evolution of nitrogen and went into solution, which at pH 6–7 with evolution of carbon dioxide afforded the triazole V showing no depression in melting point when admixed with a sample of V obtained from the previous experiment.

Synthesis of 3,5-Bis(4-pyridyl)-1,2,4-triazole (V).—An intimate mixture of isonicotinic acid hydrazide (13.7 g., 0.1 mole) and isonicotinamide (0.1 mole) was heated in an oil bath for 16 hr. at 170–220° but mainly in the vicinity of 200° for last 4 hr. Water formed in the reaction escaped as there was no condenser attached to the flask in which the experiment was being done. The reaction mixture on being cooled, solidified and dissolved on treatment with water (150 ml.) and ammonia (10 ml.). This solution, being adjusted to pH 6–7 with hydrochloric acid, afforded V, 10.5 g.; the mixture melting point with a sample of V obtained by oxidation of IV was not depressed.

Synthesis of 3,5-Bis(4-pyridyl)-1,2,4-triazole-1-carboxhydrazide (IV) from Isonicotinic Acid Hydrazide, Carbon Dioxide, and Hydrazine Hydrate.—Isonicotinic acid hydrazide (25 g., 0.18 mole) suspended in hydrazine hydrate [150 ml., 50% (w./v.), free from ammonia] was saturated with carbon dioxide under external ice cooling and then heated to reflux with a small flame. The reaction mixture became clear on heating and after 8–10 hr. of refluxing, separation of white crystalline material began. The heating to reflux was continued for 18 hr. The reaction mixture was cooled and the white crystalline material that separated was filtered, washed with water, and crystallized from water, in which it is very sparingly soluble, in white needles to afford IV, 4.2 g., m.p. 338–340° dec., no depression when admixed with a sample of IV isolated as by-product.

Synthesis of IV from Isonicotinic Acid Hydrazide, Isonicotinamide, and Carbohydrazide.—A mixture of isonicotinic acid hydrazide (13.7 g., 0.1 mole), isonicotinamide (12.2 g., 0.1 mole), and carbohydrazide (9 g., 0.1 mole) in water (100 ml.) was heated to reflux. During heating the solution became clear and after 4–5 hr. white crystalline material began to separate. After refluxing for 12 hr. the reaction mixture was cooled; the white crystalline solid that separated was isolated and finally crystallized from water to afford IV, 6 g. The mixture melting point with a sample of IV from the previous experiment showed no depression.

Lactols Derived from Steroidal 17a-Oxa-D-homo Lactones

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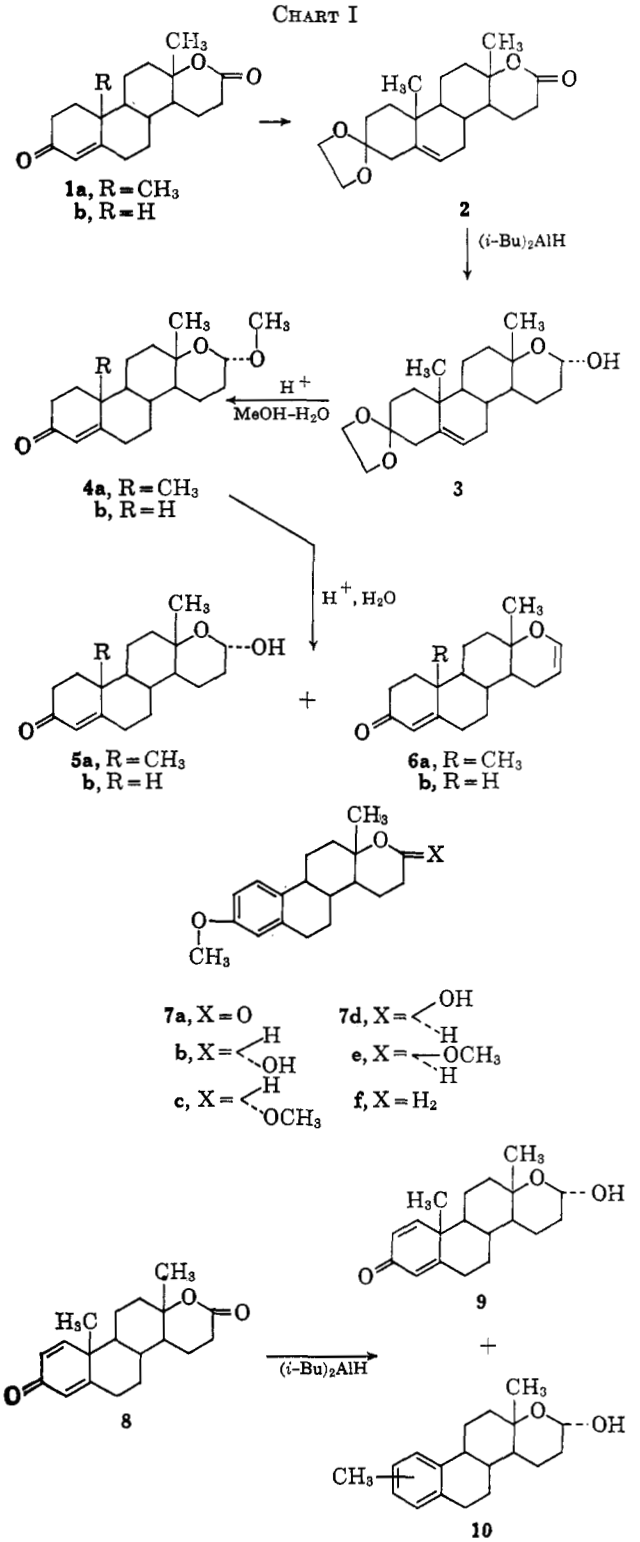
17a-Oxa-D-homoandrosta-1,4-diene-3,17-dione (1-dehydrotestololactone,[1] (**8**) has been found clinically useful in causing objective regression in breast cancer of some patients.[2] Such evidence led to the consideration that the lactols derived from testololactone (**1a**), 19-nortestololactone (**1b**), and 1-dehydrotestololactone (**8**) might have antitumor activity. The synthesis of these lactols by the reduction of the appropriate lactones with diisobutylaluminum hydride in toluene at about −70°, a mode of reduction by which esters are reduced to aldehydes,[3] was accomplished.[4]

Thus, the 3-ethylene ketal **2**, derived from **1a**, was reduced with diisobutylaluminum hydride to the lactol **3** which on methanolysis in aqueous acid to **4a** followed by hydrolysis yielded **5a** and **6a** (see Chart I). In similar fashion, the reduction of 3-methoxy-17a-oxa-D-homoestra-1,3,5(10)-trien-17-one (estrololactone 3-methyl ether, **7a**) with diisobutylaluminum hydride proceeded to the lactol **7b** which, when dissolved in methanol containing some *p*-toluenesulfonic acid, gave the dimethyl ether **7c**. This substance was then reduced with sodium, *t*-butyl alcohol, and ammonia to a 1,4-dihydro derivative which was selectively hydrolyzed to **4b**. The latter compound on hydrolysis yielded a mixture of **5b** and **6b**. An attempt to reduce 1-dehy-

CHART I



(1) J. Fried and R. W. Thoma, U. S. Patent, 2,744,120 (May 1, 1956).

(2) (a) *Cancer Chemother. Rept.*, **11**, 127 (1961); (b) *ibid.*, **41**, Supplement No. 1, 1 (1964); (c) A. Segaloff, J. B. Weeth, K. K. Meyer, E. L. Rongone, and M. E. G. Cuningham, *Cancer*, **15**, 633 (1962).

(3) L. I. Zakharkin and I. M. Khorlina, *Tetrahedron Letters*, 619 (1962).

(4) This Note further illustrates the utility of diisobutylaluminum hydride as a reducing agent capable of yielding lactols from lactones in high yields. The reduction of a lactone to a lactol with diisobutylaluminum hydride was also noted independently by J. Schmidtlin and A. Wettstein, *Angew. Chem. Intern. Ed. Engl.*, **3**, 240 (1964).

drotestololactone **8** selectively at the lactone function with diisobutylaluminum hydride only led to the estratriene **10** and a very low yield of the desired lactol **9**. Dehydrogenation of **4a** at C-1 by microbiological methods is being investigated.

The preponderance of a single isomer in the lactols and their methyl ethers was evident from their n.m.r. spectra which exhibited a singlet (about 3 protons) at 71–73 c.p.s. and a very weak but detectable singlet at 80–84 c.p.s. for the C-18 methyl groups. The consideration that steric repulsions between the C-18 methyl group and hydroxyl group of the lactols in the axial position would outweigh any anomeric[5] effect suggested that the 17a-oxa-D-homo-17α-hydroxy isomer of the lactols should be more stable. Calculations of the molecular rotations of **7d** and **7b** according to methods outlined by Whiffen[6] and Brewster[7] yield values which differ from **7f**[8] (MD 241) by $-J$ and $-J - 105°$ for the 17β-lactol **7d** and its 17-methyl ether **7e**, respectively, and by 0° and +105° for the 17α-lactol **7b** and its 17-methyl ether **7c**, respectively. The observed MD values of 236 and 398 for **7b** and **7c**, respectively, are in close agreement with the calculated values for the α isomers. Hence, from the n.m.r. and rotational data it can be concluded that the lactols and corresponding methyl ethers which have been obtained contain a preponderance (about 95%) of the 17α-oxy isomer.[9]

Experimental Section[10]

3-Ethylenedioxy-17a-oxa-D-homoandrost-5-en-17-one[11] (**2**).—A mixture of 12 g. (40 mmoles) of 17a-oxa-D-homoandrost-4-ene-3,17-dione[12] (**1a**), 1.0 g. of *p*-toluenesulfonic acid, 35 ml. of ethylene glycol, and 1.8 l. of benzene was stirred and slowly distilled over a period of about 6 hr., during which time approximately 600 ml. of benzene was collected. The reaction mixture was then cooled, washed successively with aqueous sodium bicarbonate and water, dried over anhydrous magnesium sulfate, and distilled to dryness under reduced pressure. The resulting crystalline residue was recrystallized from methylene chloride and methanol to yield 8.5 g. (64%) of crude product, m.p. 234–239°. Crystallization of the crude product from methanol–methylene chloride gave a sample: m.p. 235–238°; λ_{max} 5.83 μ; n.m.r. spectrum of 60 (C-19 methyl), 80 (C-18 methyl), 239 (ethylene dioxy), 322.5, and 326 c.p.s. (vinyl proton); $[\alpha]D$ −102°.

3-Ethylenedioxy-17a-D-homoandrost-5-en-17α-ol (**3**).—A solution of 7 g. (20.4 mmoles) of **2** in 1 l. of toluene was distilled until about 100 ml. of toluene was collected. The resulting solution was then cooled to approximately −70° and 24 ml. of a 1.4 *M* diisobutylaluminum hydride in toluene solution (Texas Alkyls, Inc.) was added. Stirring at about −70° was continued for approximately 30 min., after which time the reaction mixture was poured into 100 ml. of water containing 105 ml. of acetic acid and 100 g. of ice. The resulting aqueous mixture was stirred vigorously with 500 ml. of chloroform for about 5 min., and the organic layer was separated, washed successively with water and aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate, and distilled to dryness at reduced pressure. The crystalline residue weighed 5.5 g. (78%) and melted at about 206–212°. Recrystallization of the crude product from methylene chloride–acetone afforded an analytical sample: m.p. 206–209°; λ_{max} 2.76 and 2.96 μ; n.m.r. spectrum at 60 (C-19 methyl), 72 (C-18 methyl), 237 (ethylene dioxy), 304 (multiplet) (C-17β hydrogen), and 321 c.p.s. (vinyl proton); $[\alpha]D$ +7°.

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.49; H, 9.31.

17α-Methoxy-17a-oxa-D-homoandrost-4-en-3-one (**4a**).—To a slurry of 4.75 g. (13.7 mmoles) of **3** with 300 ml. of methanol containing 30 ml. of water, in a nitrogen atmosphere, was added 150 ml. of water containing 6 ml. of 4 *N* hydrochloric acid. The resulting reaction mixture was slowly distilled over a period of about 45 min., and the resulting solution was concentrated under reduced pressure in order to remove a portion of the organic solvent. The crystals which separated were collected by filtration, washed on the filter with water, and dried under reduced pressure to afford 4.0 g. (92%) of crude 17α-methoxy-17a-oxa-D-homoandrost-4-en-3-one, m.p. 145–153°. Recrystallization from methanol gave an analytical sample melting at 152–155°; n.m.r. spectrum at 70 (C-19 methyl), 73 (C-18 methyl), 207 (C-17α methoxyl), 277 (triplet, C-17β hydrogen), and 343 c.p.s. (vinyl proton); $[\alpha]D$ +138°.

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.23; H, 9.45.

17α-Oxa-D-homoandrosta-4,16-dien-3-one (**6a**) **and 17α-Hydroxy-17a-oxa-D-homoandrost-4-en-3-one** (**5a**).—A solution of 1.0 g. (3.1 mmoles) of **4a** in 100 ml. of tetrahydrofuran containing 10 ml. of 0.5 *N* hydrochloric acid was concentrated by slow distillation over a period of about 35 min. and cooled. The crystalline material which precipitated during the concentration was collected by filtration, washed on the filter with water, and dried under reduced pressure. Purification of this crude material was effected by chromatography on 60 g. of silica gel in benzene. Elution of the column with 5% ethyl acetate in benzene followed by recrystallization of the fraction obtained from that eluate from ether and hexane gave 100 mg. of 17a-oxa-D-homoandrosta-4,16-dien-3-one: m.p. 142–143°; n.m.r. spectrum at 71 (C-18, C-19 methyls), 276, 280, 286 (C-16 proton), 345 (C-4 proton), and 371.5 and 378 c.p.s. (C-17 proton).

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.86; H, 9.23.

The 35–50% ethyl acetate in benzene eluates were combined and concentrated to dryness, and the resulting residue was triturated with ether to yield 260 mg. (30%) of 17α-hydroxy-17a-oxa-D-homoandrost-4-en-3-one, melting at about 172–179°. Recrystallization from acetone–hexane gave an analytical sample: m.p. 175–177°; n.m.r. spectrum at 70 (C-19 methyl), 73 (C-18 methyl), 305 (C-17β hydroxyl), and 344 c.p.s. (C-4 hydrogen); $[\alpha]D$ +88°.

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.89; H, 9.48.

3-Methoxy-17a-oxa-D-homoestra-1,3,5(10)-trien-17α-ol (**7b**).—To a solution of 5 g. (16.6 mmoles) of 3-methoxy-17a-oxa-D-homoestra-1,3,5(10)-trien-17-one[13] **7a** in 400 ml. of dry toluene, at about −70°, with stirring was added 25 ml. of about 1.2 *N* diisobutyl aluminum hydride in toluene solution over a period of about 2 min. Stirring at about −60° was continued for approximately 1 hr., after which time the reaction mixture was poured slowly with stirring into a mixture of 120 g. of ice, 126 ml. of acetic acid, and 200 ml. of water. The resulting mixture was stirred for about 30 min., and the organic layer was separated and diluted with chloroform. That organic solution was then washed successively with water and aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate, and distilled to dryness under reduced pressure. Trituration of the resulting crystalline residue with ether afforded 4.7 g. (94%) of crude product, melting at about 160–165°. Two recrystallizations

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(8) G. R. Pettit, U. R. Ghatak, B. Green, T. R. Kasturi, and D. M. Piatak, *J. Org. Chem.*, **26**, 1685 (1961).

(9) When tested by injection, **5a** and **5b** had no anabolic or androgenic activity at 5 mg. and no anti-DCA activity at 2.4 mg., **7b** had no antiandrogenic activity at 5 mg., **5b** and **7b** had no antiestrogenic activity at 1 mg., and **9** exhibited antiestrogenic activity at 0.3 mg. The author is indebted to Drs. F. J. Saunders and E. F. Nutting and Mr. R. S. Jacobs of the Biological Research staff of G. D. Searle and Co. for the biological data reported herein.

(10) The author wishes to thank Dr. R. T. Dillon and staff for the analyses, spectra, and rotations, and Dr. E. G. Daskalakis and staff for the chromatography reported. The infrared spectra and rotations at 25° were determined in chloroform. The n.m.r. spectra were determined in deuteriochloroform on a Varian Model A-60 spectrometer at 60 Mc., with tetramethylsilane as an internal standard. Melting points are uncorrected.

(11) M. Amarosa, L. Caglioti, G. Cainelli, H. Immer, J. Keller, H. Wehrli, M. L. J. Mihailovic, K. Schaffner, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **45**, 2674 (1962).

(12) H. Levi and R. P. Jacobsen, *J. Biol. Chem.*, **171**, 71 (1947).

(13) R. P. Jacobsen, *ibid.*, **171**, 61 (1947).

from acetone gave an analytical sample: m.p. 182–188°; n.m.r. spectrum at 73 (C-18 methyl), 226 (C-3 methoxyl), 233 and 240 (hydroxyl), 307 c.p.s. (multiplet, C-17β hydrogen); $[\alpha]_D$ +78°.

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.33; H, 8.65.

3,17α-Dimethoxy-17a-oxa-D-homoestra-1,3,5(10)-triene (7c).—A mixture of 2.75 g. (9.1 mmoles) of **7b**, 100 ml. of methanol, and 100 mg. of *p*-toluenesulfonic acid was stirred for 1 hr., then concentrated to 40 ml. at room temperature. The product which separated was collected by filtration, washed on the filter with cold methanol, and dried to afford a crude product, weighing 2.4 g. (90%) and melting at about 116–120°. Crystallization of the crude product from methanol gave an analytical sample: m.p. 126–127°; n.m.r. spectrum at 72 (C-18 methyl), 208.5 (C-17α methoxyl), 227 (C-3 methoxyl), and 280.5 c.p.s. (multiplet, C-17β hydrogen); $[\alpha]_D$ +126.5°.

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 76.01; H, 8.75.

17a-Oxa-D-homoestra-4,16-dien-3-one (6b) and 17α-Hydroxy 17a-oxa-D-homoestra-4-en-3-one (5b).—To a mixture of 175 ml. of liquid ammonia, 20 ml. of *t*-butyl alcohol, and 125 ml. of tetrahydrofuran was added a solution of 4.5 g. (14.3 mmoles) of **7c** in 50 ml. of tetrahydrofuran. Approximately 2 g. of sodium was then added to the solution and the blue reaction mixture was allowed to stand for 1 hr. The reaction was quenched with methanol until the color was dissipated, and the mixture was then distilled to dryness under reduced pressure.

The residue was triturated with water. The crystalline product was collected by filtration, washed with water, and dried. The crude dihydro derivative, which melted at 139–140° and weighed 4.3 g., was not purified but was warmed with 55 ml. of methanol containing 8 ml. of 2 *N* hydrochloric acid for 30 min. The solution was cooled and neutralized with aqueous saturated sodium bicarbonate solution and stirred with 200 ml. of methylene chloride. The organic layer was separated, dried over anhydrous magnesium sulfate, and distilled to dryness. The residue, when triturated with hexane, yielded 2.75 g. (63%) of crude 17α-methoxy-17a-oxa-D-homoestra-4-en-3-one, m.p. 120–143°. A solution of this substance in 25 ml. of tetrahydrofuran, 30 ml. of water, and 2 ml. of 2 *M* hydrochloric acid was allowed to stand in a nitrogen atmosphere for 22 hr. The solution was then neutralized with aqueous sodium bicarbonate and extracted with chloroform. The chloroform extract was dried over magnesium sulfate and distilled to dryness. Crystallization of the crude product yielded 2.0 g. of an analytical sample: m.p. 170–173°; λ_{max} 2.80, 2.95, 6.01 and 6.18 μ; n.m.r. spectrum at 72 (C-18 methyl), 305 (multiplet, C-17β hydrogen), 235 and 242 (hydroxyl), and 342 c.p.s. (C-4 hydrogen).

Anal. Calcd. for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.53; H, 9.20.

When 2.5 g. of the crude 17α-methoxy-17a-oxa-D-homoestr-4-en-3-one was instead hydrolyzed at reflux, 400 mg. of 17a-oxa-D-homoestra-4,16-dien-3-one (**6b**), m.p. 134°, was also obtained when the crude product was purified by chromatography on silica gel in benzene and elution with 5% ethyl acetate in benzene. The n.m.r. spectrum of **6b** exhibited maxima at 72 (C-18 methyl), 280 (multiplet, C-16 hydrogen), 352 (multiplet, C-4 hydrogen), and 372 and 378 c.p.s. (C-17 hydrogen).

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.36; H, 8.72.

1- (or 4-) Methyl-17a-oxa-D-homoestra-1,3,5(10)-trien-17α-ol (10) and 17α-Hydroxy-17a-oxa-D-homoandrosta-1,4-dien-3-one (9).—A solution of 5 g. (16.7 mmoles) of 17a-oxa-D-homoandrosta-1,4-diene-3,17-dione[1] (**8**, 1-dehydrotestololactone) in 450 ml. of toluene was distilled until anhydrous, then was cooled to about −70° by means of a Dry Ice–isopropyl alcohol bath. To that solution was then added, with stirring, 16 ml. of 1.4 *M* diisobutylaluminum hydride in toluene solution, dropwise over a period of about 5 min. Stirring of the light yellow solution at about −60° continued for an additional 40 min., after which time the reaction mixture was diluted with approximately 10 ml. of methanol. After that solution was allowed to warm to approximately 0°, about 300 ml. of concentrated aqueous sodium potassium tartrate was added and the organic layer was separated. That layer was washed successively with saturated aqueous sodium potassium tartrate and water, then was dried over anhydrous magnesium sulfate, and distilled to dryness under reduced pressure. The residual glass-like material was purified by chromatography on about 300 g. of silica gel in benzene. Elution of the column with 2% ethyl acetate in benzene afforded about 600 mg. (12%) of 1- (or 4-) methyl-17a-oxa-D-homoestra-1,3,5(10)-trien-17α-ol. Crystallization of the crude fraction from acetone and hexane gave an analytical sample: m.p. 153°; n.m.r. spectrum at 73 (C-18 methyl), 133 (methyl on A ring), and 310 (multiplet, C-17β hydrogen), 421–437 c.p.s. (multiplet, aromatic hydrogens); $[\alpha]_D$ +119°.

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.63; H, 8.82.

Elution of the column with 25% ethyl acetate in benzene afforded a 170-mg. fraction which was triturated with ether to give 90 mg. (1.8%) of crude 17α-hydroxy-17a-oxa-D-homoandrosta-1,4-dien-3-one. Crystallization of the crude product from acetone and hexane gave an analytical sample: m.p. 161–164°; n.m.r. spectrum at 68 (C-19 methyl), 71 (C-18 methyl), 301 (multiplet, C-17β hydrogen), and 363, 377, 423, and 428 c.p.s. (multiplets, C-1, -2, -4 hydrogens); λ_{max}^{MeOH} 243 mμ (ε 15,400); λ_{max} 2.96, 5.98, 6.14, and 6.33 μ; $[\alpha]_D$ 0°.

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.16; H, 8.54.

A Synthesis of Orsellinic Acid

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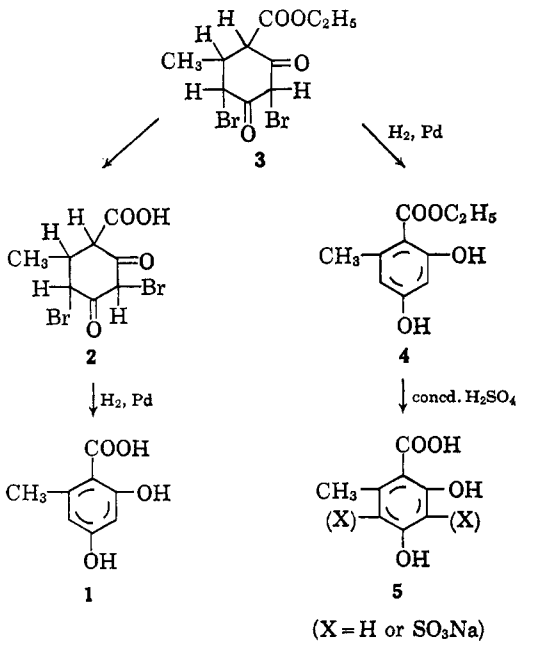
The role of orsellinic acid (**1**) in certain metabolic transformations has been established.[1,2] Investigation of the role of this compound in other transformations has created a need for a reliable synthesis.

The synthesis of Sonn[3] was not successful in this laboratory. Sonn's method, which uses a room temperature alkaline hydrolysis of ethyl orsellinate (**4**) as a final step, repeatedly resulted in decarboxylation upon acidification. Even when the acidification was done cautiously at 0° no product could be obtained. Variations on time and concentration of alkali and also an aqueous acid hydrolysis failed to yield **1**.



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