, 3 H, 9-CH_3).

Anal. Calcd for $C_{15}H_{28}O_4S_2$: C, 53.57; H, 8.33. Found: C, 53.22; H, 8.42.

The diol above (7.7 g) was treated in dry pyridine (50 mL) with *p*-toluenesulfonyl chloride (5.8 g) in pyridine (15 mL) and the mixture allowed to stir overnight at room temperature. The reaction mixture was then partitioned between Et_2O (100 mL) and water (100 mL) and the organic phase was separated, treated with a saturated copper sulfate solution to remove pyridine, washed with brine, filtered through phase-separating paper, and dried (Na_2SO_4). The solvent was removed in vacuo to give a dark yellow oil (109.6 g), which was purified via silica gel chromatography using $CHCl_3$ as the eluent to give the tosylate (5.43 g). A 200-mg portion was further purified on Quantagram PQ1F plates (5% EtOAc/$CHCl_3$) to give 2,2-(ethylenedioxy)-6-hydroxy-6-methyl-5,5-(1,3-propylenedithio)-1-(tosyloxy)nonane (116 mg). NMR ($CDCl_3$) 7.45 (d of d, 4 H, aromatic H), 3.88 (s, 6 H, OCH_2CH_2O, 1-CH_2O), 2.8 (m, 4 H, $SCH_2 \times 2$), 2.42 (s, 3 H, CH_3Ar), 2.02 (s, 4 H, 3,4-CH_2), 1.3 (s, 3 H, 6-CH_3).

Anal. Calcd for $C_{22}H_{34}O_6S_3$: C, 53.88; H, 6.94. Found: C, 53.88; H, 6.91.

The tosylate from above (29.0 g) in 80% aqueous CH_3CN (830 mL) was added dropwise to a mixture of $HgCl_2$ (33.4 g), calcium carbonate (12.5 g), and 80% aqueous CH_3CN (550 mL) and the resulting slurry was refluxed for 8 h. The reaction mixture was filtered through a bed of Celite and washed with 1:1 $CHCl_3$/hexane (3 L). The organic phase was separated, washed with 5 M ammonium acetate (700 mL) and brine (1 L), and dried (Na_2SO_4). The solvent was removed in vacuo to give a yellow oil (25.3 g). A 200-mg portion was further purified on Quantagram PQ1F plates (5% EtOAc/$CHCl_3$) to give 2,2-(ethylenedioxy)-6-hydroxy-6-methyl-5-oxo-1-(tosyloxy)nonane (86 mg). NMR ($CDCl_3$) 7.47 (d of d, 4 H, aromatic H), 3.88 (s, 6 H, OCH_2CH_2O, 1-CH_2O), 2.42 (s, 3 H, CH_3Ar), 1.28 (s, 3 H, 6-CH_3), 0.88 (t, 3 H, 9-CH_3).

Anal. Calcd for $C_{19}H_{28}O_7S$: C, 57.00; H, 7.00. Found: C, 56.82; H, 7.12.

The ketone from above (24.8 g) was treated in benzene (1 L) with distilled ethylene glycol (45.5 mL) and *p*-toluenesulfonic acid (2.36 g) and the mixture allowed to reflux (28 h) in a Dean–Stark apparatus. The reaction mixture was cooled, Na_2CO_3 (4.3 g) added, and the resulting suspension stirred for 0.5 h and partitioned between Et_2O (500 mL) and brine (500 mL). The aqueous phase was extracted with Et_2O (300 mL), and the combined extracts were washed with brine (400 mL), filtered through phase-separating paper, and dried (Na_2SO_4). The solvent was removed in vacuo to give an oil (23.55 g), which was purified via silica gel chromatography (EtOAc/$CHCl_3$) to give the bis(ketal) (13.3 g, 48%). A 200-mg portion was further purified via two preparative thin-layer chromatography purifications (20% EtOAc/$CHCl_3$) to give **6** (64 mg). IR (neat) 2.8 μm (OH); NMR ($CDCl_3$) 7.5 (d of d, 4 H, aromatic H), 3.85, 3.95 (overlapping s, 10 H, $OCH_2CH_2O \times 2$, 1-CH_2O), 2.4 (s, 3 H, CH_3Ar), 1.07 (s, 3 H, 6-CH_3); MS, no M^+ m/z 357 (M − 87).

Anal. Calcd for $C_{21}H_{32}O_8S$: C, 56.76; H, 7.20. Found: C, 57.03; H, 7.27.

3,3:6,6-Bis(ethylenedioxy)-2-methyl-2-propyloxepane (7). Compound **6** (5.8 g) in distilled Me_2SO (90 mL) was treated with 99% NaH (2.06 g), and the resulting mixture was allowed to stir

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(11) Wolinsky, J.; Erickson, K. L. *J. Org. Chem.* **1965**, *30*, 2208.

18 h at 70 °C. The reaction mixture was then poured into ice water (500 mL) and partitioned between hexane and brine. The aqueous phase was extracted with hexane, and the combined extracts were washed with brine, filtered through phase-separating paper, and dried (Na_2SO_4). The solvent was removed in vacuo to give **7** (3.44 g). A 200-mg portion was purified via preparative thin-layer chromatography (1:1 EtOAc/$CHCl_3$) to give **7** as a clear oil (35 mg). NMR ($CDCl_3$) 3.93 (br s, 8 H, $OCH_2CH_2O \times 2$), 3.5 (d of d, 2 H, 7-CH_2), 1.17 (s, 3 H, 2-CH_3), 0.9 (t, 3 H, CH_3CH_2); MS, m/z 272 (M^+).

Anal. Calcd for $C_{14}H_{24}O_5$: C, 61.74; H, 8.88. Found: C, 61.34; H, 9.20.

6,6-(Ethylenedioxy)-2-methyl-2-propyloxepan-3-one (8). Diketal **7** (2.9 g) in Et_2O (136 mL) was treated with 70% $HClO_4$ (3.3 mL) and allowed to stir at 35 °C for 3.5 h. The reaction mixture was partitioned between Et_2O and water, the aqueous phase was extracted with Et_2O, and the combined Et_2O layers were washed with brine and dried (Na_2SO_4). The solvent was removed in vacuo to give a dark brown oil (2.14 g). A duplicate run gave another 2.9 g of crude product. The crude products were combined and purified via silica gel chromatography ($CHCl_3$) to give **8** (2.8 g, 57%). A 200-mg portion was further purified on Quantagram PQ1F plates (20% EtOAc/$CHCl_3$) to give an analytical sample (64 mg). IR (neat) 5.84 μm (C=O); NMR ($CDCl_3$) 3.98 (s, 4 H, OCH_2CH_2O), 3.45 (s, 2 H, 7-CH_2), 1.27 (s, 3 H, 2-CH_3); MS, m/z 198 (M − 30).

Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.16; H, 8.77. Found: C, 63.55; H, 8.67.

(2*RS*,3*SR*)-6,6-(Ethylenedioxy)-3-hydroxy-2-methyl-2-propyloxepane and (2*RS*,3*RS*)-6,6-(Ethylenedioxy)-3-hydroxy-2-methyl-2-propyloxepane (9a and 9b). 3-Ketooxepane **8** (1.76 g) in methanol (250 mL) was treated with $NaBH_4$ (4.56 g) and the mixture allowed to stir at 0 °C for 4 h. The solvent was removed in vacuo and the resulting residue dissolved in water and acidified with 10% HCl to pH 3. The aqueous solution was extracted with Et_2O, and the combined Et_2O extracts were washed with brine and dried (Na_2SO_4). The solvent was removed in vacuo to give an oil (1.57 g), which was purified via silica gel chromatography (hexane/$CHCl_3$) to give **9b** (682 mg) as a white solid (hexane), mp 78–79 °C. IR (KBr) 2.97 μm (OH); NMR ($CDCl_3$) 3.88 (s, 4 H, OCH_2CH_2O), 3.4–3.9 (m, 7-CH_2, 3-H), 1.16 (s, 3 H, 2-CH_3); MS, m/z 230 (M^+).

Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.79; H, 9.81.

Further elution gave **9a** (395 mg) as a white solid (hexane), mp 67–68 °C. IR (KBr) 2.83 μm (OH); NMR ($CDCl_3$) 3.88 (s, 4 H, OCH_2CH_2O), 3.4–3.9 (m, 7-CH_2, 3-H), 1.16 (s, 3 H, 2-CH_3); MS, m/z 230 (M^+).

Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.29; H, 9.94.

A mixture of **9a** and **9b** (472 mg) was also obtained.

(2*RS*,3*SR*)-3-Acetoxy-2-methyl-2-propyloxepan-6-one (3a). Acetyl chloride (0.49 mL) was added to a stirred solution of **9a** (217 mg) in benzene (25 mL) and pyridine (4.0 mL). The resulting suspension was stirred for 3 h, poured into ice water, and extracted with Et_2O. The organic extract was washed with saturated copper sulfate solution and then with brine, filtered through phase-separating paper, and dried (Na_2SO_4). The solvent was removed in vacuo to give a yellow oil (246 mg, 95%), which was suitable for conversion to the ketone; further purification via preparative thin-layer chromatography on Quantum PQ1F plates (25% EtOAc/hexane) gave (2*RS*,3*SR*)-3-acetoxy-6,6-(ethylenedioxy)-2-methyl-2-propyloxepane. NMR ($CDCl_3$) 4.81 (m, CH,3β-H), 3.93 (s, 4 H, OCH_2CH_2O), 3.46 (s, 2 H, 7-CH_2), 2.03 (s, 3 H, $OCOCH_3$), 1.13 (s, 3 H, 2-CH_3); MS, m/z 229 (M − 43).

A solution of the above ketal (246 mg), anhydrous acetone (12.5 mL), and concentrated HCl (0.25 mL) was heated at 45 °C for 3 h. The acetone was removed in vacuo, and the residue was partitioned between Et_2O and brine. The aqueous layer was reextracted with Et_2O (3×), and the combined organic extracts were washed well with brine (3×), filtered through phase-separating paper, and dried (Na_2SO_4). The solvent was removed in vacuo to give an oil, which was purified by column chromatography on silica (EtOAc/hexane) to give **3a** (170 mg, 83%) as a light yellow liquid. IR (neat) 5.75, 5.83 μm (C=O); NMR ($CDCl_3$) 4.85 (d of d, 1 H, 3β-H), 4.01 (s, 2 H, 7-CH_2), 2.6 (m, 2 H, 5-CH_2), 2.03 (s, 3 H, $OCOCH_3$), 1.15 (s, 3 H, 2-CH_3); MS, m/z 228 (M^+).

Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.20; H, 8.55.

(2*RS*,3*RS*)-3-Acetoxy-2-methyl-2-propyloxepan-6-one (3b). The synthesis of **3b** from **9b** was carried out in the same manner as described for the synthesis of **3a** from **9a**. Treatment of **9b** (501 mg) as above gave (2*RS*,3*RS*)-3-acetoxy-6,6-(ethylenedioxy)-2-methyl-2-propyloxepane (567 mg, 96%) as a yellow oil, NMR ($CDCl_3$) 4.89 (br m, 1 H, 3α-H), 3.92 (br s, 4 H, OCH_2CH_2O), 3.5 (d of d, 2 H, 7-CH_2), 2.09 (s, 3 H, $OCOCH_3$), 1.18 (s, 3 H, 2-CH_3).

Anal. Calcd for $C_{14}H_{24}O_5$: C, 61.74; H, 8.88. Found: C, 62.11; H, 9.04.

Hydrolysis of the intermediate ketal above gave **3b** (391 mg, 82%) as a light yellow liquid. IR (neat) 5.75, 5.83 μm (C=O); NMR ($CDCl_3$) 4.83 (t, 1 H, 3α-H), 4.03 (s, 2 H, 7-CH_2), 2.63 (m, 2 H, 5-CH_2), 2.07 (s, 3 H, $OCOCH_3$), 1.20 (s, 3 H, 2-CH_3); MS, m/z 228 (M^+).

(1*RS*,4*RS*,5*SR*)-1-Hydroxy-4-methyl-4-pentyl-3,8-dioxabicyclo[3.2.1]octane and (1*RS*,4*SR*,5*SR*)-1-Hydroxy-4-methyl-4-pentyl-3,8-dioxabicyclo[3.2.1]octane (4c and 4d). KOH pellets (7.1 g, 0.13 mol) were added to a mixture of *cis*- and *trans*-2-[2-(bromomethyl)-2-methoxytetrahydrofuran-5-yl]heptan-2-ol[9] (11, 3.02 g, 9.8 mmol) in Me_2SO (25 mL) within 5 min, while stirring at 21 °C under N_2. The reaction was then heated to 28 °C and stirring continued for 10 days.

The mixture was then cooled to room temperature; CH_2Cl_2 (100 mL) was added and the mixture filtered through Celite on a sintered-glass funnel. The filtrate was washed with water and then with brine, dried (Na_2SO_4), filtered, and evaporated in vacuo at 25 °C and then at 45 °C at 0.5 mm for 16 h to give an oily residue (2.05 g). The residue was chromatographed on SilicAR CC-7 (200 g). Elution with $CHCl_3$ afforded the bicyclic ketals (1*RS*,4*RS*,5*SR*)-1-methoxy-4-methyl-4-pentyl-3,8-dioxabicyclo[3.2.1]octane and (1*RS*,4*SR*,5*SR*)-1-methoxy-4-methyl-4-pentyl-3,8-dioxabicyclo[3.2.1]octane. NMR ($CDCl_3$) 3.93 (m, 1 H, 5-H), 3.73 (m, 2 H, 2-CH_2), 3.43 (s, 3 H, OCH_3), 1.97 (m, 4 H, 6,7-CH_2), 1.07 (s, 3 H, 4-CH_3), 0.95 (t, 3 H, CH_2CH_3).

Aqueous hydrochloric acid (2 N, 2 mL) was added to the mixture of bicyclic methoxy ketals (315 mg, 1.38 mmol) in acetone (2 mL) and the mixture was stirred at 20 °C for 48 h. The acetone was evaporated in vacuo, and the residue was dissolved in CH_2Cl_2, washed with saturated brine, dried (Na_2SO_4), filtered, and evaporated in vacuo to give **12** (260 mg; 88%, 3:2 mixture of C_4 epimers). NMR ($CDCl_3$) 3.93 (m, 1 H, 5-H), 3.5 (overlapping d of d, 2 H, 2-CH_2), 1.33 (s, 60% of 3 H, 4-CH_3), 1.03 (s, 40% of 3 H, 4-CH_3), 0.9 (t, 3 H, CH_2CH_3).

Combined samples of **12** from several runs (4.1 g) were chromatographed on SilicAR CC-7 (196 g) with 5% Et_2O/CH_2Cl_2 as eluent to give the 1*RS*,4*RS*,5*SR* hemiketal **4c** as a yellow oil (353 mg) [NMR ($CDCl_3$) 1.33 (s, 3 H, 2-CH_3)] and the 1*RS*,4*SR*,5*SR* hemiketal **4d** as a yellow oil (1.2 g) [NMR ($CDCl_3$) 1.03 (s, 3 H, 2-CH_3)]. An intermediate fraction containing approximately a 1:1 ratio of **4c**/**4d** (1.57 g) was also obtained.

(2*RS*,3*SR*)- and (2*RS*,3*RS*)-3-Hydroxy-6-(methoxyimino)-2-methyl-2-pentyloxepane (13). Anhydrous KOAc (68.6 mg, 0.7 mmol) was added to **12** (106.0 mg, 0.49 mmol) in MeOH (1.0 mL) while stirring at 21 °C. Methoxyamine hydrochloride (64.0 mg, 0.65 mmol) was added to this solution and stirring continued for 4 days under N_2. The MeOH was evaporated in vacuo and the residue dissolved in CH_2Cl_2. The solution was washed with water, dried (Na_2SO_4), filtered, and evaporated in vacuo to give **13** as an oil (109 mg, 92%). IR (neat) 3.36 μm (OH), 6.13 (=$NOCH_3$); NMR ($CDCl_3$) 3.77–3.8 (2 s, 3 H, OCH_3), 3.57 (m, 1 H, 3-H); GC/MS, two fractions each with m/z 199 (M − 44).

(2*RS*,3*SR*)- and (2*RS*,3*RS*)-3-Acetoxy-2-methyl-2-pentyloxepan-6-one (3c and 3d). A mixture of pyridine (0.6 mL) and Ac_2O (0.3 mL) was added to **13** (53 mg, 0.2 mmol) at 21 °C. After stirring under N_2 at 21 °C for 16 h, the system was evaporated in vacuo. The residue was dissolved in CH_2Cl_2, washed with saturated brine containing a few drops of 2 N HCl (pH 2.0), washed with brine free of acid, dried (Na_2SO_4), filtered, and evaporated in vacuo to give (2*RS*,3*SR*)- and (2*RS*,3*RS*)-3-acetoxy-6-(methoxyimino)-2-methyl-2-pentyloxepane (53 mg, 93%). The acetoxy oxime–ether (53.0 mg, 0.19 mm) was dissolved in

acetone (7.6 mL) and 2 N aqueous HCl (0.4 mL), stirred, and refluxed under N_2 for 3 h. The mixture was evaporated in vacuo and the residue dissolved in CH_2Cl_2. The solution was washed with saturated brine containing a few drops of $NaHCO_3/H_2O$ to make it basic and then with brine, dried (Na_2SO_4), filtered, and evaporated in vacuo to give 44 mg (90%) of crude acetoxy ketone, which was further purified by chromatography on silica (10% Et_2O/CH_2Cl_2) to give a mixture of epimers **3c** and **3d** (25 mg, 3:2, 73%). NMR ($CDCl_3$) 4.9 (m, 1 H, 3-H), 4.08 (br s, 2 H, 7-CH_2), 2.07 and 2.10 (2 s, 3 H, $OCOCH_3$), 1.17 and 1.25 (2 s, 3 H, 2-CH_3), 0.9 (t, 3 H, CH_2CH_3).

(2*RS*,3*SR*)-3-Acetoxy-6-(carbethoxymethylidene)-2-methyl-2-propyloxepane (14). Ethyl (diethoxyphosphinyl)-acetate (728 mg) was added dropwise to a suspension of NaH (99%, 68 mg) in anhydrous benzene (25 mL). The suspension was heated to 70 °C and stirred vigorously until the evolution of hydrogen ceased. A solution of **3a** (260 mg) in anhydrous benzene (3 mL) was added slowly to the above solution and heated at 70–75 °C for 1 h. The resulting solution was cooled, Et_2O (150 mL) and 10% HCl (35 mL) were added, and the organic layer was separated. The aqueous layer was reextracted with Et_2O (3×), and the combined organic extracts were washed with brine (3×), filtered through phase-separating paper, and dried (Na_2SO_4). The solvent was removed in vacuo to give a residue (1.01 g) which contained **14** as the major component and a large quantity of excess ethyl (diethoxyphosphinyl)acetate. The residue was purified via silica gel chromatography (1% EtOAc/hexane) to give **14** (265 mg, 78%). IR (neat) 5.78, 5.86 μm (C=O), 5.1 (C=C); NMR ($CDCl_3$) 5.65 (br s, 1 H, C=CH), 4.8 (overlapping m, 3β-H and cis 7-CH_2), 3.9–4.3 (overlapping q and s, CH_3CH_2 and trans 7-CH_2), 2.04 (s, 3 H, $OCOCH_3$), 1.17 (s, 3 H, 2-CH_3) (integration indicates a 3:2 ratio of trans:cis isomers for the carbethoxymethylidene at C-6); GC/MS, m/z 298 (M^+) for each of the trans/cis isomers.

Anal. Calcd for $C_{16}H_{26}O_5$: C, 64.41; H, 8.78. Found: C, 64.78; H, 8.70.

(1*RS*,4*RS*,5*RS*)-4-Methyl-4-pentyl-3,8-dioxabicyclo-[3.2.1]octane-1-acetic Acid (15). A mixture of **4d** (350 mg) and (carbethoxymethylidene)triphenylphosphorane (1.8 g) was refluxed in xylene (10 mL) for 2 days under N_2. After the mixture was cooled, petroleum ether (30 mL) was added, refluxed for 30 min, and filtered. The petroleum ether filtrate was evaporated in vacuo and the crude residue chromatographed on SilicAR CC-7 with 10% Et_2O/CH_2Cl_2 to give the ethyl ester of **15** as a light yellow oil (470 mg, 96%). $NaOH/H_2O$ (2 N, 5 mL) was added, while stirring at 0 °C under N_2, to the ester in MeOH (5 mL). The mixture was then stirred at 20 °C for 3 days under N_2. The solvent was evaporated in vacuo and the residue extracted with CH_2Cl_2. The basic, aqueous solution was carefully acidified to pH 5 with 2 N HCl, extracted with CH_2Cl_2, washed with water and brine, dried (Na_2SO_4), filtered, and evaporated to give **15** as a yellow oil (210 mg, 50%). IR (neat) 5.72, 5.83 μm (C=O); NMR ($CDCl_3$) 3.90 (t, 1 H, 5-H), 3.56 (d of d, 2 H, 2-CH_2), 2.63 (s, 2 H, CH_2CO_2H), 1.03 (s, 3 H, 4-CH_3), 0.9 (t, 3 H, CH_2CH_3); GC/MS, Me_3Si derivative, m/z 328 (M^+).

Acknowledgment. We thank Dr. M. L. Cotter for spectroscopic results and C. Shaw for GC/MS data. We also thank Dr. S. D. Levine and Prof. J. A. Marshall for many helpful discussions.

Metabolites of Cibenzoline: Synthesis of Hydroxylated 1,1-Diphenyl-2-imidazolylcyclopropanes and 5,5-Diphenyl-2*H*-pyrrolo[1,2-*a*]imidazolines

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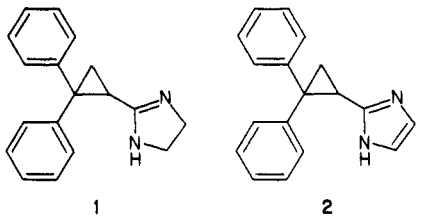
Received November 23, 1984

The (hydroxyphenyl)pyrrolo[1,2-*a*]imidazolines **7a** and **7b**, which are of interest as oxidative metabolites of the antiarrhythmic agent cibenzoline (1), were synthesized by the base-catalyzed rearrangement of the cyclopropylphenols derived from benzyl ethers **6a** and **6b**, respectively. The unsubstituted diphenylpyrrolo[1,2-*a*]-imidazoline **18** was prepared by treatment of the pyrrolidone imidate **17** with bromoethylamine.

Cibenzoline (1) is a class I antiarrhythmic agent which is currently undergoing clinical trials in the United States. The metabolism of ^{14}C-cibenzoline has been investigated in rats and dogs; after oral dosing, these animals excrete unchanged cibenzoline, the imidazole **2**,[1] and several hydroxylated metabolites in their conjugated form. Two of the conjugated metabolites were hydrolyzed, separated, and assigned structures **7a** and **7b** on the basis of NMR studies.[2] Since these compounds appear to represent rearranged products of primary metabolites, the corresponding (hydroxyphenyl)cyclopropanes, we have undertaken the work described in this paper to provide reference samples of these cyclopropanes as well as **7a** and **7b**. We also describe the synthesis of the "parent" 5,5-diphenyl-2*H*-pyrrolo[1,2-*a*]imidazoline (**18**), which was prepared for biological testing as an analogue of **1**.



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The syntheses of **7a** and **7b** and the cyclopropyl derivatives **11** and **1i** are outlined in Scheme I. Thus the benzophenone **3a**[3] was converted to the hydrazone **4a** with excess hydrazine in ethanol. The crude hydrazone was oxidized with manganese dioxide in dichloromethane to the corresponding purple diphenyldiazomethane which was in turn reacted with acrylonitrile to give the nitriles **5a** in good yield as a mixture of diastereomers. While these

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