1275 (PhNC), 905 cm^{-1}; NMR ($CDCl_3$) δ 7.33 and 6.61 (AA'BB', 4 H, ^3J = 9.5 Hz, PhH), 5.10 (s, 1 H, 2-H), 3.30 (q, 4 H, ^3J = 7.0 Hz, NCH_2), 2.8–2.95 (m, 4 H, 4, 6-H), 1.85–2.0 (m, 2 H, 5-H), 1.12 (t, 6 H, CH_3). Anal. Calcd for $C_{14}H_{21}NS_2$: C, 62.87; H, 7.91; N, 5.24; S, 23.98. Found: C, 63.00; H, 8.02; N, 5.32; S, 23.79.

2-[2'-(1',3'-Dithianyl)]thiophene (14). The crude product contained, besides **14** (~40%), considerable amounts of **9** and **12** [NMR ($CDCl_3$) δ 2-H in **9** and **12** 4.92 (s), and δ formyl-H in **12** 10.16 (s)].[1] Purification of **14** was achieved by careful column chromatography (G, benzene), followed by crystallization from hexane: white needles; mp 77–78 °C; IR 855, 760, 700 (thiophene), 905 cm^{-1}. The 2 substitution could be inferred from the NMR spectrum by analysis of the coupling constant magnitudes: NMR ($CDCl_3$) δ 7.22 (dd, 1 H, ^3J = 5.0, ^4J = 1.3 Hz, 5-H), 7.14 (ddd, 1 H, ^3J = 3.6, $^4J_{5\text{-H}}$ = 1.3, $^4J_{2'\text{-H}}$ = 0.7 Hz, 3-H), 6.92 (dd, 1 H, ^3J = 5.0 and 3.6 Hz, 4-H), 5.38 (d, 1 H, ^4J = 0.7 Hz, 2'-H), 2.95 (m, 4 H, 4',6'-H), 1.9–2.1 (m, 2 H, 5'-H). Anal. Calcd for $C_8H_{10}S_3$: C, 47.53; H, 4.99; S, 47.49. Found: C, 47.36; H, 4.99; S, 47.41.

1-Methyl-2-[2'-(1',3'-dithianyl)]pyrrole (15).[27] The crude product contained ~30% of this compound. An ~80% pure sample was obtained by column chromatography (G, 1:2 ethyl acetate–hexane). The NMR spectrum indicated the 2 substitution: NMR ($CDCl_3$) δ 6.48 (dd, 1 H, ^3J = 2.5, ^4J = 1.8 Hz, 5-H), 6.21 (dd, 1 H, ^3J = 3.5, ^4J = 1.8 Hz, 3-H), 6.00 (dd, 1 H, ^3J = 3.5 and 2.5 Hz, 4-H), 5.22 (s, 1 H, 2'-H), 2.85–3.0 (m, 4 H, 4',6'-H), 1.9–2.1 (m, 2 H, 5'-H).

NMR spectra of the products obtained by reaction of **2** with indole, benzo[*b*]furan, and benzo[*b*]thiophene indicated the presence of small amounts of dithianylated products besides products **9** and **12**.

Registry No.—**1**, 36049-90-8; **2**, 57529-04-1; **4a**, 108-86-1; **4b**, 106-39-8; **4c**, 108-37-2; **4d**, 90-11-9; **4e** (*E* isomer), 588-72-7; **4e** (*Z* isomer), 588-73-8; **4f**, 100-44,7; **4g**, 108-85-0; **4h**, 78-76-2; **4j**, 507-20-0; **5a**, 5425-44-5; **5b**, 10359-09-8; **5c**, 57009-71-9; **5d**, 57009-77-5; **5e** (*E* isomer), 69178-10-5; **5e** (*Z* isomer), 69178-11-6; **5f**, 31593-52-9; **5g**, 56698-00-1; **5h**, 69178-00-3; **5j**, 6007-21-2; **6**, 69178-01-4; **7**, 21875-49-0; **8a**, 63822-64-0; **8b**, 69178-02-5; **8c**, 69178-03-6; **8d**, 69178-04-7; **8e**, 69178-05-8; **9**, 38336-42-4; **10**, 69178-12-7; **11a**, 57529-05-2; **11b**, 6842-36-0; **11c**, 54810-45-6; **11d**, 54810-44-5; **11e**, 54810-43-4; **11f**, 69178-06-9; **11g**, 69178-07-0; **12**, 69178-13-8; **13**, 69178-08-1; **14**, 57009-79-7; **15**, 69178-09-2; sodium diethyl propanedioate, 996-82-7; sodium diethyl methylpropanedioate, 18424-77-6; sodium di-*tert*-butyl methylpropanedioate, 66702-41-8; sodium diethyl phenylpropanedioate, 28744-77-6; sodium diethyl (*p*-methoxyphenyl)propanedioate, 69178-14-9; phenol, 108-95-2; *p*-methoxyphenol, 150-76-5; *p*-methylphenol, 106-44-5; *p*-chlorophenol, 106-48-9; resorcinol, 108-46-3; 2-naphthol, 135-19-3; sulfuryl chloride, 7791-25-5; 1,3-dithiane, 505-23-7; thiophene, 110-02-1; *N*-methylpyrrole, 96-54-8; *N*,*N*-diethylaniline, 91-66-7.

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Synthesis of (±)-Cacalol[1]

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The synthesis of cacalol (**1**), a structurally unusual sesquiterpenoid tetrahydronaphthofuran, is described. The starting compound for the synthesis, 6-acetyl-5-hydroxy-1,8-dimethyl-1,2,3,4-tetrahydronaphthalene (**10**), was prepared in several steps from either 5-methoxy-8-methyl-1-tetralone (**5**) or 4,5-dimethyl-8-hydroxy-1-tetralone (**11**). The methyl ether of **10** (**13**) on Baeyer–Villiger oxidation followed by hydrolysis gave 5-methoxy-6-hydroxy-1,8-dimethyl-1,2,3,4-tetrahydronaphthalene (**15**). Hantzsche benzofuran synthesis gave a carbethoxy derivative of (±)-cacalol methyl ether (**17**) which on hydrolysis, decarboxylation, and ether cleavage afforded (±)-cacalol.

The structurally unusual sesquiterpene cacalol (**1**) is the parent member of a group of tetrahydronaphthofurans isolated from the roots of *Cacalia decomposita*, a shrub indigeneous to northern Mexico.[2] Following several revisions,[2] the indicated structure was proposed essentially simultaneously in three publications.[3] It has been suggested that cacalol is

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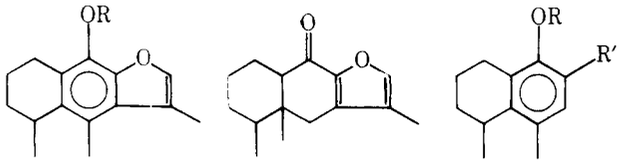
derived in vivo from the rearrangement of an eremophilane precursor,[4] presumably decompostin (2), which is also isolated from *Cacalia decomposita*.[2d]



1, R = H
12, R = $CH_2C_6H_5$
18, R = CH_3

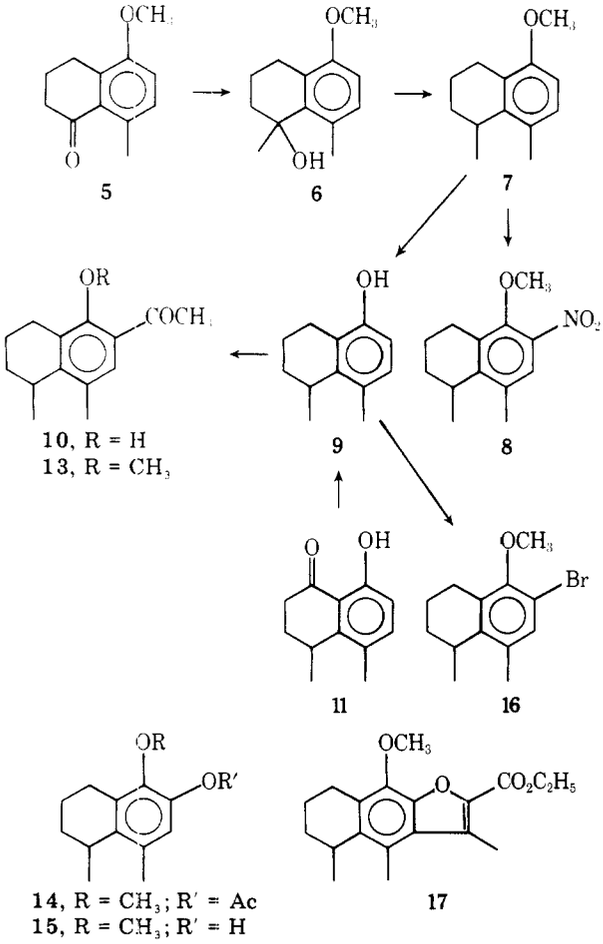
2

3, R = alkyl; R′ = OH
4, R = alkyl; R′ = H

The synthesis of cacalol appeared superficially to be quite straightforward, demanding only the preparation of an appropriate derivative of a substituted tetrahydronaphthalenediol (3) in which the oxygen which will ultimately become the phenolic hydroxyl in cacalol is protected with an appropriate blocking group, presumably an alkyl substituent. The benzofuran ring could then be added by any one of several classical methods. In order to maintain regioselectivity in the synthesis of a derivative of 3, it was considered necessary to introduce the two hydroxyl groups at different stages in the synthesis, presumably through a monooxygenated precursor such as 4. The second hydroxyl group would then be added by a standard method.

A compound of the type of 4 was prepared with little difficulty as depicted in Scheme I. 5-Methoxy-8-methyl-1-tetralone (5),[5] although recovered unchanged on treatment with methylmagnesium iodide,[6] gave tetralol 6 upon reaction with methyllithium. Dehydration followed by reduction afforded methoxytetralin 7, an apparently reasonable substrate for the introduction of the second oxygen function. It was ultimately found possible to effect the conversion of ketone 5 to tetralin 7 in one operation, using the procedure of Hall and Lipsky.[7]

Scheme I



5 6 7 8 9 10, R = H 13, R = CH_3 11 16 14, R = CH_3; R′ = Ac 15, R = CH_3; R′ = H 17

The initial approach to the introduction of the second oxygen function was by the traditional method of nitration, reduction to the amine, diazotization, and acid-catalyzed decomposition of the diazonium salt. It proved possible to obtain nitro compound 8 in only very low yield, and although the reduction to the corresponding amine proceeded smoothly, treatment of the derived diazonium salt with acid under a variety of conditions gave only unidentified materials and little if any of the desired phenol. A variety of alternative approaches to the introduction of a suitable functional group at this position were explored; however, they either failed entirely or gave mixtures resulting from attack at both unsubstituted positions on the aromatic ring.[8] The introduction of the hydroxyl group in the desired position was ultimately accomplished by a variation of a procedure used in the diterpene series.[9] Cleavage of the *o*-methyl ether (boron tribromide) afforded phenol 9, the acetate of which on Fries rearrangement gave in mediocre yield hydroxy ketone 10.

The synthesis of phenolic ketone 10 could be accomplished much more efficiently by a three-step sequence having as a key step the Friedel–Crafts reaction of δ-valerolactone and *p*-cresol to give 4,5-dimethyl-8-hydroxy-1-tetralone (11). Although the Friedel–Crafts reaction of δ-valerolactone with phenols in an aluminum chloride sodium chloride melt has been reported to give 3-ethyl-1-indanone derivatives,[10] the reaction of the lactone with *p*-cresol under these conditions afforded tetralone 11 cleanly and in fair yield.[11] The NMR spectrum of the reaction product (See Experimental Section) was in agreement with the assigned structure, and this assignment was confirmed by Clemmensen reduction to tetralol 9. The direct acylation of tetralol 9 with acetic anhydride in poly(phosphoric acid)[12] proved to be far superior to the classical Fries rearrangement for the preparation of ketone 10.

The initial synthetic approach for the conversion of hydroxy ketone 10 to cacalol utilized a benzyl group to protect the phenolic hydroxyl. Although this route led ultimately to small quantities of cacalol benzyl ether (12), the overall yields were sufficiently poor that they precluded the completion of the synthesis by this route.[1,8] As it appeared probable that the steric bulk and acid lability of the benzyl ether were responsible for the difficulties encountered in the synthesis of the benzofuran system, phenolic ketone 10 was converted to the methyl ether (13) by prolonged treatment with methyl sulfate and base. Baeyer–Villiger oxidation with *m*-chloroperoxybenzoic acid at 0 °C for slightly over 1 week afforded acceptable yields of acetate 14,[13] basic hydrolysis of which gave the requisite phenol (15).

Phenol 15 could also be obtained from 9 in three steps by Cava's modification of the Buck–Kobrich reaction.[14] Bromination of phenol 9 followed by ortho methylation afforded bromo methyl ether 16.[15] Although treatment of 16 with butyllithium followed by reaction of the derived aryllithium with excess nitrobenzene afforded phenol 15 in apparently good yield, considerable decomposition of this air-sensitive material occurred while separating the reaction product from residual nitrobenzene. Although the sequence from phenol 9, through ketone 13, is slightly longer than that via the Buck–Kobrich reaction, the ease of carrying out the individual steps makes the former the preferable route for the preparation of reasonable quantities of 15.

Acid-catalyzed cyclization of the 2-aryloxy acetoacetic ester derived from phenol 15[16] using warm poly(phosphoric acid) gave a tetrahydronaphthofuran carboxylic ester (17), hydrolysis of which, followed by pyrolytic decarboxylation in the presence of copper powder,[17] gave (±)-cacalol methyl ether (18). The spectral properties of the synthetic material agreed with those reported for the derivative of the natural product.[2a]

The methyl ether was cleaved cleanly in reasonable yield using sodium thiopropoxide in dimethylformamide[18] to give (±)-cacalol (1).[19] The infrared spectra of synthetic cacalol and the derived acetate were identical to those of natural cacalol and cacalol acetate, respectively.[20]

Following the announcement of our synthesis of cacalol benzyl ether[1] two syntheses of (±)-cacalol were reported, both proceeding by routes dissimilar to that described above.[21]

Experimental Section[22]

5-Methoxy-1,8-dimethyl-1-tetralol (6). To a solution of 30.0 g of 5-methoxy-8-methyl-1-tetralone (**5**)[5] in 300 mL of anhydrous ether was added slowly 230 mL of methyllithium (2.1 M in ether). The reaction mixture was stirred at room temperature under nitrogen for 20 h, cooled (ice bath), and acidified with 10% aqueous hydrochloric acid. The ethereal and aqueous layers were separated, and the aqueous phase was extracted with two portions of ether, and the combined ether layers were washed successively with dilute hydrochloric acid, water, and brine. After drying, evaporation of the ether gave 32.7 g of light-brown solid, which upon recrystallization from hexane gave 16.5 g (51%) of white crystals, mp 93–94 °C. The analytical sample crystallized from pentane as irregular prisms: mp 96 °C; IR 3.02 μm; NMR δ 1.63 (s, 3 H, CH_3COH), 2.62 (s, 3 H, $ArCH_3$), 3.83 (s, 3 H, $ArOCH_3$), 6.91 (q, J = 8 Hz, 2 H, ArH); mass spectrum m/e (rel intensity) 207 (10), 206 (93), 191 (93), 188 (100).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.47; H, 8.61.

5-Methoxy-1,8-dimethyl-1,2,3,4-tetrahydronaphthalene (7). A. To 37.25 g of 5-methoxy-1,8-dimethyl-1-tetralol (**6**) in 1000 mL of benzene was added 5 g of *p*-toluenesulfonic acid and the mixture heated at reflux under a Dean-Stark trap for 10 h. The benzene was removed, the residue was taken up in ether, and the solution was washed with two portions of 5% sodium bicarbonate, water, and brine. After drying, evaporation of the solvent gave 37.14 g of dark yellow oil. Distillation under reduced pressure afforded 24.07 g (71%) of a colorless oil, bp 90–93 °C (0.35 mm). This material was a mixture of isomeric olefins and was reduced without further purification. A solution of 6.0 g of this olefin mixture in 200 mL of ethanol was hydrogenated at 45 psig using 1.60 g of Adam's catalyst. The mixture was filtered through Celite and the ethanol removed to give 6.3 g of colorless oil. The analytical sample, bp 90–100 °C (0.35 mm), was obtained as a colorless oil by distillation (air-bath): NMR δ 1.10 (d, J = 7 Hz, 3 H, $CHCH_3$), 2.17 (s, 3 H, $ArCH_3$), 3.48 ($ArOCH_3$), 6.58 (d, J = 8 Hz, 2 H ArH).

Anal. Calcd for $C_{13}H_{16}O$: C, 82.06; H, 9.53. Found: C, 82.23; H, 9.40.

B. To a solution of 25.0 g of 5-methoxy-8-methyl-1-tetralone (**5**) in 200 mL of anhydrous ether was added slowly 108 mL of methyllithium (1.85 M in ether) diluted with 100 mL of anhydrous ether. The reaction mixture was stirred for 22 h at room temperature in a nitrogen atmosphere, and approximately 650 mL of ammonia was distilled into the reaction vessel. To this reaction mixture was added 5.5 g of lithium in small pieces, keeping the vigorous reaction under control. After stirring the reaction mixture for 1.5 h in a nitrogen atmosphere, approximately 85 g of solid ammonium chloride was cautiously added in small amounts. When the blue color of the reaction mixture had been discharged, the ammonia was allowed to evaporate and the product was isolated with ether. The ethereal solution was washed successively with water, dilute hydrochloric acid, water, and brine. Evaporation of the ether gave 25.6 g (100%) of nearly colorless oil. The spectral properties of this material were identical with those of 5-methyl-1,8-dimethyl-1,2,3,4-tetrahydronaphthalene described above.

4,5-Dimethyl-8-hydroxy-1-tetralone (11). To a stirred mixture of 150 g of anhydrous aluminum chloride and 30 g of sodium chloride, preheated to 140 °C, was added slowly a mixture of 15.0 g of γ-valerolactone and 15.0 g of redistilled *p*-cresol. The temperature rose rapidly to ca. 200 °C and the mixture was maintained at that temperature for 2 min. After cooling to approximately 100 °C the molten reaction mixture was poured cautiously, with stirring, into iced, concentrated hydrochloric acid. The mixture was heated to near the boiling point to destroy the aluminum complex of the product, cooled, and combined with another run carried out on the same scale. The reaction mixture was extracted with two portions of ether, the ethereal extracts were combined, washed with successive portions of 10% sodium hydroxide and brine, and dried, and the solvent was removed to give a viscous black oil. Distillation afforded 13.94 g (26%) of pale yellow oil, bp 158–168 °C (3 mm), which crystallized on standing. Recrystallization of a small portion from aqueous methanol gave pale yellow needles: mp 58–59 °C (This material was previously reported as an oil.[11]); IR 6.06 μm; NMR δ 1.29 (d, 3 H, J = 7 H $CHCH_3$), 2.23 (s, 3 H, $ArCH_3$), 6.98 (q, 2 H, J = 8 Hz, ArH).

The 2,4-dinitrophenylhydrazone was obtained as fine orange crystals, mp 242–244 °C (lit.[11] mp 247 °C), from ethyl acetate.

5-Hydroxy-1,8-dimethyl-1,2,3,4-tetrahydronaphthalene (9). A. To a solution of 29.8 g of 5-methoxy-1,8-dimethyl-1,2,3,4-tetrahydronaphthalene (**7**) in 1000 mL of methylene chloride was added carefully 25 g of boron tribromide, and the mixture was stirred at room temperature for 20 h. After reducing the volume of the reaction mixture, the residue was taken up in ether, washed successively with saturated aqueous sodium bicarbonate, water, and brine, and dried. Evaporation of the solvent gave 27.1 g (100%) of phenol **9** as a dark oil: IR 2.88 μm; NMR δ 1.12 (d, J = 7 Hz, 3 H, $CHCH_3$), 2.18 (s, 3 H, $ArCH_3$), 5.59 (br s, 1 H, OH), 6.58 (q, 2 H, $J \mp 8$ Hz, ArH); mass spectrum m/e (rel intensity) 177 (4), 176 (46), 175 (5), 161 (100), 134 (15), 99 (24). This air-sensitive material was used for further reactions without additional purification.

B. The Clemmensen reduction of 4,5-dimethyl-8-hydroxy-1-tetralone was carried out in the usual manner.[23] From 11.88 g of ketone there was obtained 9.56 g (87%) of phenol, identical with that described in part A above.

5-Acetoxy-1,8-dimethyl-1,2,3,4-tetrahydronaphthalene. To 27.1 g of 5-hydroxy-1,8-dimethyl-1,2,3,4-tetrahydronapthalene (**9**) was added 21.9 mL of acetyl chloride, and the mixture was heated at reflux for 1 h. The excess acetyl chloride was removed under vacuum to give 30.4 g of acetate as a brown oil. Chromatography of the crude product on silica gel followed by crystallization from aqueous methanol gave white plates: mp 50–51 °C; IR 5.65 μm; NMR δ 1.17 (d, J = 7 Hz, 3 H, $CHCH_3$), 2.22, 2.27 (s, 3 H each, $-COCH_3$ and $ArCH_3$), 6.79 (d, J = 7 Hz, 2 H, ArH).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.22; H, 8.33.

6-Acetyl-5-hydroxy-1,8-dimethyl-1,2,3,4-tetrahydronaphthalene (10). A. To a solution of 30.0 g of 5-acetoxy-1,8-dimethyl-1,2,3,4-tetrahydronaphthalene in 50 mL of redistilled nitrobenzene was added 24.5 g of anhydrous aluminum chloride and the mixture was heated on the steam bath for 1 h. After cooling to room temperature, the reaction mixture was poured into 1000 mL of iced 10% hydrochloric acid. After removing the nitrobenzene by steam distillation, the residue was taken up in ether, washed with water and brine, and dried, and the solvent was removed to give 25 g of dark brown gum. This material was dissolved in benzene and chromatographed on Woelm neutral alumina. Elution with benzene gave 12.7 g of semisolid which was essentially homogeneous to TLC. Repeated crystallization from ethanol gave 4.0 g (13%) of yellow plates: mp 56.5 °C; IR 3.40, 6.12; NMR δ 1.05 (d, J = 6 Hz, 3 H, $CHCH_3$), 2.03 (s, 3 H, $ArCH_3$), 2.27 (s, 3 H, $-COCH_3$), 6.55 (s, 1 H, ArH), 11.17 (s, 1 H, ArOH); mass spectrum m/e (rel intensity) 219 (3), 218 (100), 204 (12), 203 (71), 176 (219), 174 (25), 161 (15).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.22; H, 8.20.

B. A mixture of 8.83 g of 5-hydroxy-1,8-dimethyl-1,2,3,4-tetrahydronaphthalene (**9**) and 7.11 g of acetic anhydride was added to ca. 135 mL of poly(phosphoric acid) and the mixture was heated on a steam bath for 2.5 h with occasional stirring. The reaction mixture was poured into ice water and extracted with three portions of ether. The ethereal extracts were combined, washed successively with water, 10% sodium hydroxide, water, and brine, and dried, and the solvent was removed to give 6.54 g of brown gum. This material was taken up in 3:1 hexane–benzene and chromatographed on 150 g of Woelm silica gel. Elution with hexane–benzene (2:1) gave 3.37 g (31%) of pale yellow solid identical with that described in part A.

6-Acetyl-5-methoxy-1,8-dimethyl-1,2,3,4-tetrahydronaphthalene (13). To a solution of 3.38 g of 6-acetyl-5-hydroxy-1,8-dimethyl-1,2,3,4-tetrahydronaphthalene (**10**) in 300 mL of dry, redistilled acetone was added 70 g of anhydrous potassium carbonate and 35 mL of methyl sulfate. The reaction mixture was stirred at reflux under nitrogen for 48 h, with 10-mL portions of methyl sulfate added at 12-h intervals. The reaction mixture was filtered and the filtrate evaporated to dryness leaving a pale yellow oil which was dissolved in hexane–benzene (1:1) and chromatographed on 90 g of Woelm silica gel. Elution with hexane–benzene (1:1) gave 0.23 g of recovered phenol, while the benzene fractions afforded 2.43 g (73% based on phenol consumed) of methyl ether **13** as a colorless oil: IR 5.99 μm; NMR δ 1.19 (d, J = 7 Hz, 3 H, $CHCH_3$), 2.30 (s, 3 H, $ArCH_3$), 2.60 (s, 3 H, $COCH_3$), 3.70 (s, 3 H, OCH_3), 7.21 (s, 1 H, ArH). The 2,4-dinitrophenylhydrazone was obtained as red-orange platelets, mp 187–189 °C, from ethyl acetate.

Anal. Calcd for $C_{21}H_{24}N_4O_5$: C, 61.16; H, 5.87; N, 13.58. Found: C, 61.18; H, 5.91; N, 13.60.

6-Acetoxy-5-methoxy-1,8-dimethyl-1,2,3,4-tetrahydronaphthalene (14). To a solution of 2.43 g of 6-acetyl-5-methoxy-1,8-dimethyl-1,2,3,4-tetrahydronaphthalene (**13**) in 180 mL of methylene chloride was added 4.10 g of *m*-chloroperoxybenzoic acid (80–90%) and 0.60 g of toluenesulfonic acid. The reaction mixture was stored in the dark at 5 °C for 192 h. The precipitated *m*-chlorobenzoic acid was filtered off and washed thoroughly with methylene chloride. The filtrates were washed with successive portions of 10% aqueous potassium iodide, 10% sodium bisulfite, saturated sodium bicarbonate, water, and brine and dried, and the solvent was removed to give 1.88 g of amber oil. This material was dissolved in benzene and chromatographed on 65 g of Woelm silica gel. Elution with benzene afforded 1.28 g (49%) of acetate as a thick, nearly colorless oil. This material was contaminated with 5–10% of an unidentified impurity which could not be removed by repeated rechromatography: IR 5.65 μm; NMR δ 1.12 (d, J = 7 Hz, 3 H, CH**CH**$_3$), 2.20, 2.23 (s, 3 H each, Ar**CH**$_3$ and **CH**$_3$CO), 3.62 (s, 3 H, O**CH**$_3$), 6.53 (s, 1 H, ArH); mass spectrum *m/e* (rel intensity) 248 (22), 206 (62), 192 (15), 191 (100), 160 (15), 145 (6).

6-Bromo-5-methoxy-1,8-dimethyl-1,2,3,4-tetrahydronaphthalene (16). To a chilled (ice bath) solution of 3.05 g of 5-hydroxy-1,8-dimethyl-1,2,3,4-tetrahydronaphthalene (**9**) in 20 mL of acetic acid was added slowly with stirring 6.42 g of pyridinium hydrobromide perbromide. The reaction mixture was allowed to warm to ambient temperature, stirred for 1 h, and then poured into water and extracted with two portions of ether. The combined ethereal solutions were washed with water and brine and dried, and the solvent was removed at reduced pressure to give the bromophenol as a dark brown, lachrymatory oil: IR 2.69 μm; NMR δ 1.10 (d, J = 7 Hz, 3 H, CH**CH**$_3$), 2.18 (s, 3 H, Ar**CH**$_3$), 7.00 (s, 1 H, ArH). Without further purification, this material was dissolved in 350 mL of dry acetone, 40 g of anhydrous potassium carbonate and 22 mL of methyl sulfate were added, and the mixture was stirred at reflux under nitrogen for 22 h. After cooling, the potassium carbonate was filtered off and washed with additional dry acetone, and the filtrate was evaporated to leave an amber oil which contained methyl sulfate. The residue was suspended in 100 mL of water and heated at reflux for 30 min. After cooling, the product was taken up in ether, the ethereal solution was washed with water and brine and dried, and the solvent was removed to give a pale brown oil. Distillation afforded 2.18 g (51%) of ether **16**, bp 140–160 °C (air bath, 0.2 mm), as a nearly colorless oil: NMR δ 1.14 (d, J = 7 Hz, 3 H, CH**CH**$_3$), 2.20 (s, 3 H, Ar**CH**$_3$), 3.72 (s, 3 H, O**CH**$_3$), 7.11 (s, 1 H, ArH). A small sample was dissolved in hexane–benzene (1:1) and filtered through Woelm silica gel; redistillation gave the analytical sample, bp 130–145 °C (air bath, 0.10 mm), as a colorless oil.

Anal. Calcd for $C_{13}H_{17}BrO$: C, 58.00; H, 6.37; Br, 29.69. Found: C, 57.86; H, 6.37; Br, 29.56.

6-Hydroxy-5-methoxy-1,8-dimethyl-1,2,3,4-tetrahydronaphthalene. A. A solution of 1.247 g of 6-acetoxy-5-methoxy-1,8-dimethyl-1,2,3,4-tetrahydronaphthalene (**14**) in 40 mL of methanol and 20 mL of 15% aqueous potassium hydroxide was heated at reflux under nitrogen for 2.5 h. After cooling, the reaction mixture was acidified with concentrated hydrochloric acid and extracted with two portions of ether. The combined ethereal extracts were washed with water and brine and dried, and the solvent was removed at reduced pressure to give 0.945 g (91%) of phenol **15** as an air-sensitive, pale-brown oil, which was used immediately for the subsequent step: IR 2.88 μm; NMR δ 1.10 (d, J = 7 Hz, 3 H, CH**CH**$_3$), 2.20 (s, 3 H, Ar**CH**$_3$), 3.69 (s, 3 H O**CH**$_3$), 5.41 (br s, 1 H, OH), 6.54 (s, 1 H, ArH).

B. To a stirred solution of 1.396 g of 6-bromo-5-methoxy-1,8-dimethyl-1,2,3,4-tetrahydronaphthalene (**16**) in 25 mL of dry tetrahydrofuran at −78 °C and under nitrogen was added a mixture 13.0 mL of 1.9 M butyllithium in hexane and 25 mL of dry tetrahydrofuran. The mixture was stirred at −78 °C for 0.75 h and cooled to −100 °C (liquid nitrogen), and 3.0 mL of freshly distilled nitrobenzene was added. The reaction mixture was allowed to warm to −78 °C, stirred at that temperature for 2.5 h, allowed to warm to ambient temperature, and poured into ice water. The aqueous suspension was acidified with concentrated hydrochloric acid and separated, and the aqueous phase was extracted with three portions of ether. The combined organic extracts were washed with water and extracted with four portions of 15% aqueous potassium hydroxide. The combined basic extracts were washed with ether and acidified, and the product was isolated with ether to give 0.078 g (7%) of phenol **15**, identical with that described in part A. The neutral fraction was dried and the solvent removed to give 4.098 g of a dark oil which was taken up in benzene and chromatographed on 200 g of Woelm silica gel. Elution with benzene–ethyl acetate (7:1) gave 0.782 g of impure phenol, which on rechromatography afforded 0.308 g (29%) of phenol **15**, identical with that described above.

2-Carbethoxy-9-methoxy-3,4,5-trimethyl-5,6,7,8-tetrahydronaphtho[2,3-*b*]furan (17). To 0.50 g of sodium hydride (50% dispersion in mineral oil, which had been washed thoroughly with dry hexane) was added a solution of 0.954 g of phenol **15** in 35 mL of dry benzene, and the reaction was stirred under nitrogen at room temperature for 0.5 h. To this suspension of the sodium salt was added cautiously a solution of 3.30 g of ethyl 2-chloroacetoacetate in 10 mL of benzene, and the reaction was stirred at reflux under nitrogen for 16 h. After cooling, the reaction mixture was poured into water, and the aqueous layer was drawn off and extracted with two portions of ether. The combined organic extracts were washed with water, 10% aqueous sodium hydroxide, and brine and dried, and the solvents were removed at reduced pressure to give 1.61 g of dark-brown oil. This material was cyclized without further purification by adding to it ca. 50 mL of poly(phosphoric acid) and heating the mixture on the steam bath with occasional stirring for 0.75 h. The resulting dark-brown reaction mixture was poured into ice water, allowed to warm to room temperature, and extracted with three portions of ether. The combined ethereal extracts were washed three times with water, two times with 10% aqueous sodium hydroxide, with water, and with brine and dried, and the solvent was removed to give 0.667 g of brown oil. This oil was taken up in hexane–benzene (1:1) and chromatographed on 20 g of Woelm silica gel. Elution with benzene gave 0.210 g (14%) of naphthofuran **17** as a pale yellow solid: IR (KBr) 5.89, 6.23 μm; NMR δ 1.20 (d, J = 7 Hz, 3 H, CH**CH**$_3$), 1.47 (t, J = 7 Hz, CH$_2$**CH**$_3$), 2.62, 2.83 (s, 3 H each, Ar**CH**$_3$, furyl **CH**$_3$), 4.22 (s, 3 H, O**CH**$_3$), 4.55 (m, 2 H, **CH**$_2$CH$_3$). Recrystallization from methanol gave the analytical sample, mp 100–101 °C.

Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.13; H, 7.65. Found: C, 72.22; H, 7.70.

(±)-Cacalol Methyl Ether [9-Methoxy-3,4,5-trimethyl-5,6,7,8-tetrahydronaphtho[2,3-*b*]furan] (18). A suspension of 0.129 g of ethyl ester **17** in 15 mL of methanol and 15 mL of 10% aqueous potassium hydroxide was stirred at ambient temperature for 18 h. The reaction mixture was heated to drive off the methanol and then cooled, causing the potassium salt of the naphthofuran carboxylic acid to precipitate. The salt was collected as 0.107 g (80%) of off-white solid which slowly decomposed above 235 °C (IR 6.34 μm). This material was suspended in water, heated, and acidified to give the carboxylic acid as an amorphous solid which began to decompose at 196 °C. This material would not be induced to crystallize and was decarboxylated without further purification. A mixture of 0.066 g of this acid and 0.023 g of copper powder was heated to 210 °C and held at this temperature for 5 min. After cooling, the residue was taken up in hexane–benzene (1:1) and filtered through a short column of Woelm silica gel. Evaporation of the solvents afforded 0.038 g (68%) of (±)-cacalol methyl ether (**18**) as a colorless oil which solidified on standing in the freezer. The IR spectrum (solution) agreed with that reported by Romo for the corresponding derivative of the natural product:[2a] NMR δ 1.15 (d, J = 7 Hz, 3 H, CH**CH**$_3$), 2.38 (d, J = 1 Hz, 3 H, furyl **CH**$_3$), 2.52 (s, 3 H, ArH), 3.99 (s, 3 H, O**CH**$_3$), 7.18 (d, J = 1 Hz furyl H); mass spectrum *m/e* (rel intensity) 244 (100), 229 (53), 215 (17), 206 (64), 190 (49).

(±)-Cacalol [9-Hydroxy-3,4,5-trimethyl-5,6,7,8-tetrahydronaphtho[2,3-*b*]furan] (1). To a suspension of 0.068 g of sodium hydride (50% dispersion in mineral oil, thoroughly washed with hexane) in 3 mL of dry dimethylformamide at 0 °C was added cautiously 0.13 mL of propanethiol. This solution of sodium thiopropoxide was allowed to warm to room temperature and a solution of 0.029 g of (±)-cacalol methyl ether (**18**) in 2 mL of dry dimethylformamide was added. The reaction mixture was stirred under nitrogen at 78 °C for 27 h, cooled, poured into 20 mL of 10% aqueous ammonium chloride, and extracted with two portions of ether. The combined extracts were washed with water and brine and dried, and the solvent was removed to give 0.019 g (70%) of (±)-cacalol as a viscous pale-brown oil which would not crystallize. The IR (solution) was identical with that of the natural product. A solution of 0.017 g of (±)-cacalol in 2 mL of pyridine and 1 mL of acetic anhydride was heated on the steam bath 2 h. The crude acetate was isolated in the usual manner, dissolved in benzene, and filtered through Woelm silica gel to give 0.016 g (80%) of (±)-cacalol acetate as a crystalline solid, the IR (solution) of which was identical with that of the acetate of the natural product. Recrystallization from hexane gave white needles, mp 117–119 °C (lit. mp 119–120 °C[21a] and 115 °C[21b]).

Registry No.—**1**, 62212-09-3; **1** acetate, 69684-55-5; **5**, 53863-68-6; **6**, 69611-11-6; **7**, 69611-12-7; **9**, 69611-13-8; **10**, 69611-14-9; **11**, 69611-15-0; **11** 2,4-dinitrophenylhydrazone, 69611-16-1; **13**, 69611-

17-2; **14**, 69611-18-3; **15**, 69611-19-4; **15** sodium salt, 69622-57-7; **16**, 69611-20-7; **17**, 69611-21-8; **17** free acid potassium salt, 69611-29-6; **17** free acid, 69611-28-5; **18**, 69651-43-0; 5-methoxy-8-dimethyl-3,4-dihydronaphthalene, 69611-27-4; 5-methoxy-8-methyl-1-methylene-1,2,3,4-tetrahydronaphthalene, 69611-26-3; 5-acetoxy-1,8-dimethyl-1,2,3,4-tetrahydronaphthalene, 69611-22-9; 6-bromo-5-methoxy-1,8-dimethyl-1,2,3,4-tetrahydronaphthalone, 69611-25-2; ethyl 2[2-(1-methoxy-4,5-dimethyl-5,6,7,8-tetrahydronaphthaleneoxy)]-3-oxobutanoate, 69611-24-1; *p*-cresol, 106-44-5; ethyl 2-chloroacetoacetate, 609-15-4; δ-valerolactone, 108-29-2.

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Amide Acetal Hydrolysis. 2-Aryl-2-(*N*,*N*-dimethylamino)-1,3-dioxolanes. Rapid and Reversible Ring Opening in Neutral and Basic Solutions. Rate-Determining Decomposition of Hydrogen Ortho Esters in Acidic Solutions

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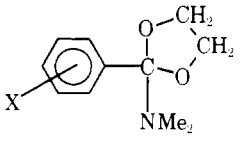
A kinetic and mechanistic investigation of the title amide acetals is reported. At pH >7.5, ring opening to an imidatonium ion (III) is rapid and reversible. Subsequent products are formed at pH >10 by hydroxide attack on III and at pH 7–10 by loss of amine from N-protonated amide acetal. The ion III can be trapped in more acidic solutions (pH <6.5) and its further hydrolysis followed. This proceeds via ring closure reforming amide acetal, which then rapidly decomposes via 1,3-dioxolenium ion. With amide acetal at pH <6.5 hydrolysis proceeds via 1,3-dioxolenium ion, the process leading to this ion now being more rapid than ring opening. At pH >6.0 the formation of the 1,3-dioxolenium ion is the slow step in the overall reaction, but at pH <5.5 there is a changeover, and the rate-limiting step in the overall hydrolysis is the decomposition of the hydrogen ortho ester which results on hydration of the ion.

Recently, we reported[1] a mechanistic investigation of the decomposition in aqueous solutions of the amide acetals Ar-$C(OMe)_2NMe_2$. A scheme was proposed whereby N-protonated amide acetal can lose amine (C–N cleavage), giving rise to a dialkoxycarbonium ion, or the neutral amide acetal can lose alcohol (C–O cleavage), generating an imidatonium ion.

In this paper we report a study of the amide acetals I, molecules which despite their obvious similarity to the substrates of the previous study show a significantly different pattern of behavior.



Ia, X = 4-MeO
b, X = 4-Me
c, X = H
d, X = 4-Cl
e, X = 3-Cl

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