[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE CHEMICAL DIVISION OF MERCK & CO., INC.]

Synthesis of a Tricyclic Analog of Cortisone

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RECEIVED FEBRUARY 27, 1956

The conversion of tricyclic methyl hydroxy ketone I in ten steps to the open D-ring analog XIV of cortisone propionate is described. Biological tests failed to show appreciable cortisone-like activity for XIV.

The goal of a number of investigators[1] in the past few years has been the preparation of a simple analog of an adrenal steroid hormone which might show the biological activity of the natural material after which it was modeled. Although very weak life maintenance activity has been claimed for benzoylcarbinol and several dibenzyl derivatives,[1a,b] and certain cyclic glycoloylcarbinols show deposition of liver glycogen at very high dose levels,[1b] there seems to be no evidence that any of the numerous synthetic analogs that have been prepared[1] have more than a faint trace of adrenal cortical hormone activity.

Despite this lack of success with simple analogs, the possibility remains that a compound more closely related in structure to the adrenal cortical hormones than those heretofore prepared might have appreciable biological activity. The high estrogenic potency of the open D-ring doisynolic acids[2] suggested that a completed steroid D-ring might not be necessary for hormonal activity. We decided accordingly to investigate the synthesis of structure XIV, an open D-ring analog very similar to cortisone and yet reasonably easy to prepare from our steroid total synthesis[3] intermediates.

Alkylation of methyl hydroxy ketone I[4] with allyl iodide proceeded in the same manner as with methallyl iodide[5] to yield 2β-methyl-2α-allyl hydroxy ketone II.[6] Sodium borohydride reduction of the latter provided a good yield of the corresponding 1β,4β-diol III.[7] Methylation of the C_1-hydroxyl group of this diol proved to be somewhat difficult. Several of the conditions normally used to methylate sugars (silver oxide—methyl iodide and sodium hydride—methyl sulfate) failed to give appreciable yields of ethers. When III was heated with potassium in benzene and then treated with methyl iodide,[8] a mixture of 1-monoether IV (3 parts) and 4-monoether V (2 parts) was obtained along with either unchanged diol III or the dimethyl ether VI, depending upon the conditions. Alumina chromatography served to separate the products in a satisfactory manner. The least polar bis-ether VI was eluted first followed by the two monoethers (IV and V). On the basis of the expected lesser polarity of the 4-hydroxy than the 1-hydroxy group,[7] the desired 1-methyl ether structure IV seemed likely for the monoether first eluted. Attempted acetylation of the latter substance with acetic anhydride in pyridine returned 97% of the starting compound, while under similar conditions both diol III and monoether V were converted to the 1-acetates. Thus the less-polar monoether must be compound IV.

Conversion of the allyl side chain in IV to a dihydroxy acetonyl group was carried out as follows: selective hydroxylation of the terminal double bond of IV with osmium tetroxide provided a mixture of stereoisomeric glycols VII. This mixture was subjected to acylation with a limited amount of propionic anhydride in a mixture of benzene and pyridine at room temperature. Preparation of the propionate was chosen in order to augment selective acylation of the primary hydroxyl group and at the same time yield a final product that could be tested biologically as the ester. There was obtained a mixture that was separated chromatographically into 25% of a diester fraction and 65% of a monoester fraction (VIII). The latter, without further purification, was oxidized with the chromium trioxide–pyridine reagent. Chromatography of this product yielded 45% of ketol propionate IX along with 20% of a non-reducing more polar mixture that appeared to be incompletely oxidized. Reoxidation of the latter substance provided an additional 15% of IX. Compound IX reduced blue tetrazolium reagent and showed infra absorption bands at 5.75 μ (propionate carbonyl), 5.8 μ (ketol carbonyl) and 5.87 μ (4-carbonyl). Mild acid hydrolysis of IX gave X, the open D-ring analog of 11-dehydrocorticosterone propionate. With hydrogen cyanide, IX was converted in excellent yield to the corresponding cyanohydrin XI. Dehydration of the latter led to α,β-unsatu-

(1) For example see (a) W. H. Linnell and I. M. Roushdi, *Quart. J. Pharm.*, **14**, 270 (1941); *Nature*, **148**, 595 (1941); (b) G. Brownlee and W. M. Duffin, British Patent 550,262, May 14, 1942; U. S. Patent 2,376,415, May 22, 1945; (c) L. Long and A. Burger, *J. Org. Chem.*, **6**, 852 (1941); (d) J. Walker, *J. Chem. Soc.*, 347 (1942); (e) W. C. J. Ross, *ibid.*, 538 (1945); (f) G. P. Hager and H. A. Shonle, THIS JOURNAL, **68**, 2167 (1946); (g) G. P. Hager and R. M. Burgison, *J. Am. Pharm. Assn. Sci. Ed.*, **39**, 7 (1950); (h) A. L. Wilds, *et al.*, THIS JOURNAL, **71**, 2132, 3946 (1949); **72**, 2388 (1950); **76**, 1733, 1737 (1954); (i) D. R. Satriana, A. Loter and M. M. Baizer, *ibid.*, **73**, 866 (1951); (j) K. Rorig, Abstracts of Papers, 119th Meeting, Am. Chem. Soc., Boston, Mass., April, 1951, p. 20M; (k) J. H. Burckhalter, *et al.*, THIS JOURNAL, **74**, 187 (1952); **76**, 4112 (1954); (l) D. Papa, H. F. Ginsberg and F. J. Villani, *ibid.*, **76**, 4441 (1954); (m) G. W. Stacy, R. A. Mikulec and L. D. Starr, Abstracts of Papers, 128th Meeting, Am. Chem. Soc., Minneapolis, Minn., Sept., 1955, p. 49-O; (n) J. D. Billimoria, *et al.*, *J. Chem. Soc.*, 2626 (1953); 3257 (1954); 1126 (1955).

(2) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publ. Corp., New York, N. Y., 1949, pp. 346–354.

(3) G. I. Poos, R. M. Lukes, G. E. Arth and L. H. Sarett, THIS JOURNAL, **76**, 5031 (1954), and references therein.

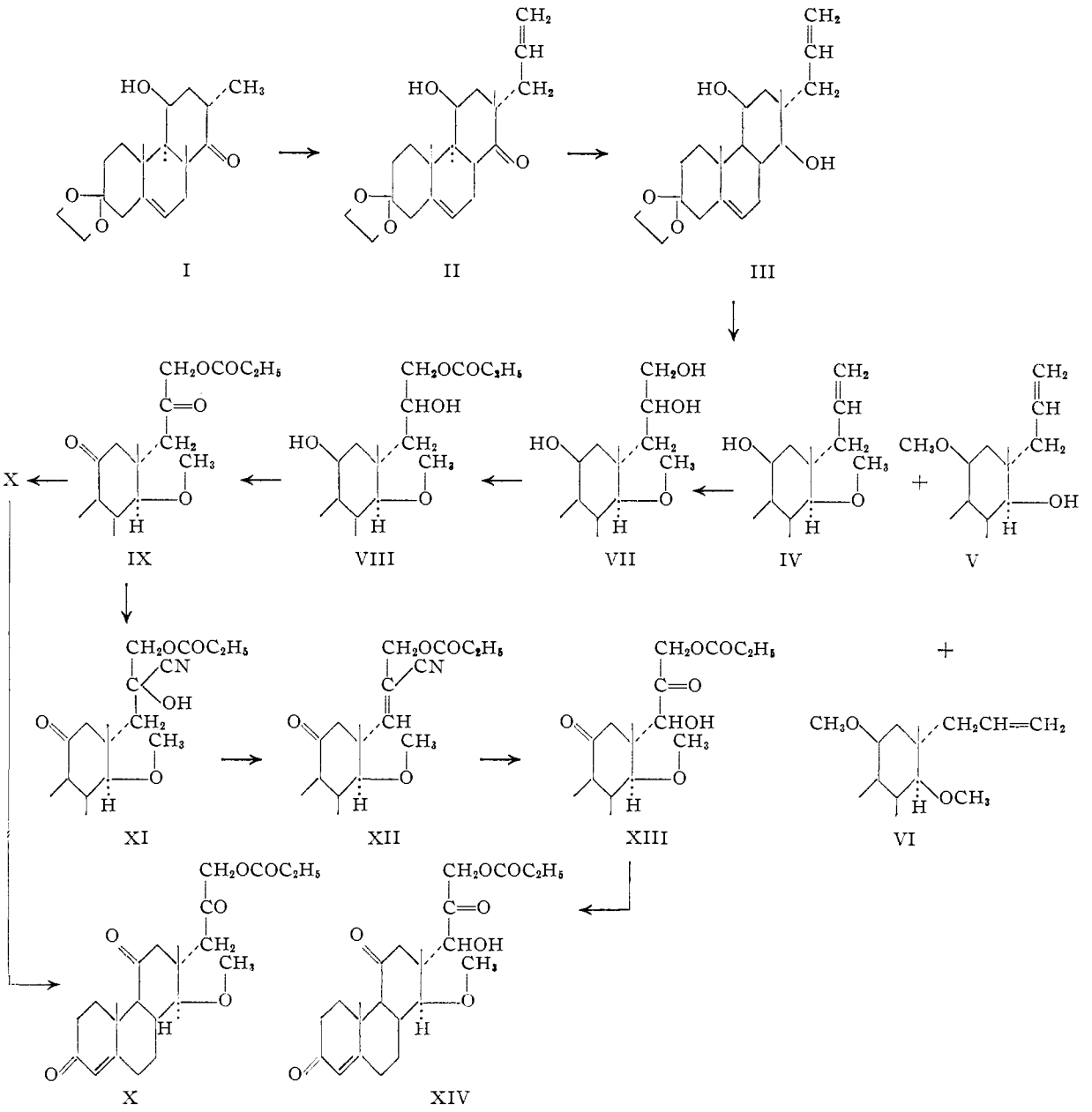
(4) R. M. Lukes, G. I. Poos, R. E. Beyler, W. F. Johns and L. H. Sarett, *ibid.*, **75**, 1707 (1953).

(5) L. H. Sarett, W. F. Johns, R. E. Beyler, R. M. Lukes, G. I. Poos and G. E. Arth, *ibid.*, **75**, 2112 (1953).

(6) This compound was first prepared by Dr. W. F. Johns in connection with some earlier work in these laboratories.

(7) A 1β (equatorial) configuration was assigned to the new hydroxyl group by analogy with results of lithium aluminum hydride reduction of the C-1 keto group in a related tricyclic hydroxy ketone; G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

(8) J. R. Lewis and C. W. Shoppee, *J. Chem. Soc.*, 1375 (1955); *Chemistry and Industry*, 897 (1953).



rated nitrile XII (55%) which was hydroxylated with potasium permanganate.[9] As might be expected the yield of desired dihydroxy acetone derivative was low; 24% of compound XIII was obtained. It was hydrolyzed with *p*-toluenesulfonic acid in acetone to produce the analog of cortisone propionate XIV.

Open D-ring analog XIV was tested in the local granuloma,[10a] eosinophil[10b] and liver glycogen[10c] assays against cortisone propionate as positive control. A weak, equivocal inhibition of granuloma formation in the local test was produced by XIV but no effect was obtained in the eosinophil and liver glycogen assays; cortisone propionate was fully active in the same tests. The analog X of 11-dehydrocorticosterone was also tested and showed no significant activity in the same assays.

This result points up further the high degree of structural specificity inherent in adrenal cortical hormone activity. In the cortisone analog, all of the functional groups are present and in the same general relationship as in cortisone. The stereochemistry at all of the carbon atoms but C_{2a} (C_{17}-steroid nomenclature) is known to be the same as in the adrenal steroids. The ether oxygen atom at C_1 is in the position (β) of the steroid C_{15}-methylene group while the ether-methyl group can occupy the steroid C_{16}-position. At C_{2a} the situation is not so straightforward since two isomers are possible and only one was obtained from permanganate hydroxylation of the unsaturated precursor XII. From an inspection of molecular models, it appeared that the isomer of XII most

(9) R. Tull, R. E. Jones, S. A. Robinson and M. Tishler, THIS JOURNAL, **77**, 196 (1955).

(10) Tests carried out by (a) Drs. C. A. Winter, (b) R. C. Mason and (c) C. C. Porter of the Merck Institute for Therapeutic Research.

closely related to Δ^{17}-20-cyanopregnenes was definitely favored. Hydroxylation of this isomer from the less hindered (rear) side of the molecule to produce the same configuration at C_{2a} as in cortisone at C_{17} (hydroxyl α-oriented) seems probable. Thus it would appear from the biological results that free rotation about C_1 and C_2 in the tricyclic analog allows a different constellation of atoms than in the more rigid tetracyclic steroid.

Acknowledgment.—The authors are indebted to Mrs. Rae Taub for valuable technical assistance.

Experimental[11]

2β,4b-Dimethyl-2-allyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4β-ol-1-one (II).[6]—Four grams of methyl hydroxy ketone I[4] in 80 ml. of benzene was dried by distilling *ca.* 30 ml. of the solvent. The solution was cooled to about 40° and treated with 20 ml. of *t*-butyl alcohol containing 0.8 g. of potassium followed by 3 ml. of redistilled allyl iodide. After 50 minutes, the potassium iodide which had separated was collected on a filter and washed with benzene. The filtrate was diluted with ether, washed with water, dried and concentrated to dryness. Chromatography on 170 g. of acid-washed alumina gave 3.9 g. of crude crystalline II from the 3:7 ether–petroleum ether fractions. Recrystallization from ethanol and then ether provided 2.5 g. (55%) of allyl derivative II, m.p. 145–147°. A sample was recrystallized from ether for analysis, m.p. 148–150°; λ_{max} 2.81, 5.94, 6.07 μ.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.68; H, 8.13.

2β,4b-Dimethyl-2-allyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-1β,4β-diol (III).—Five grams of methyl allyl hydroxy ketone II in 50 ml. of methanol was treated with 1.0 g. of sodium borohydride. After 1.8 hr. at room temperature, the reaction mixture was heated under reflux for 10 minutes. Dilution with water followed by distillation of the methanol *in vacuo* provided a suspension of crystals which were collected by filtration, washed with water and dried. Recrystallization from acetone gave 3.99 g. (80%), m.p. 191–194°. A sample recrystallized from acetone and then ether for analysis showed m.p. 194–195.5°; λ_{max} 2.85, 2.9 and 6.10 (weak) μ.

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.28; H, 8.96.

Acetylation of 100 mg. of III was carried out in 1 ml. of pyridine and 0.5 ml. of acetic anhydride on the steam-bath for 25 minutes. The cooled mixture was diluted with water and the crystalline 1-monoacetate was collected, washed and dried; 103 mg., m.p. 125–135°. The analytical sample melted at 137–140° after recrystallization from methanol and ether–petroleum ether; λ_{max} 2.82, 5.85, 6.10 (weak) μ.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 71.05; H, 8.90.

2β,4b-Dimethyl-1β-methoxy-2-allyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4β-ol-(IV).—The diol III, 260 mg., was dissolved in 10 ml. of dry benzene and to the solution was added 50 mg. of potassium metal. The mixture was heated under reflux with rapid stirring for 1 hr. and then was cooled to room temperature and treated with 0.5 ml. of methyl iodide. The reaction mixture was stirred at room temperature for 3 hr., and then excess potassium was destroyed by the addition of ethanol. The reaction mixture was distributed between water and ether, and the aqueous phase was extracted with ether. The combined ether solution was washed with water, dried and concentrated to dryness under vacuum to yield 270 mg. of a yellow gum. The entire residue was dissolved in 25 ml. of 1:9 ether–petroleum ether and adsorbed onto 11 g. of acid-washed alumina. Elution with 2:8, 3:7 and 4:6 ether–petroleum ether gave 150 mg. of crude crystalline 1-methyl ether IV which after recrystallization from petroleum ether amounted to 108 mg. (40%), m.p. 121–124° and 135–137°. Several recrystallizations from petroleum ether provided a sample with m.p. 125–126° and 135–137°; λ_{max} 3.08 and 6.09 μ.

(11) Melting points were determined on a Kofler micro hot-stage and infrared spectra are of the crystalline solids in Nujol.

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.94; H, 9.82.

Further elution with 4:6 ether–petroleum ether gave mixtures followed by 44 mg. (17%) of 4-methyl ether, m.p. 108–113°. A sample recrystallized from petroleum ether melted at 112–115°, showed λ_{max} 2.82 and 6.08 μ and began to melt at 95° when mixed with IV. Acetylation (acetic anhydride–pyridine, 100°, 20 minutes) gave the corresponding 1-acetate, m.p. 122–124°, from petroleum ether; λ_{max} 5.78 and 6.08 (weak) μ.

Finally, the column was eluted with ether which gave 50 mg. of impure recovered starting diol.

When the reaction was run using a larger proportion of potassium (100 mg. for 200 mg. of diol) and under reflux overnight, chromatography yielded from the 1:9 ether–petroleum ether fractions 25% of the 1,4-dimethyl ether. It was purified by recrystallization from methanol and petroleum ether and had m.p. 92–93°, λ_{max} 6.08 μ. In this case, each of the monoethers described above was found, but no starting diol was recovered.

Attempted Acetylation of IV.—A solution of 37 mg. of IV in 0.5 ml. of pyridine and 0.25 ml. of acetic anhydride was heated in the steam-cone for 15 minutes. The cooled mixture was diluted with water, whereupon 36 mg. of unchanged IV, m.p. 125° and 135°, precipitated.

Hydroxylation and Acylation of IV.—The monoether IV (1.62 g.) and 1.26 g. of osmium tetroxide were dissolved in 50 ml. of ether. After 2 hr. at room temperature, the precipitated osmate ester was dissolved in 70 ml. of ethanol and then shaken vigorously with a solution of 14 g. of sodium sulfite in 50 ml. of water. The mixture was diluted to 500 ml. with ethanol and filtered. The filtrate was concentrated *in vacuo* to a small volume and diluted with water, and the crystalline precipitate of VII was collected, washed and dried; 1.44 g., m.p. 155–175°.

This crude glycol mixture (1.44 g., m.p. 155–175°) was dissolved in 6 ml. of pyridine and 6 ml. of benzene containing 0.605 g. of propionic anhydride and kept at room temperature overnight. Ice and dilute sodium bicarbonate solution were added, and the reaction mixture was extracted with ether. The ether solution was washed with water, dried and evaporated to dryness. The 1.65 g. of residue was dissolved in benzene and adsorbed onto 60 g. of acid-washed alumina. With ether there was eluted 540 mg. (28%) of a dipropionate fraction. Chloroform elution provided 1.03 g. (62%) of crude crystalline monopropionate VIII, m.p. 90–125°.

2β,4b-Dimethyl-1β-methoxy-2-(γ-propionoxyacetonyl)-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4-one (IX).—The entire crude monopropionate fraction above (1.03 g.) was dissolved in 15 ml. of pyridine and added to the complex prepared from 1 g. of chromium trioxide and 10 ml. of pyridine. After stirring at room temperature overnight, the mixture was diluted with 20 ml. of water and extracted with four portions of ether. The combined extract was washed with water and concentrated to dryness. Recrystallization of the residue from ether–petroleum ether, methanol, ether and chloroform–ether gave 293 mg. (29%) of IX, m.p. 139–143°. The analytical sample melted at 143.5–144.5° after recrystallization from ether and gave a positive reducing test with tetrazolium reagent; λ_{max} 5.75, 5.81 and 5.87 μ.

Anal. Calcd. for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 66.50; H, 8.21.

Chromatography of the remaining material gave first 270 mg. of crude IX which after recrystallization amounted to 179 mg., m.p. 142–144.5°, bringing the yield of IX to 472 mg. (46%). Following IX was 325 mg. of a more polar substance which failed to give a reducing test. It was reoxidized and the product chromatographed to provide an additional 144 mg. of IX, m.p. 142–144°, total yield 616 mg. (60%).

2β,4b-Dimethyl-1β-methoxy-2-(γ-propionoxyacetonyl)-1,2,3,4,4aα,4b,5,6,7,9,10,10aβ-dodecahydrophenanthrene-4,7-dione (X).—To 22 mg. of IX in 1 ml. of acetone was added 5 mg. of *p*-toluenesulfonic acid. The solution was kept overnight at room temperature, water was added, and the product was extracted with chloroform. The dried extract was concentrated to dryness and the crystalline residue recrystallized from ether; 18 mg., m.p. 167–169°; λ_{max} 5.73 (shoulder), 5.78, 5.86, 6.03 and 6.18 μ.

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 67.64; H, 7.61.

2β,4b-Dimethyl-1β-methoxy-2-(γ-propionoxy-β-hydroxy-β-cyanopropyl)-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,-10aβ-dodecahydrophenanthrene-4-one (XI).—A solution of 500 mg. of IX in 4 ml. of ethylene chloride was treated with 0.07 ml. of triethylamine, 3 ml. of ether and 0.6 ml. of hydrogen cyanide. After 5 minutes, crystals of product began to separate. The mixture was kept at 0° overnight and then diluted with petroleum ether to complete precipitation of the product which was collected, washed with petroleum ether and dried; 510 mg. (96%), m.p. 174–180° dec.

2β,4b-Dimethyl-1β-methoxy-2-(γ-propionoxy-β-cyano-1-propenyl)-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4-one (XII).—Cyanohydrin XI, 500 mg., was dissolved in 2.5 ml. of pyridine and treated with 0.25 ml. of phosphorus oxychloride. The reaction solution was kept at room temperature overnight, ice and dilute sodium bicarbonate were added, and the product was extracted with ether. The ether solution was washed with water, dried and concentrated to provide 408 mg. of crude crystalline residue. Recrystallization from ether–petroleum ether gave 260 mg. (54%) of unsaturated nitrile XII, m.p. 125–130°. Ether recrystallization provided pure XII, m.p. 134–136°; λ_{max} 4.59, 5.77 and 5.86 μ.

Anal. Calcd. for $C_{26}H_{35}O_6N$: C, 68.25; H, 7.71; N, 3.06. Found: C, 67.97; H, 7.54; N, 3.20.

2β,4b-Dimethyl-1β-methoxy-2-(γ-propionoxy-α-hydroxyacetonyl)-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4-one (XIII).—A solution of 120 mg. of XII in 3.5 ml. of acetone and 0.1 ml. of piperidine was cooled to 0° and treated with 90 mg. of powdered potassium permanganate. The mixture was stirred cold for 1 hour, allowed to warm to room temperature and treated with 0.2 ml. of acetone containing 0.002 ml. of acetic acid. After stirring another hour at room temperature, the reaction mixture was rinsed into a separatory funnel with chloroform and the manganese dioxide was reduced with limited acidified sodium bisulfite solution. The chloroform layer was separated and the aqueous part extracted with chloroform. To the combined chloroform was added 12 ml. of 5% potassium carbonate solution and the total volume was reduced to *ca.* 20 ml. *in vacuo*. After 0.75 hr. stirring at room temperature, the chloroform was separated, washed, dried and concentrated giving 97 mg. of a gum. Chromatography over 5 g. of acid-washed alumina provided from the ether–chloroform fractions 54 mg. of crude crystalline XIII. Recrystallization from ether–petroleum ether gave 29 mg. (24%), m.p. 181–184°, positive tetrazolium test; λ_{max} 2.9–2.95, 5.74, 5.78 and 5.85 μ.

2β,4b-Dimethyl-1β-methoxy-2-(γ-propionoxy-α-hydroxyacetonyl)-1,2,3,4,4aα,4b,5,6,7,9,10,10aβ-dodecahydrophenanthrene-4,7-dione (XIV).—Eighteen milligrams of XIII was treated with a small amount of *p*-toluenesulfonic acid in acetone at room temperature overnight. Recovery of the product as described previously gave 11 mg. of pure XIV, m.p. 184–186° after recrystallization from ether. It reduced tetrazolium reagent and showed λ_{max} 2.9–2.95, 5.74, 5.78, 5.84, 6.08, 6.19, 8.12 and 9.14 μ.

Anal. Calcd. for $C_{23}H_{32}O_7$: C, 65.69; H, 7.67. Found: C, 65.67; H, 7.55.

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[CONTRIBUTION FROM THE DONNER LABORATORY, DIVISION OF MEDICAL PHYSICS, AND THE CHEMICAL LABORATORY, UNIVERSITY OF CALIFORNIA]

Composition of Fatty Acids from Certain Fractions of Blood Lipoproteins[1]

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RECEIVED FEBRUARY 6, 1956

The fatty acids from fractions S_f0-20 and S_f20-400 of the blood lipoproteins have been analyzed. Data on the mixed acids were combined with information obtained by chromatography on charcoal to yield an approximate composition for each lot of acids. Two significant differences in composition were noted: (a) more than 20% of C_{16} monounsaturated acid (palmitoleic) is present in Fraction S_f20-400, whereas this acid is either absent from Fraction S_f0-20 or is present at very low abundance; (b) poly-unsaturated acids are essentially absent from Fraction S_f20-400, whereas Fraction S_f0-20 contains about 4% tetra-unsaturated acid (arachidonic) and 18% di-unsaturated acid (linoleic).

Human sera contain fatty acids of a wide variety, both with respect to chain length and degree of unsaturation. Since nearly all the fatty acids found in the blood stream are present in the form of lipoproteins, it is of interest to study the fatty acids present in some of the different classes of lipoproteins. Selected for the present study were the S_f0–20 and S_f20–400 class[2] lipoproteins. These classes are of particular interest for several reasons. First, lipoproteins of the S_f12-400 class have been shown[3] to be more atherogenic than those of the S_f0-12 class. (The fractionation split at S_f20 rather than at S_f12 would not substantially alter this consideration.) Second, the chemical compositions of the two classes of lipoproteins contrast sharply. On the one hand, the dominant lipid component of the S_f20–400 class lipoproteins is triglyceride, whereas cholesterol esters and phospholipid comprise most of the lipid present in the S_f0–20 class molecules. Further, a relationship between these classes of molecules has been shown by *in vivo* and *in vitro* heparin transformation studies[4,5] which suggest that molecules of the S_f20–400 class normally may be converted to S_f0–20 class lipoproteins during the process of fat absorption.

Since the quantities of fatty acids available for investigation were rather small (170 mg. in the case of frac. S_f0–20), analysis has been based primarily on a partial separation accomplished by chromatography on charcoal, employing the methods described in detail in another journal.[6] Analytical data on the mixed acids were combined with the data obtained on the fractions from chromatography in order to arrive at the approximate compositions shown in Table I. It may be noted that a significant difference in composition of the two fractions concerns the content of poly-un-

(1) This investigation was supported in part by the United States Atomic Energy Commission.

(2) The customary unit of migration rate in the ultracentrifuge is the Svedberg unit. A molecule which undergoes flotation at a rate of 20 × 10^{-13} cm. per sec. per unit field of force has an S_f value of 20 or is a molecule of the S_f20 class.

(3) J. W. Gofman, B. Strisower, O. de Lalla, A. Tamplin, H. B. Jones and F. T. Lindgren, *Modern Medicine* (June 15, 1953).

(4) D. Graham, T. Lyon, J. W. Gofman, H. B. Jones, A. Yankley, J. Simonton and S. White, *Circulation*, **4**, 66 (1951).

(5) F. T. Lindgren, N. K. Freeman and D. M. Graham, *ibid.*, **6**, 474 (1952).

(6) J. Cason and G. A. Gillies, *J. Org. Chem.*, **20**, 419 (1955).