Monocyclic Terpene Alcohols. VIII. *p*-Mentha-2,4(8)-dien-9-ol and *p*-Mentha-2,4(8)-dien-10-ol[1,2]

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Dehydration of ethyl 8-hydroxy-*p*-menth-3-en-9-oate (I) to afford dienic esters was studied under a variety of conditions. It was found that ethyl *p*-mentha-2,4(8)-dien-9-oate (V) was formed predominantly by phosphorus oxychloride–pyridine treatment of I, whereas pyrolysis of the acetate of I yielded ethyl *p*-mentha-2,4(8)-dien-10-oate (IV) and V in a 1:1 ratio. The same ratio was reached by thermal isomerization of V. *p*-Mentha-2,4(8)-dien-9-ol and *p*-mentha-2,4(8)-dien-10-ol were obtained by lithium aluminum hydride reduction of the corresponding esters.

In connection with our studies related to the synthesis of monocyclic terpene alcohols, the dehydration of the easily available[3] ethyl 8-hydroxy-*p*-menth-3-en-9-oate (I) as a potential source of dienic intermediates was investigated.

Treatment of this hydroxy ester with acidic dehydrating agents afforded complex mixtures containing six main components (glpc analysis), whose relative ratio was dependent on the conditions used. These products were isolated by preparative glpc and were submitted to spectral analyses (nmr, uv, and ir) which pointed to structures II–VII (Scheme I).

Structures II and III were confirmed by comparison with authentic specimens synthesized by an independent route.[4]

The stereochemical problem posed by isomers IV and V was settled on the basis of the well-known deshielding effect of an ethoxycarbonyl group,[5] structure V being assigned to that isomer in which the C_3-vinyl proton absorbed at lower field (IV, τ 3.55; V, τ 3.0).

Structure VI was based on spectral and analytical data.[6] Ir bands characteristic of the carbonyl absorption of α,β-unsaturated γ-lactone[7] appeared at 5.67 and 5.92 μ, uv absorption was at λ_{max} 218 mμ (ϵ 12,700), and nmr absorption occurred at τ 5.45, 8.25, and 8.98. While our work was in progress, an optically active form of lactone VI was isolated,[8,9] and the structure and stereochemistry of the four diastereomeric (asymmetric centers C_1 and C_8) keto acids, resulting from its hydrolysis, were elucidated.[10]

The hydrolysis of our racemic lactone afforded two crystalline derivatives, mp 110–112° and 123–124°. The spectral features of the former were consistent with those expected for keto acid XI. Ir absorption was at 3–4.25 and 5.9 μ; nmr absorption occurred at τ 0.9, 8.8, 8.93, and 7.2–8.7 (broad). The poor resolution of the C_1-methyl protons and the broad bands observed in the cyclohexane protons region substantiate the *trans*-*p*-menthane configuration assigned.[11,12]

Properties of the other crystalline compound pointed to the pseudo-acid (lactol) structure XII. Ir absorption was at 2.95 and 5.73 μ; nmr absorption occurred at τ 4.3, 8.8, and 7.2–8.6 (multiplet). In this case, the clearer splitting in the C_1-methyl group and the more acute cyclohexane ring protons envelope observed are consistent with a *cis*-*p*-menthane configuration.[11–13]

In view of the particular aim of our work, no serious attempt was made to isolate the other possible diastereomeric keto acids from the hydrolysis mixture or to elucidate the relative configuration at the C_8 center of our crystalline derivatives.

When lactone VI was reduced with lithium aluminum hydride, a liquid product was obtained with the features expected for diol X. This product afforded a crystalline bis-3,5-dinitrobenzoate derivative, which seemed to be a mixture of epimers because of the C_1-methyl protons' nmr absorption at τ 8.63 and 8.9. An optically active form of diol X has been recently prepared by lithium aluminum hydride reduction of menthofuran photoperoxide.[14]

Structure VII, assigned to the last product present in small amounts in the mixture after treatment of hydroxy ester I with acidic dehydrating agents, was substantiated by spectral data: uv, λ_{max} 219 mμ (ϵ 8200); ir, 5.68 and 5.93 μ; nmr, τ 8.24 and 5.14–5.4.

For preparative purposes, the dehydration of hydroxy ester I with *p*-toluenesulfonic acid in boiling benzene

(1) Parts V–VII of this series were presented at the XIII Meeting of the Real Sociedad Española de Física y Química, Pamplona-San Sebastián, June 1967; *An. Real Soc. Espan. Fis. Quim.*, in press.

(2) Supported by Grant FG-Sp-135 from the U. S. Department of Agriculture.

(3) F. Camps, J. Castells, and J. Pascual, *J. Org. Chem.*, **31**, 3510 (1966).

(4) F. Camps and J. Pascual, *An. Real Soc. Espan. Fis. Quim., Ser. B*, **64**, 167 (1968).

(5) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Ltd., Oxford, 1959, p 121.

(6) Project UR-E-25-(50)-36, Grant FG-Sp-135, U. S. Department of Agriculture, Report 6, Feb 1966–Jan 1967, p 8.

(7) L. V. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1958, p 185.

(8) C. S. Foote, M. T. Wuesthoff, S. Wexler, I. G. Burstain, R. Denny, G. O. Schenk, and K. H. Schulte-Elte, *Tetrahedron*, **23**, 2583 (1967).

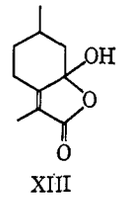
(9) J. A. Hirsch and R. H. Eastman, *J. Org. Chem.*, **32**, 2915 (1967).

(10) C. S. Foote, M. T. Wuesthoff, and I. G. Burstain, *Tetrahedron*, **23**, 2601 (1967).

(11) J. Albaigés, J. Castells, and J. Pascual, *J. Org. Chem.*, **31**, 3507 (1966).

(12) H. Booth, *Tetrahedron*, **22**, 615 (1966).

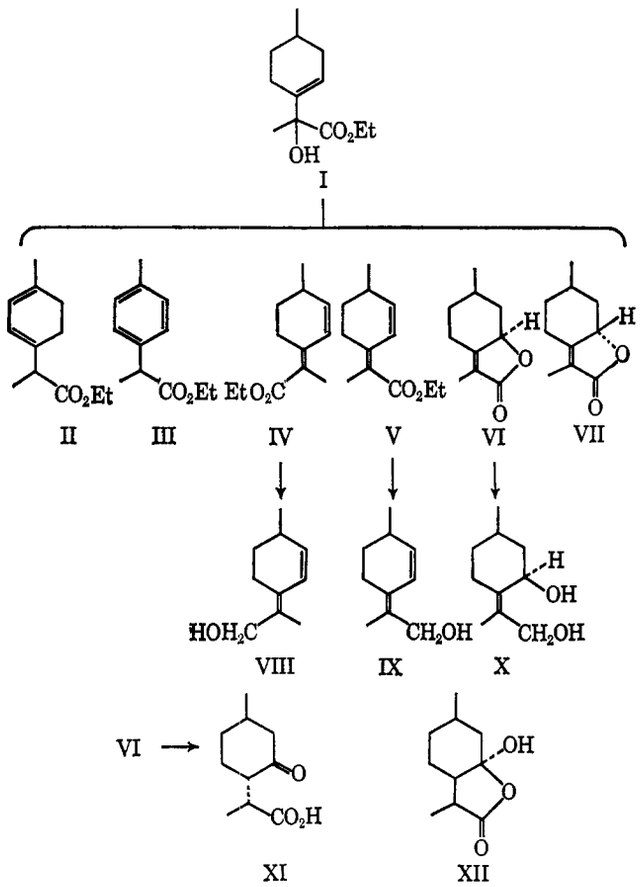
(13) Foote and coworkers[10] isolated two crystalline acids, mp 143–144 and 97–98°, assumed to be identical with the keto acids, mp 146–147 and 97–98°, previously obtained by R. B. Woodward and R. H. Eastman [*J. Amer. Chem. Soc.*, **72**, 399 (1950)] by reduction of the crystalline pseudo-acid XIII with sodium amalgam. The former with a *cis*-*p*-menthane configuration, appears to be mainly in the lactol form, whereas the latter exhibits the properties of a true keto acid and has a *trans*-*p*-menthane configuration. In both cases the configuration at C_8 center was elucidated. It is worth pointing out also that K. J. Crowley [*J. Chem. Soc.*, 4254 (1964)] isolated a keto acid, mp 151°, by hydrolysis of a liquid stereoisomer of XIII but made no structural assignment to it.



XIII

(14) K. H. Schulte-Elte and G. Ohloff, *Helv. Chim. Acta*, **50**, 153 (1967).

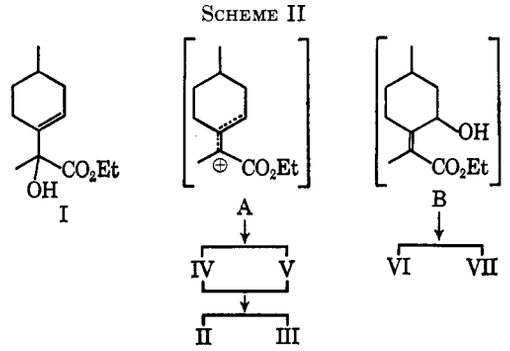
SCHEME I



was studied more closely. The results obtained showed that the amount of the esters IV and V in the mixture reached a maximum (about 50% in a 1:1 ratio) and then decreased steadily, ester II and lactone VI being the major components (about 75%) after prolonged treatment.

In a separate experiment, starting from a 1:1 mixture of esters IV and V, it was found that compounds II and III were formed directly from these esters, whereas lactones VI and VII should arise from hydroxy ester I, through a possible intermediate hydroxy ester B[15,16] (Scheme II).

SCHEME II



To improve our results, other methods of dehydration were investigated. Treatment of hydroxy ester I with phosphorus oxychloride and pyridine afforded ester V almost exclusively. Reduction of V with lithium aluminum hydride yielded *p*-mentha-2,4(8)-dien-9-ol (IX), that was purified *via* the 3,5-dinitrobenzoate derivative, mp 82.5–3.5°, followed by hydrolysis on alkaline aluminum oxide.[17]

From the aqueous mother liquors of this phosphorus oxychloride–pyridine treatment a crystalline by-product, mp 118–120°, was isolated with the properties expected for a pyridinium salt and the molecular formula $C_{17}H_{26}NO_3Cl$, consistent with the addition of pyridine hydrochloride to hydroxy ester I. When this product was refluxed in dry pyridine, a liquid mixture was formed in which the presence of esters II, IV, V, and lactone VI was detected by glpc analysis.

Preparation of ester IV could be accomplished by slow pyrolysis of the acetate of hydroxy ester I at 500° (0.9 mm) which gave an 80–85% 1:1 mixture of esters IV and V. Careful distillation of this mixture afforded ester IV which was submitted to the same treatment described above to yield *p*-mentha-2,4(8)-dien-10-ol (VIII) purified also through its 3,5-dinitrobenzoate derivative, mp 71–72.5°.

To increase the yield of ester IV several methods of isomerization of ester V were attempted and although some promising results were obtained by photochemical or iodine–benzoyl peroxide isomerizations,[18] it was found that the best results were reached by thermal treatment. Thus, submitting fractions rich in isomer V to the same conditions described above for the pyrolysis of the acetate of I, a 1:1 ratio of esters IV and V was obtained; when the temperature was lower, the isomer V was still predominant in the mixture.

The stereospecifity observed in the phosphorus oxychloride treatment is not clear at this stage, but could be explained by some kind of interaction (polar, proton bonding, π complex) between the double bond and the ethoxycarbonyl group in the intermediate state of the dehydration, leading to the predominant formation of V by a kinetically controlled process. This interaction would be absent in the presence of acid reagents that gave the 1:1 thermodynamic ratio of IV:V. However the elucidation of this point would deserve further work before drawing definitive conclusions.

Experimental Section

Melting points were taken on a Koffler hot-stage apparatus and are corrected. Infrared spectra were measured on Perkin-Elmer Infracord 137 and Infracord 137 G spectrophotometers. Ultraviolet spectra were run on a Perkin-Elmer 137 apparatus. The nmr spectra were recorded on a Perkin-Elmer R-10 at 35° operating at 60 Mc/sec with TMS as an internal reference. Bands due to hydroxyl protons in the nmr spectra have been routinely identified by their diamagnetic shift with increasing dilution. The glpc analyses and preparative separations were carried out on an Aerograph A-705 with flame ionization detector on different columns. Fractional distillation was achieved with a Büchi spinning-band column, Dr. H. Abegg system.

Treatment of Ethyl 8-Hydroxy-*p*-menth-3-en-9-oate (I) with *p*-Toluenesulfonic Acid.—Ethyl 8-hydroxy-*p*-menth-3-en-9-oate (I) (1 g) in dry benzene (10 ml) was refluxed under nitrogen in presence of *p*-toluenesulfonic acid (0.2 g). The course of the reaction was monitored by glpc using a 20 ft × 0.375 in. 20% SE-30 on Chromosorb W column at 175°. Analysis of aliquot parts of this mixture revealed the presence of six components besides the starting product, which were isolated by preparative glpc under the conditions above mentioned and identified as com-

(15) By an alternative explanation of formation of lactone VI, see ref 8.

(16) Two optically active isomers of postulate intermediate B (as the acid) have been described, although no structural assignments were made: R. Robinson and G. I. Fray, *Tetrahedron*, **9**, 295 (1960).

(17) J. Castells and G. A. Fletcher, *J. Chem. Soc.*, 3245 (1956).

(18) R. Grewe, E. Nolte, and R. H. Rotzoll, *Chem. Ber.*, **89**, 600 (1956).

pounds II–VII by spectral means. (The spectral data are given in the sections dealing with the preparation of the corresponding products using the most convenient method found.) The relative amounts of these products changed with the time of refluxing. Thus, after 4 hr the following relative amounts were found: II (14), III (2), I (14), IV (26), V (24), VI (14), VII (6). By increasing the reaction time, the relative amounts of esters IV and V diminished whereas those of esters II and III and lactones VI and VII increased. After 24 hr, the following ratios were determined: 36, 9, 3, 3.5, 2.5, 37, and 9.

Lactone VI.—Ethyl 8-hydroxy-*p*-menth-3-en-9-oate (I) (15 g) treated with *p*-toluenesulfonic acid (3 g) in boiling dry benzene (150 ml) for 30 hr under a nitrogen atmosphere afforded, after the usual work-up, a yellowish oil (12.7 g) having a relative ratio similar with that observed above. Fractional distillation in a spinning-band column at reduced pressure yielded already known[4] ethyl *p*-mentha-1,3-dien-9-oate (II) (3 g), bp 95–97° (6 mm), among other fractions containing mixtures of the above mentioned products. The residue of this distillation (6 g) was fractionated at higher vacuum to give lactone VI (3.5 g): bp 87–89° (0.25 mm); $n^{21.5}$D 1.5002; λ_{max}^{EtOH} 218 mμ (ε 12,700); $\lambda_{max}^{CCl_4}$ 5.67, 5.92, 9.13, 9.35, and 9.70 μ; τ_{CCl_4} 5.45 (broad band, half-band width = 20 cps, 1 H), 8.25 (triplet, J = 1 cps, 3 H), 8.98 (doublet, J = 6 cps, 3 H), 7–9.1 (broad absorption, 7 H).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.40; H, 8.84.

From the higher boiling fractions of this distillation, a small amount of product could be isolated by preparative glpc with the spectral features expected for VII: λ_{max}^{EtOH} 219 mμ (ε 8200); $\lambda_{max}^{CCl_4}$ 5.68, 5.93, 8.05, 9.18, and 9.70 μ; τ_{CCl_4} 5.1–5.5 (broad band, 1 H), 8.24 (triplet, J = 1 cps, 3 H), 8.84 (doublet, J = 7 cps, 3 H), 7.3–9 (broad absorption, 7 H).

Ethyl *p*-Mentha-2,4(8)-dien-9-oate (V).—Phosphorus oxychloride (5 ml) was added dropwise under stirring to an ice-cooled solution of ethyl 8-hydroxy-*p*-menth-3-en-9-oate (I) (5 g) in dry pyridine (50 ml) under nitrogen atmosphere. The mixture was kept overnight in a refrigerator. Then, it was hydrolyzed with cool 2 *N* sulfuric acid and extracted several times with ethyl ether. After the usual treatment, the joined organic fractions were evaporated at reduced pressure to yield a colorless oil (2.7 g). Glpc analysis of this oil, under the conditions mentioned above, revealed the presence of V (65–70%) and IV (10–15%) together with minor amounts of II (5–10%) and starting hydroxy ester I (8–10%). Fractional distillation of this oil (13.5 g) in a spinning-band column gave pure ester V (4 g): bp 124° (8 mm), 69° (0.2 mm); n^{25}D 1.5068; λ_{max}^{EtOH} 267.5 mμ (ε 13,500); λ_{max}^{film} 5.86 6.2, 6.35, 8.1–8.3, 8.65, 8.95, 9.1–9.2, 12.2, 12.55, and 12.8 μ; τ_{CCl_4} 2.98 (double doublet, J = 10 cps, J' = 2 cps, 1 H), 4.25 (broad bands, doublet, J = 10 cps, 1 H), 5.85 (quartet, J = 7 cps, 2 H), 8.1 (singlet, 3 H), 8.7 (triplet, J = 7 cps, 3 H), 8.95 (doublet, J = 7 cps, 3 H), 7.2–8.3 (broad band, 5 H).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.93; H, 9.40.

The mother liquors of the dehydration (from 5 g of hydroxy ester I) were extracted with chloroform to give after the usual treatment and evaporation of the organic solvent a thick brown oil (3.5 g), which crystallized by addition of acetone. Recrystallization from methylene chloride–acetone gave bright flakes, mp 118–120°, which turned red upon heating. This product gave a positive halide test (Beilstein) and exhibited the spectral features consistent with a pyridinium salt: λ_{max}^{KBr} 3, 5.75, 6.15, 8, 8.7, 9.82, 12.7, 14, and 14.55 μ; τ_{CCl_4} 0.52 (split doublet, J = 6 cps, 2 H), 1.17–1.57 (multiplet, 3 H), 3.96 (broad band, 1 H), 5.62 (quartet, J = 6 cps, 2 H), 6.92 (broad singlet, 1 H), 7.60 (singlet, 1 H), 8.67 (triplet, J = 6 cps, 3 H), 8.97 (doublet, J = 5 cps, 3 H), 7.4–8.5 (broad absorption).

Anal. Calcd for $C_{17}H_{26}NO_3Cl$: C, 62.12; H, 7.99; N, 4.27; Cl, 10.79. Found: C, 62.19; 62.05; H, 7.93; 7.95; N, 4.33; Cl, 11.27.

When this product (0.5 g) was heated in dry pyridine (5 ml), a liquid (0.2 g) was recovered after the usual treatment, which after glpc analysis (peak enhancement) revealed the presence of compounds II (16%), V (41%), IV (28%), and VI (14%).

Ethyl *p*-Mentha-2,4(8)-dien-10-oate (IV).—A mixture of hydroxy ester I (10.5 g) and melted sodium acetate (10.5 g) in acetic anhydride (105 ml) was refluxed 90 hr under nitrogen atmosphere. After evaporation of the solvent at reduced pressure, the residue was extracted several times with ethyl ether. The joined organic fractions afforded after the usual treatment a brown oil (2 g) which exhibited a single band in the glpc analysis and the features expected for the acetate of I in the nmr spectrum: τ_{CCl_4} 4.2 (broad band, 1 H), 5.9 (quartet, J = 7 cps, 2 H), 8 (singlet, 3 H), 8.4 (singlet, 3 H), 8.8 (triplet, J = 7 cps, 3 H), 9.05 (doublet, J = 6 cps, 3 H), 7.8–8.5 (broad absorption, 7 H). Slow distillation of this crude acetate at 0.9 mm through a 58 × 1.5 cm quartz tube, packed with glass wool, heated at 500°, collecting the exit gases in a cool trap, afforded a yellowish oil (6.2 g), glpc analysis of which revealed the presence of three components: II (17%), IV (42%), and V (41%). Careful distillation of the pyrolysate (21.3 g) in a spinning-band column at reduced pressure afforded pure ester IV: bp 112–113° (5 mm); n^{23}D 1.5032; λ_{max}^{EtOH} 269.5 mμ (ε 14,900); λ_{max}^{film} 5.86, 6.2, 6.33, 8.1, 8.3, 8.65, 8.95, 9.15, 11.6, 12.25, 12.9, and 13.35; τ_{CCl_4} 3.55 (doublet, J = 10 cps, J' = 1.5 cps, 1 H), 4.06 broad bands, (doublet, J = 10 cps, 1 H), 5.82 (quartet, J = 7 cps, 2 H), 8.05 (singlet, 3 H), 8.7 (triplet, J = 7 cps, 3 H), 8.92 (doublet, J = 7 cps, 3 H), 7–8.3 (broad band, 5 H).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.39. Found: C, 74.07; H, 9.56.

Thermal Rearrangement of Esters IV and V.—A mixture of esters IV and V (5.4 g) in a 38:62 ratio was distilled under the same conditions described in the preceding section for the pyrolysis of the acetate of I. The condensed pyrolysate (4.9 g) was analysed by glpc which showed a 1:1 ratio of both esters. No other products were detected. This ratio remained unchanged by further distillation under the same conditions.

Treatment of Esters IV and V with *p*-Toluenesulfonic Acid.—A 1:1 mixture of esters IV and V (2 g) and *p*-toluenesulfonic acid (0.2 g) in dry benzene (20 ml) was refluxed under nitrogen atmosphere. Analysis of aliquot parts by glpc revealed its rapid transformation into esters II and III. After 6 hr, the following ratio was found: II (67%), III (18%), IV (6%), and V(9%). When the reaction was carried out in presence of some drops of water, the reaction was slower and the formation of a small amount of lactone VI was observed. Under these conditions after 36 hr, the following ratio was found: II (56%), III (13%), IV (7.5%), V (18%), and VI (5%).

***p*-Mentha-2,4(8)-dien-9-ol (IX).**—To a well-stirred solution of ester V (95% steric purity) (1.7 g) in dry ethyl ether (20 ml), lithium aluminum hydride (0.25 g) was added at −40° under nitrogen. Stirring was maintained for 10 hr during which the mixture was warmed slowly to room temperature. After the usual treatment, a colorless oil (1.3 g) was obtained which exhibited no carbonyl absorption in the spectrum ir. Dinitrobenzoylation by the conventional procedure yielded a crude dinitrobenzoate derivative (2.9 g) which, by repeated crystallization from ethanol–ethyl ether, gave yellow spheric aggregates: mp 83.5–84.5° (0.9 g); τ_{CDCl_3} 0.85 (multiplet, 3 H), 3.5 (double doublet, J = 10 cps, J' = 1.5 cps, 1 H), 4.3 (broad bands, doublet, J = 10 cps, 1 H), 4.98 (singlet, 2 H), 8.1 (singlet, 3 H), 8.96 (doublet, J = 7 cps, 3 H), 7.4–8.8 (broad absorption, 5 H).

Anal. Calcd for $C_{17}H_{18}N_2O_6$: C, 58.96; H, 5.24; N, 8.09. Found: C, 59.03; H, 5.50; N, 7.84.

Hydrolysis of this derivative (0.9 g) on alkaline aluminum oxide (40 g) under nitrogen using a 2:1 *n*-hexane–benzene elution mixture yielded *p*-mentha-2,4(8)-dien-9-ol (IX) (0.4 g): bp 76.5–77.5° (0.7 mm); n^{23}D 1.5301; λ_{max}^{EtOH} 243 mμ (ε 21,000); λ_{max}^{film} 3.05, 6.15 (weak), 10, 10.5, 12.35, 13.3, and 13.6 μ; τ_{CCl_4} 3.58 (double doublet, J = 10 cps, J = 1.5 cps, 1 H), 4.47 (broad bands doublet, J = 10 cps, 1 H), 5.9 (singlet, 2 H), 8.2 (singlet, 3 H), 8.98 (doublet, J = 6 cps, 3 H), 7.3–8.8 (broad absorption, 5 H).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.65; H, 10.32.

***p*-Mentha-2,4(8)-dien-10-ol (VIII).**—A solution of ester IV (95% steric purity) (2.3 g) in dry ethyl ether (25 ml) was reduced with lithium aluminum hydride (0.35 g) under the same conditions described in the precedent section. After the usual procedure, a colorless oil (1.8 g) was isolated which was submitted to dinitrobenzoylation to give a crude derivative (3.5 g) which by repeated crystallizations from ethanol–ethyl ether yielded pure dinitrobenzoate of VIII: mp 71–72.5°; τ_{CDCl_3} 0.8 (multiplet, 3 H), 3.6 (double doublet, J = 10 cps, J' = 1.5 cps 1 H), 4.23 (broad bands doublet, J = 10 cps, 1 H), 4.93 (singlet, 2 H), 8.08 (singlet, 3 H), 8.95 (doublet, J = 7 cps, 3 H), 7.2–8.7 (broad absorption, 5 H).

Anal. Calcd for $C_{17}H_{18}N_2O_6$: C, 58.96; H, 5.24; N, 8.09. Found: C, 58.71; H, 5.08; N, 7.91.

Hydrolysis of this 3,5-dinitrobenzoate (1.2 g) on alkaline aluminum oxide (30 g) under the same conditions described above

afforded *p*-mentha-2,4(8)-dien-10-ol (VIII) (0.5 g): bp 77.5–79° (0.6 mm); $n^{23}D$ 1.5312; λ_{max}^{EtOH} 245 mμ (ε 28,500); λ_{max}^{film} 3.05, 6.15 (weak), 6.25 (weak), 8.8, 10, 10.5, 12.35, 13.35, and 13.65 μ; τ_{CCl_4} 3.63 (double doublet, J = 10 cps, J' = 1.5 cps, 1 H), 4.36 (broad bands, doublet, J = 10 cps, 1 H), 5.9 (singlet, 2 H), 6.2 (broad singlet, 1 H), 8.2 (singlet, 3 H), 8.98 (doublet, J = 7 cps, 3 H), 7.2–8.8 (broad absorption, 5 H).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 79.14; H, 10.59.

***p*-Menth-4(8)-ene-3,9-diol (X).**—Lithium aluminum hydride (0.5 g) was added to a well-stirred solution of lactone VI (2 g) in ethyl ether (20 ml) at 0° under nitrogen. Stirring was maintained for 10 hr while the mixture was warmed slowly to room temperature. After the usual work-up procedure, a colorless, thick oil (1.8 g) was obtained which failed to crystallize from *n*-hexane after standing several days in the refrigerator. Features of the nmr spectrum of this compound pointed to structure of diol X: τ_{CCl_4} 5.3–6 (broad band), 8.25 (singlet), and 8.95 (doublet). Dinitrobenzoylation by the conventional procedure gave a thick brown oil (4.3 g) which upon repeated crystallization with acetone afforded a bis-3,5-dinitrobenzoate (0.3 g): mp 133–134.5°; τ_{CDCl_3} 0.95 (multiplet), 3.55 (broad band), 4.5 (doublet, J = 12 cps), 4.85 (doublet, J = 12 cps), 7.2–7.9 (broad band), 8.03 (singlet), 8.63 (doublet, J = 4 cps), 8.9 (doublet, J = 4 cps).

Anal. Calcd for $C_{24}H_{22}N_4O_{12}$: C, 51.61; H, 3.97; N, 10.03. Found: C, 51.44; H, 3.92; N, 9.79.

Keto Acid XI and Lactol XII.—A solution of lactone VI (3.6 g) in 25% methanolic potassium hydroxide (36 ml) was refluxed 2 hr under nitrogen atmosphere. The solution was diluted with water and extracted with ethyl ether. The aqueous layer was acidified with 6 *N* hydrochloric acid and extracted with ethyl ether to give after the usual treatment a yellow oil (3.4 g) which crystallized upon cooling. Methylation of this product with diazomethane ethyl ether solution and glpc analysis on a 20 ft × 0.375 in. 20% XF-1150 on Chromosorb W column at 190° revealed the presence of three main components in a 26:62:12 ratio. Recrystallization with benzene–hexane afforded a mixture of crystals, mp 85–105° (0.5 g), which, after three new recrystallizations, gave pure lactol XII (0.1 g): mp 123–124; λ_{max}^{KBr} 2.95, 5.73, 9.3, 10.5, 10.65, 12.05, 12.4, and 13.65 μ; τ_{CCl_4} 4.3 (broad singlet, 1 H), 8.8 (doublet, J = 6 cps, 3 H), 9.05 (doublet, J = 6 cps, 3 H), 7.2–8.6 (multiplet, 7 H).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.18; H, 8.76. Found: C, 65.13; H, 9.01.

From the first mother liquors a new crop of crystals (0.6 g), mp 75–95°, was obtained, which by repeated crystallization from benzene–hexane afforded keto acid XI: mp 110–112°; λ_{max}^{KBr} 3–4.25 (broad), 5.9, 7.78, 7.85, 8.03, 8.15, 8.4, and 10.65 μ; τ_{CCl_4} 0.9 (broad absorption, 1 H), 8.8 (doublet, J = 7 cps, 3 H), 8.93 (doublet, J = 4 cps, 3 H); $\tau_{CCl_4-C_6H_6}$ 8.85 (doublet, J = 7 cps), 9.05 (doublet, J = 4 cps), 7.2–8.7 (broad absorption, 7 H).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.18; H, 8.76. Found: C, 65.15; H, 8.47.

Glpc analysis of the methylated keto acid under the conditions described above gave a single band identified by peak enhancement as the major component (62%) of the original oil. On the other hand, application of the same method to lactol XII gave puzzling results not consistent with the spectral data. Under the conditions described, the methylated lactol exhibited two bands in a similar ratio which corresponded to the two major products of the starting mixture (26 and 62%).

Registry No.—IV, 16434-34-7; V, 16434-35-8; VI, 16434-36-9; VII, 16434-37-0; VIII, 16434-38-1; dinitrobenzoate of VIII, 16434-39-2; IX, 16452-31-6; dinitrobenzoate of IX, 16434-40-5; X, 16434-41-6; XI, 16434-42-7; XII, 16434-43-8; $C_{16}H_{26}NO_3Cl$, 16450-58-1.

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The Synthesis of 2- and 4-Fluoroestradiol[1]

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The 2- and 4-fluoro isomers of estradiol, which were of interest in the National Institutes of Health cancer program, have been synthesized by an unambiguous route *via* a Schiemann type of reaction from the respective amino precursors; the preparation of these as well as the consecutive steps is described below. A remarkably easy formation of a steroid nitrite ester and its decomposition to the corresponding ketone at low temperatures (15–25°) is reported. A striking difference in the intensities of the ultraviolet spectra enables a facile differentiation of the 2- from the 4-substituted series.

The synthesis of the 2- and 4-fluoroestradiol (2- and 4-fluoro-1,3,5(10)-estratriene-3,17β-diol, VIIa and b) was undertaken for the cancer program of the Cancer Chemotherapy National Service Center of the National Institutes of Health.[1,2] The 4-fluoro isomer had been prepared earlier by Neeman and Osawa[3] *via* a lengthy route starting with 19-nortestosterone. This route, however, was inapplicable to the preparation of the 2 isomer and for the 4 isomer the present route appears also to be the preferred one. Our initial attempts to introduce the fluorine by an unpublished procedure[4] requiring ultraviolet irradiation of the pertinent diazotized aminoestradiol 3-methyl ethers in a mixture of anhydrous hydrogen fluoride and dioxane in the presence of a copper powder catalyst were unsuccessful. The melting points reported in this procedure, which were the only physical data given, differed markedly (30–50°) from those found in this laboratory. On the other hand, our physical data for the 4 isomer agree fully with those reported by Neeman and Osawa.

We adopted the Schiemann reaction for the introduction of the fluorine into the aromatic ring., *i.e.*, thermal decomposition of the solid estrone 2- and 4-diazonium fluoroborate salts. For reasons explained below estrone was used as a starting material rather than estradiol and was nitrated with 1 equiv of nitric

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(2) Both 2- and 4-fluoroestradiol were found active in anti-implantation and estrogen tests (30 and 140% of estradiol, respectively) in the laboratories of Dr. J. R. Brooks and Dr. D. J. Patanelli of the Merck Institute for Therapeutic Research, Rahway, N. J. The uterotropic results were confirmed in the laboratories of the National Institutes of Health, Bethesda, Md., while at higher doses (*i.e.*, ten times) both epimers exhibited androgenic activities. With respect to cancer, no information has as yet been received by us from the National Institutes of Health.

(3) N. Neeman and Y. Osawa, *Tetrahedron Lett.*, **28**, 1987 (1963).

(4) This procedure was made available to us through the Cancer Chemotherapy National Service Center, Bethesda, Md. A mixture from this source was purified by thin layer chromatography and tested biologically by E. Hecker and G. Farthofer-Boeckh, *Biochem. Z.*, **338**, 1628 (1963).