Methyl 4-Thiochromanone-3-glyoxalate (IV).—A mixture of sodium methoxide (prepared from 2.6 g. of sodium) and 13.5 g. of dimethyl oxalate in 80 ml. of benzene was refluxed for 10 min. in order to dissolve most of the solid. To the cooled solution was added a solution of 9.8 g. of 4-thiochromanone in 50 ml. of benzene and the mixture was stirred at room temperature for 3 hr. to give a light yellow solution. The mixture was hydrolyzed with 150 ml. of water and a small amount of NaOH solution was added. After drawing off the aqueous layer, the benzene solution was extracted with 2% NaOH solution and the combined aqueous solution was acidified with dilute HCl. The yellow crystalline glyoxalate was filtered off, dried, and recrystallized from methanol to give 12.0 g. of IV. Additional 1.5 g. of IV was isolated from the mother liquor. The total yield of IV, m.p. 92–94°, was 13.5 g. (90%).

An analytically pure sample, m.p. 96–97°, was obtained as stout yellow fine needles by further recrystallization from methanol.

Anal. Calcd. for $C_{12}H_{10}O_4S$: C, 57.60; H, 4.03. Found: C, 57.77; H, 4.13.

3-Carbomethoxy-4-thiochromanone (V).—A mixture of 11.0 g. of IV and 5.5 g. of powdered glass was heated at 180° for 30 min. A vigorous evolution of CO took place, all of the gas being evolved in 10 min. After cooling, the dark product was dissolved in acetone and the solution was decanted from the glass and allowed to evaporate. Distillation of the residue gave 7.9 g. (81%) of V, b.p. 158–160° (3 mm.), m.p. 45–47°.

Anal. Calcd. for $C_{11}H_{10}O_3S$: C, 59.46; H, 4.54. Found: C, 59.87; H, 4.62.

3-Carbomethoxy-3-methyl-4-thiochromanone.—To a solution of 3.2 g. of sodium in 50 ml. of methanol was added a solution of 6.0 g. of V in 60 ml. of benzene. The mixture was refluxed for 1 hr., cooled, and treated with 8 ml. of methyl iodide. After 30 min. at room temperature, an additional 8 ml. of methyl iodide was added. The orange solution was stirred at room temperature for 30 min., then refluxed for 2 hr., cooled, neutralized with acetic acid, and evaporated nearly to dryness. The residue was treated with benzene and water, and the organic solution after separating was washed with dilute NaOH solution and with water, dried, and evaporated. Recrystallization of the residue from methanol gave 5.0 g. (78%) of the product, m.p. 82–84°. Further recrystallizations from methanol gave a pure sample, m.p. 85–86°.

Anal. Calcd. for $C_{12}H_{12}O_3S$: C, 61.01; H, 5.12. Found: C, 61.59; H, 5.39.

The Partial Synthesis of 1,2,3,4,4aα,9,10,10aβ-Octahydro-1α-(2-hydroxyethyl)-7-methoxy-2β-methyl-2α-phenanthrenecarboxylic Acid δ-Lactone[1]

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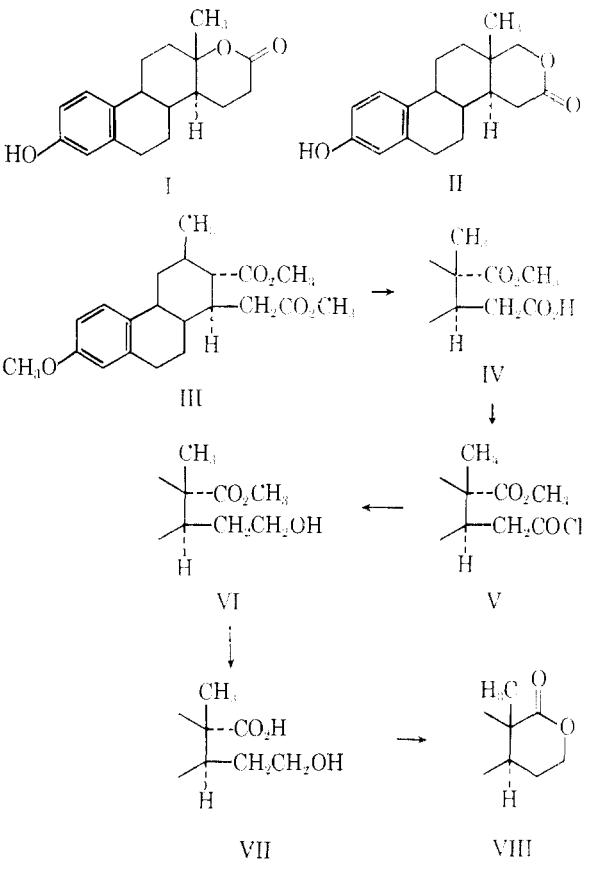
Interest in steroidal lactones was stimulated by the recent effective use of the spirolactones in adrenal pathology. Two different ring D lactones (I and II) derived from estrone are known (see Scheme I).[2] This paper describes the preparation of the methyl ether of a third one (VIII).

The infrared spectra[3] for the three lactone methyl ethers were different in that the carbonyl band of Westerfeld's lactone I (as the methyl ether) was at 1717 cm.$^{-1}$, or 7 cm.$^{-1}$ lower than the new lactone methyl ether VIII. This may be due to the increased strain in the ring of this lactone VIII caused by interaction between the 17-ester group and the C-18 methyl group. The methyl ether of Huffman's lactone II absorbed 9 cm.$^{-1}$ lower in the carbonyl region. In this lactone there would be even less interaction of the type mentioned above than in the methyl ether of estrolactone I.

SCHEME I



The n.m.r. spectrum[4] for methyl ether VIII showed τ values of 2.83, 3.11, and 3.37 for the aromatic protons; 6.23 for the methoxy protons; 8.76 for the C-18 methyl protons; and 5.57 (multiplet) for the structure CH_2OCO, as expected. The spectrum for estrolactone 7-methyl ether had values of 2.83, 3.11, and 3.38 for the aromatic protons; 6.24 for the methoxy protons; and 8.65 for the C-18 methyl protons. The absence of the 5.57 band in the spectrum of estrolactone 7-methyl ether is in agreement with structure I since it does not have the group CH_2OCO. The τ-value for the C-18 methyl protons of Δ^1-testololactone (lactone structure corresponds to that of estrolactone) is 8.60. Therefore, the shift to 8.65 for estrolactone 7-methyl ether (I) may be expected.

Experimental Section[5]

Hemimethyl Ester (IV).—7-Methoxydimethyl marrianolate[6] (1.08 g.) (III), in 20 ml. of methanol (refluxing), was treated with 0.04 *M* K_2CO_3 in 5-ml. aliquots every 15 min. for 4–5 hr. Faster addition of the carbonate tended to cause precipitation. The alcohol was evaporated, and the concentrate was transferred to a separatory funnel with carbonate, washed well with ether, and acidified to pH 1 with concentrated HCl. The precipitated oil was extracted with ether. The ether was washed with water and evaporated to give 1.0 g. of IV which melted at 90–92° after crystallization from aqueous acetone.

Anal. Calcd. for $C_{20}H_{26}O_8$: C, 69.34; H, 7.56; neut. eq., 346. Found: C, 69.11; H, 7.50; neut. equiv., 330.

(1) Supported in part by U. S. Public Health Service Grant HD-01199 and Research Career Development Award AM-14,013.

(2) W. W. Westerfeld, *J. Biol. Chem.*, **143**, 177 (1942); R. P. Jacobsen, *ibid.*, **171**, 61 (1947); M. Keller and J. Weiss, *J. Chem. Soc.*, 1247 (1951); M. N. Huffman, M. H. Lott, and J. Ashmore, *J. Biol. Chem.*, **196**, 367 (1952).

(3) Infrared spectrophotometry was performed on a Perkin-Elmer 421 instrument using KBr pellets.

(4) Performed through the courtesy of Dr. Edward Becker, Squibb Institute for Medical Research; $CDCl_3$ was used as solvent.

(5) All melting points were taken on a Fisher-Johns apparatus, uncorrected.

(6) J. C. Touchstone, W. H. Elliott, S. A. Thayer, and E. ... *Am. Chem. Soc.*, **77**, 3562 (1955).

Hemimethyl Ester Acid Chloride (V).—The monoester IV (572 mg.) was covered with 5 ml. of redistilled oxyalyl chloride, cooled in an ice bath, and allowed to stand for 1 hr. The excess oxalyl chloride was removed *in vacuo*. Dry benzene was added to the residue and distilled *in vacuo* to remove last traces of chlorinating agent. This acid chloride was used in the next step without further purification.

1,2,3,4,4aα,10aβ-Octahydro-1α-(2-hydroxyethyl)-7-methoxy-2β-methyl-2α-phenanthrenecarboxylic Acid δ-Lactone (VIII).—The acid chloride V was dissolved in 15 ml. of dry ether and at once added to a solution of 35 mg. of lithium aluminum hydride in 15 ml. of dry ether maintained at $-10°$ and protected with dry nitrogen. The thick milky gel was stirred at $-10°$ and protected with dry nitrogen. The thick milky gel was stirred at $-10°$ for 1 hr. and at room temperature for an additional hour. Then 20 ml. of 1% H_2SO_4 was added with stirring and the mixture was partitioned between 200 ml. of ether and 100 ml. of 1% H_2SO_4. The ether layer was washed with 3% K_2CO_3 and water. The ether was evaporated to give 444 mg. of an oil representing a mixture of the lactone VIII and diol. While refluxing this oil in 20 ml. of ethanol, 11.2 g. of NaOH in 100 ml. of 50% ethanol was added in 25-ml. aliquots every hour for 4 hr. After most of the alcohol was evaporated, the reaction mixture was diluted with water and extracted with ether. The alkaline phase was acidified with concentrated H_2SO_4, ether was added, and the two layers were shaken intermittently to form the lactone. The aqueous phase was separated and re-extracted with ether. The combined ether phases were washed three times with water, with 5% $NaHCO_3$, and again with water, then evaporated to give 248 mg. of VIII. This lactone was recrystallized from a mixture of acetone–petroleum ether (b.p. 60–80°), aqueous ethanol, and aqueous acetone to provide colorless crystals, m.p. 170–171°.

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.74; H, 7.94.

The melting point of this product was depressed 20° by admixture with the methyl ether of lactone I. On admixture with the methyl ether of lactone II the depression was 30°.

Myelographic Agents. II. Some Iodophthalates[1]

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As part of our extensive program in the field of radiopaque, diagnostic agents we have prepared series of 3- and 4-iodophthalates, 5-iodoisophthalates, and iodoterephthalates (Table I).[2] For the most part, these compounds were synthesized as potential myelographic agents. When the liquid members of these series were injected into the subarachnoid space of cats and dogs, they permitted visualization of the details of the spinal-cord structure. Many of these compounds were eliminated from the animals in periods ranging from a few weeks to a few months.

The bis esters were prepared from the iodo acids and an alcohol with an acid catalyst. The mixed esters of 3-iodophthalic acid were prepared from 3-iodophthalic anhydride. When the anhydride was refluxed with methanol or 1-butanol, a half ester was obtained. By analogy with the reactions of 3-nitrophthalic anhydride[3] and the preparation of the two half ethyl esters of 3-iodophthalic acid,[4] it is presumed that the isolated products were the 2-esters. The sodium salts were prepared from the half esters and allowed to react with an alkyl halide or tosylate; the mixed esters were obtained.

The mixed 5-iodoisophthalate esters were prepared generally by the reaction of alkyl halides, sulfates, or tosylates with the half ester sodium salts (Table II). The latter were prepared by partial hydrolysis of the bis esters.

Paper I: J. Siggins, J. H. Ackerman, and A. A. Larsen, *J. Med.* **8**, 728 (1965).

any of the compounds listed in Table I are mentioned in British 9,083 (May 31, 1961); *Chem. Abstr.*, **56**, 4683*h* (1962).

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Chaudhari and K. S. Nargund, *J. Univ. Bombay*, **A17**, 25

Experimental Section

Iodophthalic Acids.—3-Iodophthalic acid was prepared from 3-aminophthalic acid by a procedure similar to that of Kenner and Mathews.[5] 4-Iodophthalic acid was prepared from 4-nitrophthalic acid. The nitro group was reduced to the amine with Raney nickel and hydrazine hydrate by the general procedure of Balcom and Furst.[6] The amine was diazotized and converted to the iodo compound by the Sandmeyer reaction. 5-Iodoisophthalic acid was prepared from 5-aminoisophthalic acid by a procedure similar to that of Grahl.[7] Iodoterephthalic acid was prepared from nitroterephthalic acid by the method used to prepare 4-iodophthalic acid.

3-Iodo-2-methoxycarbonylbenzoic Acid.—A mixture of 137 g. (0.50 mole) of 3-iodophthalic anhydride[8] and 350 ml. of absolute methanol was refluxed for 20 hr. The excess methanol was removed under reduced pressure. The residue (163 g., m.p. 125–140°) was recrystallized from dilute methanol and then benzene to give 81.4 g. (53%) of colorless, elongated prisms, m.p. 164–165°.

Anal. Calcd. for $C_9H_7IO_4$: I, 41.47; neut. equiv., 306.1. Found: I, 41.78; neut. equiv., 306.4.

Sodium 3-Iodo-2-methoxycarbonylbenzoate.—To a solution of 306 g. (1.0 mole) of 3-iodo-2-methoxycarbonylbenzoic acid in 1 l. of acetone was added 505 ml. of 2.0 *N* (1.0 mole) NaOH. Acetone was added to turbidity, and the mixture was cooled overnight. Solid separated and was collected and dried at 100° to give 209.7 g. (64%) of colorless product.

Sodium 2-butoxycarbonyl-3-iodobenzoate was prepared in a similar manner.

Sodium Alkyl (or Alkoxyalkyl) 5-Iodoisophthalates. Sodium Butyl 5-Iodoisophthalate.—A solution of 634 g. (1.6 moles) of undistilled dibutyl 5-iodoisophthalate (**46**) in 2.5 l. of dimethylformamide was cooled to 5° and a solution of 62.8 g. (1.6 moles) of NaOH pellets in 500 ml. of water was added in one batch with rapid stirring. After 2 min. the reaction had warmed to about 40° and was then heated on a steam bath at 78–85° for 0.5 hr. The solvents were removed by distillation (reduced pressure) to give a residue of diester, half ester sodium salt, and disodium salt which was stirred with about 3 l. of water at 85°. The aqueous layer was separated from the insoluble diester by decantation and was treated with Darco G60, filtered, and cooled to 5°. The crystalline half ester sodium salt crystallized and was removed by filtration and washed with pentane. The slightly damp solid was dissolved in 2.5 l. of hot water. The solution was treated with Darco G60, filtered, and cooled. The solid was removed by filtration, washed with pentane, and dried at 90° *in vacuo* to give 420 g. (73%) of colorless needles: neut. equiv., 370 (calcd., 370).

The other sodium alkyl (or alkoxyalkyl) 5-iodoisophthalates (Table II) were prepared in a similar manner.

Alkyl and Alkoxyalkyl *p*-Toluenesulfonates.—The *p*-toluenesulfonates were prepared from a number of alcohols by the general procedure of Tipson.[9] The tosylates made were the propyl,[10] butyl,[11] methoxyethyl,[9] 2-ethoxyethyl,[9] 2-butoxyethyl,[9] 3-methoxypropyl, 3-ethoxypropyl,[12] 3-propoxypropyl, 3-methoxybutyl,[13] 2-(2-ethoxyethoxy)ethyl,[14] 2-(2-butoxyethoxy)ethyl, and 1,3-diethoxy-2-propyl. These tosylates were used as intermediates to prepare mixed esters.

Most of the alcohols used for the preparation of the tosylates are commercially available (Eastman, Aldrich). 3-Methoxypropanol[15] was prepared from 3-methoxypropionitrile. Reaction of the nitrile with ethanol and concentrated H_2SO_4 gave ethyl 3-methoxypropionate which was converted to the alcohol with lithium aluminum hydride.

3-Propoxypropanol[16] was prepared from 3-propoxypropionitrile in the same manner. The nitrile was made by cyanoethylation[17] of 1-propanol.

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