refluxed for 0.5 hour and the solution filtered. On cooling, the reduction product separated in long white needles, m.p. 69–70°, α_D +63 ± 2° Chf (lit.[6] 68–69°, α_D +64° Chf), yield 1.3 g. (55%).

The dibromide, crystallized twice from ethanol–acetone (3:1), formed small plates, m.p. 123–124°, α_D +76° Chf (Mauthner,[6] 125°, α_D +75° Chf).

Anal. Calcd. for $C_{27}H_{46}Br_2$ (530.48): C, 61.34; H, 8.63; Br, 30.13. Found: C, 61.24; H, 8.66; Br, 30.13.

Hydrogenation of 2β-Bromocholestane-3β-ol.—A mixture of 300 mg. of 2β-bromocholestane-3β-ol, 150 mg. of 5% palladium–charcoal and a solution of 2 g. of potassium hydroxide in 40 cc. of absolute ethanol was shaken at 25° with hydrogen until absorption stopped (30 min.). The solution was filtered, acidified with dilute acid, and extracted with ether. The residue left on evaporation (m.p. 136°) on crystallization from ethyl acetate afforded 162 mg. (65%) of cholestane-3β-ol, m.p. 138–140°, α_D +22.2 ± 2° Chf, no depression in mixed m.p. determination.

CAMBRIDGE, MASS.

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

Approaches to the Total Synthesis of Adrenal Steroids. VI. 2,4b-Dimethyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4β-ol-1-one and Related Compounds

BY R. M. LUKES, G. I. POOS, R. E. BEYLER, W. F. JOHNS AND L. H. SARETT

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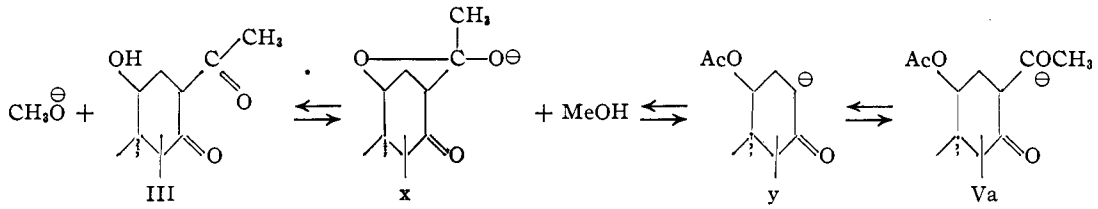
Several methods for attaching a methyl group to the C-2 position of 4b-methyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,-10aβ-dodecahydrophenanthrene-4β-ol-1-one are described. Among these the most satisfactory was found to be the direct methylation with methyl iodide–potassium *t*-butoxide. The corresponding 2-methyl-1,4-diketone XIV could be smoothly prepared by hydrolysis of the 2-methyl-2-carbomethoxy derivative XII as well as by oxidation of the 2-methyl hydroxy ketones. The stereochemical configuration of the C-2 methyl group is discussed.

Methylation of the 4β-Hydroxy-1-ketone (I).—The attachment of a methyl group at the C-2 position of 4b-methyl-7-ethylenedioxy-1,2,3,4,4aα,4b,-5,6,7,8,10,10aβ-dodecahydrophenanthrene-4β-ol-1-one (I)[1] was a necessary preliminary to the final stages of construction of the steroid skeleton. A number of procedures yielded the desired 2-methyl derivative II. Among these the direct methylation of the hydroxy ketone with methyl iodide–potassium *t*-butoxide was the most productive.[2,3] Although an excess of these reagents led to the formation of considerable amounts of a dimethylated derivative, it was possible with a short reaction time and a limited amount of base to produce a mixture consisting chiefly, after removal of unreacted starting material, of the monomethylated ketone II. Separation of the methylation mixture could be accomplished quite easily by fractional crystallization. In view of the inaccessibility of the 4β-hydroxyl group, no 4β-methoxy derivative was expected nor was any found.



Another approach, consisting of acylation, methylation and cleavage, also afforded the desired monomethyl ketone. This reaction series served both to illumine the rather intricate internal reactions of ring C and to confirm the location of the methyl group of II at the C-2 position. The tricyclic ketone condensed with methyl acetate in the presence of sodium methoxide to give the 2-acetyl derivative III along with a second enolic substance in variable amount. Methylation of the former and alkaline cleavage of the resulting 2-methyl-2-acetyl derivative IV afforded the same monomethyl ketone II obtained by direct methylation.

The second enolic substance had no free hydroxyl group but instead possessed an ester linkage (5.80 μ band in the infrared) as well as the 1,3-diketone system (broad band at 6.18–6.30 μ). Analyses indicated an empirical formula in agreement with that of the 2-acetyl 4-acetate V. A corresponding 2-methyl derivative VI was obtained from the methylation of V. Confirmation of the structure of the acetyl acetate V could be obtained by subjecting the methyl derivative VI to vigorous saponification, thereby cleaving the 2-acetyl group and hydrolyzing the 4-acetate to give the 2-methyl ketone II described above. Of the two likeliest mechanisms leading to the appearance of an acetate at C-4, namely, the direct base-catalyzed transesterification of the hydroxyl group with methyl acetate or methyl acetoacetate[4] and the intramolecular shift shown below, the latter is probably to be preferred since 11β-hydroxyl groups in the steroids appear

(1) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

(2) The use of these reagents for the methylation of ketones was introduced by D. A. Peak and R. Robinson, *J. Chem. Soc.*, 1581 (1937). See also N. A. McGinnis and R. Robinson, *ibid.*, 404 (1941); A. Koebner and R. Robinson, *ibid.*, 566 (1941).

(3) The direct methylation of α-decalone has been investigated by W. S. Johnson and his students (W. S. Johnson, THIS JOURNAL, **65**, 1317 (1943); W. S. Johnson and H. Posvic, *ibid.*, **67**, 504 (1945); (see also R. Robinson (ref. 2)). They have shown that the methylene group is attacked in preference to the bridgehead methine. By analogy the C-2 position should be preferred over C-10a in the direct methylation of 1-ketopolyhydrophenanthrene.

(4) *Cf.* A. R. Bader, L. O. Cummings and H. A. Vogel, *ibid.*, **73**, 4195 (1951).

to be quite unaffected under the usual conditions of the Claisen condensation.[5]

Acylation of the hydroxy ketone I with methyl formate gave the 2-formyl derivative VII which yielded, after methylation and alkaline cleavage,[6] a small amount of the desired 2-methyl-1-ketone II. Direct hydrogenolysis[7] of the formyl derivative VIII over a palladium catalyst gave the epimeric 2-methyl-1-ketone VIII in low yield and apparently none of the normal isomer II. The new epimer isomerized rapidly and completely in the presence of alkali to the stable epimer II. Tentative assignment of the 2α-methyl structure II to the stable epimer was made on the following basis. First, in the alpha configuration this methyl group is *trans* to the (polar) 4β-hydroxyl group and should thus incur less steric interference. (Support for this notion was gained from reactions which will be described in a succeeding paper.) Second, conformational analysis[8,9] if applied to the present case leads to the same assignment since the more stable epimer should have the equatorial (2α) configuration.[10] It is apparent from the present series of methylated derivatives that steric effects of greater magnitude than the non-bonded repulsions of the cyclohexane ring may supervene, as in the case of the epimeric 2-methyl-1,4-diketones described below.

The epimeric 2-methyl hydroxy ketones II and VIII were characterized by a rather striking difference in the carbonyl stretching frequency in the infrared (Nujol mull). The more stable epimer possessed a band at 5.93 μ[11] and the less stable, a band at 5.85 μ. Since the corresponding carbonyl frequency in the parent hydroxy ketone lay at 5.90 μ, introduction of a methyl group thus shifts this band in either direction, depending only on the configuration at C-2.[12]

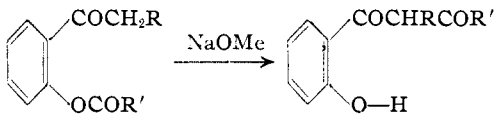
Methylation of the 1,4-Diketone (IX).—Condensation of the diketone IX with dimethyl carbonate[13] gave the single carbomethoxy derivative X in good yield; methylation followed by cleavage with potassium bicarbonate afforded a mixture of the epimeric methyl diketones XIII and XIV. Similarly, condensation of the diketone IX with methyl acetate followed by methylation gave the 2-methyl-2-acetyl derivative XV, the structure of which could be demonstrated by alkaline cleavage to the epimeric methyl diketones. Oxidation of the 2-methyl-2-acetyl derivative IV of the hydroxy ketone also gave XV.

The surprising positional selectivity of these acylation reactions of the 1,4-diketone IX was hardly predictable and merits some inquiry. Inspection of the molecular model of the diketone reveals no real difference in steric hindrance between the C-2 and C-3 positions in either the chair or boat conformations. In point of fact the C-12 position in the steroids (corresponding to the C-3 position in the tricyclic intermediate) is only slightly hindered, certainly no more than one would predict for a carbon atom flanked by two alkyl groups. A case in point also is the relative slowness of an *anti-cis*-4-ketone to epimerize to the *syn-trans* isomer,[1] indicating that it is unusually difficult to generate a negative charge at C-4a as well as at C-3, compared with C-10a and C-2, respectively. It would appear then that the relative slowness of condensation reactions at C-3 is connected not so much with the sluggishness of a mesomeric anion at C-3–C-4–C-4a but with lack of an effective concentration of this anion.

A second route to the 2-methyl-1,4-diketones XIII and XIV consisted of the direct oxidation of the epimeric 2-methyl hydroxy ketones II and VIII. Thus the stable methyl hydroxy ketone II gave the pure methyl diketone XIV and similarly the epimeric methyl hydroxy ketone VIII gave XIII.

Although the steroisomerism of the methyl ketones was not of significance from the purely synthetic standpoint since configuration at C-2 is not

(5) It is apparent that this intramolecular shift is analogous to the (reversible) cleavage of 1,3-diketones with alkoxide ion. (See C. R. Hauser, F. W. Swamer and B. I. Ringler, THIS JOURNAL, **70**, 4023 (1948) and leading references cited therein.) A closely related rearrangement is that of 2-acyloxyphenyl alkyl ketones to the isomeric 2-hydroxyphenacyl alkyl (or aryl) ketone



This intramolecular Claisen condensation first noted by W. Baker (*J. Chem. Soc.*, 1381 (1933)) and also studied extensively by Wheeler and his associates (B. G. Doyle, F. Gogan, J. E. Gowan, J. Keene and T. S. Wheeler, *Sci. Proc. Roy. Dublin. Soc.*, **24**, 291 (1948)) corresponds to the reverse path of the mechanism suggested above for the formation of the 4β-acetoxy-2-acetyl-1-ketone (V). Inasmuch as the Claisen condensation is reversible, the equilibrium favoring the more acidic products (C. R. Hauser and B. E. Hudson, Jr., "Organic Reactions," Vol. I, John Wiley and Sons, New York, N. Y. (1950)), the favored product in Baker's rearrangement is clearly the phenolic diketone. In contrast, the acetyl acetate (V) must have its origin in a small quantity of the carbanion of the keto acetate (y) in equilibrium with a larger concentration of the anion x and other anionoid forms of III. By further reaction with methyl acetate, y should be converted to the more stable ion (weaker base) Va.

(6) H. K. Sen and K. Mondal, *J. Ind. Chem. Soc.*, **5**, 609 (1928); J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, 676 (1946); *Nature*, **160**, 737 (1947); A. L. Wilds, J. W. Ralls, W. C. Wildman and K. E. McCaleb, THIS JOURNAL, **72**, 5794 (1950).

(7) A. Kötz and E. Schaeffer, *J. prakt. Chem.*, **88**, 604 (1913); A. Kötz and E. Schaeffer, *Ber.*, **45**, 1952 (1912).

(8) C. W. Beckett, K. S. Pitzer and R. Spitzer, THIS JOURNAL, **69**, 2488 (1947).

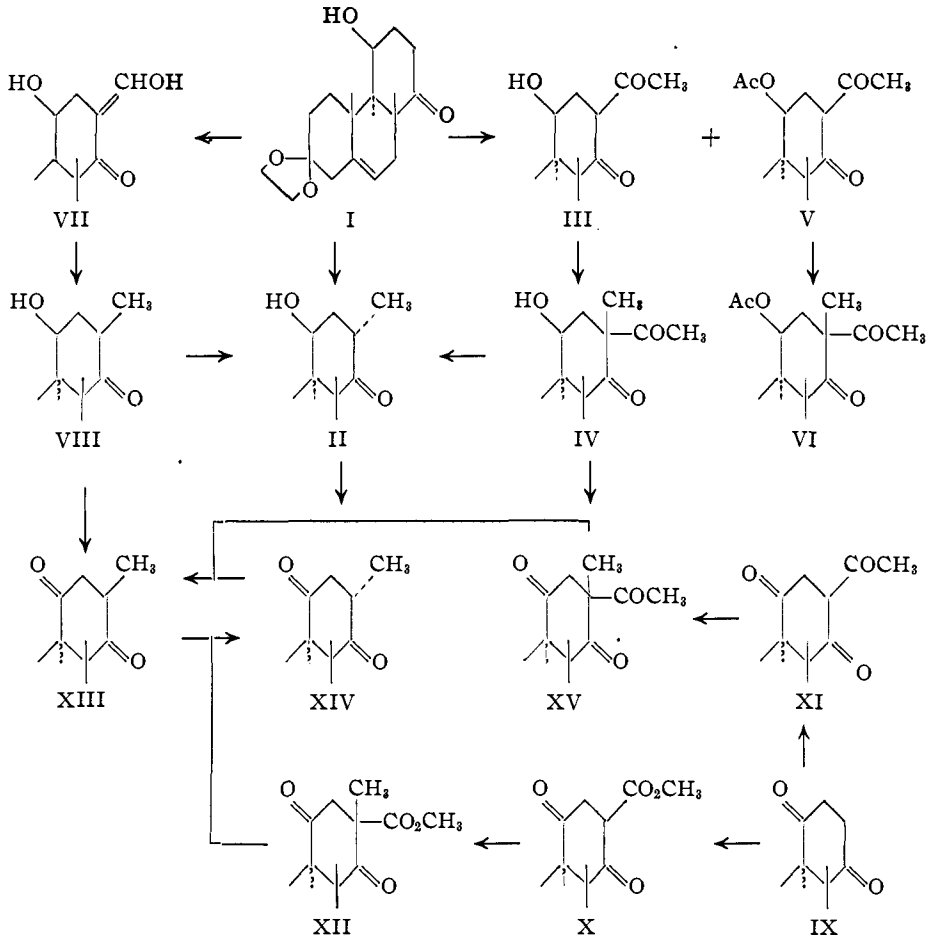
(9) D. H. R. Barton, *Experientia*, **6**, 316 (1950).

(10) It should be noted, however, that conformational analysis can be used only with considerable reservation for cyclohexane rings possessing keto or alkylidene substituents. The internal strain imposed by these groups (with preferred internal bond angles of approximately 120°) would be expected to alter normal conformational equilibria to an appreciable extent.

(11) We have found that the Köster–Logemann ketone [H. Köster and W. Logemann, *Ber.*, **73**, 298 (1940)], (−)2,4b-dimethyl-1,2,3,-4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-7β-ol-1-one acetate, also shows a ketonic carbonyl band at 5.93 μ (ester carbonyl at 5.80 μ, Nujol mull). Because of the conditions employed in the preparation of this compound it undoubtedly possesses the more stable configuration at C-2, and the carbonyl stretching frequencies of the *stable* epimers are thus identical in both series.

(12) In view of these results it is interesting to note the effect of an adjacent bromine atom on the carbonyl stretching frequency in steroidal ketones (R. N. Jones, D. A. Ramsay, F. Herling and K. Dobriner, THIS JOURNAL, **74**, 2828 (1952)). While the presence of a polar bromine atom appears to be without effect, a bromine atom with the equatorial configuration was found to cause a shift of about 0.05 μ toward *shorter* wave lengths. This shift was interpreted as being the result of coulombic field effects. Since an explanation applicable to the *general* case of α-substituted ketones is, however, unavailable, it is not at present feasible to use these shifts as a reliable criterion for the assignment of configuration.

(13) F. W. Swamer and C. R. Hauser, *ibid.*, **72**, 1352 (1950).



finally fixed until the succeeding step (*cf.* paper VII in this series), a few interesting observations were made which may be recorded here. Unlike the methyl hydroxyketones, one epimer of which was pronouncedly unstable with respect to the other in the presence of alkali, the methyl diketones appeared to be of more nearly equal stability. Thus mixtures of the two epimers were obtained upon alkaline cleavage of the 2-methyl-2-acyl derivatives XII and XV. When potassium carbonate was the saponifying agent, the major component of the mixture was the methyl diketone XIII; with potassium bicarbonate the epimer XIV could generally be isolated as the major product. XIV was obtained by hydrolysis of either of the steroisomeric modifications of XII.

In addition to the pair of epimeric methyl diketones XIII and XIV, another substance isomeric with these was also obtained. This isomer was derived from XIV by treatment with alkaline alumina. Its infrared absorption spectrum in chloroform solution was very similar to that of the 2β-methyl diketone XIII but sufficiently different to show that it was not simply a polymorphic form of the latter. On treatment with potassium carbonate, it isomerized to XIII. Since the unmethylated 1,4-diketone (IX) was not isomerized by alkali or by alkaline alumina, it seemed unlikely that formation of the third isomer involved inversions at the bridgehead carbon atoms. Its precise configuration remains undetermined.

Acknowledgment.— The authors are indebted to Mrs. Joan Vogel for the solubility analysis and to Mr. F. A. Bacher and his associates for the ultraviolet absorption spectra reported in this series of papers.

Experimental[14]

Direct Methylation of 4b-Methyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,-10aβ-dodecahydrophenanthrene-4β-ol-1-one (I).—To a refluxing solution of 10.0 g. of the hydroxy ketone I in 300 cc. of benzene and 100 cc. of *t*-butyl alcohol was added 102 cc. of a hot 1 *M* solution of potassium *t*-butoxide in *t*-butyl alcohol. A solution of 10 cc. of methyl iodide in 10 cc. of benzene was then quickly added to the reaction mixture. After heating two minutes under reflux, the reaction mixture was carefully quenched with 50 cc. of water. The solvent volume was reduced *in vacuo* to *ca.* 50 cc. The residue was then taken up in water and extracted with chloroform. The chloroform extract was washed with water, dried over anhydrous sodium sulfate and evaporated *in vacuo*. When nearly all the solvent had been removed, 50 cc. of benzene was added and then distilled *in vacuo*. The dry crystalline residue was thoroughly triturated and washed with a total of *ca.* 1 l. of warm ether, leaving 4.9 g. of crude starting material, m.p. 205–212°.

Careful recrystallization of the 5.1 g. of ether-soluble material from ethyl acetate yielded 1.80 g. of prisms, m.p. 178–183°; a second crop gave an additional 0.35 g., m.p. 175–179°. Combination of the two crops and recrystallization from ethyl acetate yielded pure 2α,4b-dimethyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4β-ol-1-one (II), m.p. 189–192°, λ_{max} 5.93 μ.

Anal. Calcd. for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.58; H, 8.42.

From the remaining 2.95 g. of ether-soluble material there was obtained 1.65 g. of lustrous plates, m.p. 145–151°. Recrystallization of this material from ethyl acetate gave a substance, m.p. 160–162°, which was shown by solubility analysis[15] to be a mixture consisting of 37% of the monomethylated derivative (II), 53% of a second compound, probably 2,2,4b-trimethyl-7-ethylenedioxy-1,2,3,4,4aα,4b,-5,6,7,8,10,10aβ-dodecahydrophenanthrene-4β-ol-1-one, and 7% of impurity.

Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 70.79; H, 8.77.

Chromatography of the 1.30 g. of ether-soluble residue on acid-washed alumina yielded an additional 0.40 g. of the crystalline mixture of m.p. 160–162° described above, 0.60 g. of starting material (I), and 100 mg. of a third compound, 2β,4b-dimethyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,-6,7,8,10,10aβ-dodecahydrophenanthrene-4β-ol-1-one (VIII), m.p. 194–197°.

(14) All melting points were determined on the Kofler micro hot-stage. Ultraviolet absorption spectra were determined in methanol. Infrared absorption spectra were determined in a Nujol mull.

(15) The method of T. J. Webb, *Anal. Chem.*, **20**, 100 (1948), was used.

Anal. Calcd. for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.81; H, 8.28.

A mixture of this compound (VIII) with the normal monomethylated compound (II) melted at 170–180°.

4b-Methyl-2-acetyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,-7,8,10,10aβ-dodecahydrophenanthrene-4β-ol-1-one (III) and 4b-Methyl-2-acetyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,-8,10,10aβ-dodecahydrophenanthrene-4β-ol-1-one Acetate (V).—To a rapidly stirred suspension of 3.2 g. (0.059 mole) of sodium methoxide (baked at 200° and 0.05 mm. for 1.5 hours) in 15 cc. of anhydrous benzene were added in succession, 4.0 g. of 4b-methyl-7-ethylenedioxy-1,2,3,4,4aα,-4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4β-ol-1-one (I) and 15 cc. of methyl acetate; the flask was stoppered and the mixture was stirred for about 16 hours. The mixture was then poured into 50 cc. of water and 50 cc. of benzene. The aqueous layer was separated, and the organic layer was extracted twice with water, and then with cold 1 *N* aqueous potassium hydroxide. The combined aqueous extracts were acidified with solid sodium dihydrogen phosphate and extracted thrice with chloroform. Evaporation of the combined chloroform extracts left 3.4 g. of crystalline residue which could be fractionally crystallized from acetone–petroleum ether into 1.8 g. (40%) of III, m.p. 201–204°, λ_{max} 291 mμ, E_{mol} 10,300, and 1.6 g. (31%) of V, m.p. 159–161°, λ_{max} 290 mμ, E_{mol} 10,700. The infrared absorption spectra showed maxima at 2.84 μ (OH) and 6.22–6.30 μ (COCHCO) for III, and at 5.80 μ (COO), 6.23 μ (COCHCO) and 8.03 μ (COOC) for V.

Anal. Calcd. for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found (III): C, 68.06; H, 8.25. Calcd. for $C_{21}H_{28}O_6$: C, 67.00; H, 7.50; acetyl, 22.87. Found (V): C, 67.10; H, 7.67; acetyl, 26.47.

2,4b-Dimethyl-2-acetyl-7-ethylenedioxy-1,2,3,4,4aα,4b,-5,6,7,8,10,10aβ-dodecahydrophenanthrene-4β-ol-1-one (IV).—To a solution of 1.0 g. of 4b-methyl-2-acetyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4β-ol-1-one (III) in 25 cc. of acetone was added 2.5 g. of anhydrous potassium carbonate and 6 cc. of methyl iodide. The mixture was stirred for 24 hours, after which it was evaporated *in vacuo* without warming. The pasty residue was extracted several times with benzene, and the combined extracts were evaporated to a crystalline mass. Fractional crystallization from ether yielded the methyl acetyl ketone (IV) in two epimeric forms: (a) 100 mg. (10%), m.p. 190–195°, (b) 600 mg. (58%), m.p. 132–134.5°. The ratio of (a) to (b) varied widely from experiment to experiment. Infrared absorption spectra showed maxima at 2.86 μ (OH) and 5.87 μ (CO) for IV (a), and at 2.82 μ (OH) and 5.90 μ (CO) for IV (b).

Anal. Calcd. for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: (a) C, 68.91; H, 8.10. (b) C, 69.22; H, 7.79.

2,4b-Dimethyl-2-acetyl-7-ethylenedioxy-1,2,3,4,4aα,4b,-5,6,7,8,10,10aβ-dodecahydrophenanthrene-4β-ol-1-one Acetate (VI).—Four grams of anhydrous potassium carbonate and 8 cc. of methyl iodide were added to a solution of 1.2 g. of 4b-methyl-2-acetyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,-7,8,10,10aβ-dodecahydrophenanthrene-4β-ol-1-one acetate (V) in 25 cc. of acetone, and the mixture was stirred overnight in a stoppered flask. The solvent was evaporated *in vacuo* without warming and the resultant paste was extracted several times with benzene. The combined extracts were evaporated, and the residual oil was crystallized from acetone-petroleum ether, yielding 0.7 g. (56%) of 2,4b-dimethyl-2-acetyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,-10aβ-dodecahydrophenanthrene-4β-ol-1-one acetate (VI), m.p. 107–110°. The infrared spectrum of VI showed maxima at 5.79 μ (COO), 5.93 μ (CO) and 8.0 μ (COOC).

Anal. Calcd. for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.66; H, 7.79.

Alkaline Hydrolysis of 2,4b-Dimethyl-2-acetyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4β-ol-1-one (IV).—Ninety-two milligrams of 2,4b-dimethyl-2-acetyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,-10,10aβ-dodecahydrophenanthrene-4β-ol-1-one (IVa), m.p. 189–195°, was dissolved in 10 cc. of 50% aqueous methanol containing 1.4 g. of potassium carbonate. The solution was boiled under reflux for 2.25 hours, the methanol was evaporated *in vacuo*, and the aqueous residue was extracted with ether. Evaporation of the ether extract left 67 mg. of crystalline residue, which upon recrystallization from ether yielded 60 mg. (74%) of 2α,4b-dimethyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4β-ol-1-one (II), m.p. and mixed m.p. 185–188°.

Alkaline Hydrolysis of 2,4b-Dimethyl-2-acetyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4β-ol-1-one Acetate (VI).—Fifty milligrams of 2,4b-dimethyl-2-acetyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,-10,10aβ-dodecahydrophenanthrene-4β-ol-1-one acetate (VI) was dissolved in 10 cc. of 50% aqueous methanol along with 0.7 g. of potassium carbonate. The solution was boiled under reflux for 16 hours, the methanol was evaporated *in vacuo*, and the aqueous residue was thrice extracted with chloroform. Evaporation of the combined chloroform extracts left an amorphous residue which, upon crystallization from ether, deposited 30 mg. (76%) of 2α,4b-dimethyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4β-ol-1-one (II), m.p. and mixed m.p. 185–188°.

4b-Methyl-2-hydroxymethylene-7-ethylenedioxy-1,2,3,4,-4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4β-ol-1-one (VII).—Sodium methoxide was prepared from 4.6 g. (0.2 g. atom) of sodium and 110 cc. of methanol. To this was added 14.6 g. (0.05 mole) of 4b-methyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4β-ol-1-one (I) and 30.0 g. (0.5 mole) of methyl formate. The resultant heterogeneous mixture was stirred under a nitrogen atmosphere at room temperature for 22.5 hours. During this period the reaction mixture slowly became tan and part of the solid went into solution. This mixture was poured into 600 cc. of water; extraction with ether gave, after drying and concentration, 0.6 g. of neutral crystalline residue. The aqueous layer was acidified with sodium dihydrogen phosphate; this buffered solution was carefully acidified further (to *p*H 4) with hydrochloric acid and rapidly extracted with benzene several times. After drying and concentration there was obtained 16.3 g. of crude enolic fraction as a tan solid residue. It was dissolved in acetone, decolorized with Darco and the solution concentrated until crystallization began in the hot solvent. After cooling a first crop of 10.5 g., m.p. 185–200°, of white crystals was collected. Further concentration of the mother liquor gave a second crop of 2.4 g., m.p. 180–195°, bringing the yield to 81%. Recrystallization from ethylene dichloride gave crystals melting at 203–204°. An immediate violet color was obtained with alcoholic ferric chloride. The infrared spectrum showed maxima at 2.82 μ (OH) and a broad band centered at 6.15 μ (COCHCO). A maximum occurred in the ultraviolet region at 287 mμ, E_{mol} 1950.

Anal. Calcd. for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.55; H, 7.44.

An isomer, m.p. 182–185°, was occasionally obtained from the above formylation. The ferric chloride test with this compound developed slowly, suggesting a cyclic lactol structure involving the C-4-hydroxyl.

Anal. Found: C, 66.77; H, 7.60.

2β,4b-Dimethyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,-10,10aβ-dodecahydrophenanthrene-4β-ol-1-one (VIII).—A suspension of 1.0 g. of 4b-methyl-2-hydroxymethylene-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4β-ol-1-one (VII) in 125 cc. of absolute ethanol was treated with 0.5 g. of palladium oxide and the mixture shaken under 20 p.s.i. of hydrogen. The crystals dissolved rapidly. At the end of 15 minutes, the hydrogen uptake amounted to the theoretical value (2.0 molecular equivalents plus the catalyst blank). The solution was filtered, concentrated nearly to dryness, dissolved in chloroform and washed with aqueous potassium hydroxide solution to remove unreacted starting material. Evaporation of the chloroform left 570 mg. of partially crystalline residue which was dissolved in benzene and chromatographed rapidly over 10 g. of acid-washed alumina, using mixtures of ether and petroleum ether for elution. The fractions eluted with 6:4 petroleum ether–ether were combined and recrystallized from ethyl acetate, giving 131 mg., m.p. 191–194°. A mixed melting point with a sample of the 2β-methyl hydroxy ketone, m.p. 194–197°, found as a by-product of the direct methylation melted at 192–195°. The infrared spectra of the two 2β-methyl hydroxy ketone samples were essentially identical (λ_{max} 2.83 μ (OH), 5.85 μ (CO)).

A sample of the 2β-methyl hydroxy ketone, m.p. 191–194° (10 mg.) was dissolved in 0.5 cc. of methanol, treated with two drops of aqueous 10% potassium hydroxide and the

solution was boiled for 2 minutes. Dilution with water gave crystals (9 mg.) m.p. 185–188°, not depressed on admixture with the 2α-methyl hydroxy ketone II, m.p. 189–192°.

2α,4b-Dimethyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,-10,10aβ-dodecahydrophenanthrene-1,4-dione (XIV).—To the complex prepared from 300 mg. of chromium trioxide and 3 cc. of pyridine was added a solution of 285 mg. of II in 3 cc. of pyridine. After two hours at room temperature, the mixture was poured into water and extracted with ether–benzene. The organic solution was dried and evaporated giving 268 mg. of crystalline XIV. Recrystallization from ether gave prisms melting at 135–136° (λ_{max} 5.83 μ).

Anal. Calcd. for $C_{18}H_{24}O_4$: C, 71.02; H, 7.95. Found: C, 70.94; H, 7.79.

Isomerization of XIV on Alkaline Alumina.—Four hundred milligrams of XIV, m.p. 134–136°, was dissolved in benzene and adsorbed on 12 g. of alkaline alumina. Elution with 1:1 petroleum ether–ether gave 370 mg. of an isomer, m.p. 112–116°. One recrystallization from ether gave prisms, m.p. 115–116° (λ_{max} 5.83 μ).

Anal. Found: C, 70.87; H, 7.97.

Further elution with petroleum ether–ether gave a few crystals of XIII as platelets from ether, m.p. 147–150°.

A solution of 123 mg. of the isomeric methyl diketone, m.p. 115–116°, with 70 mg. of potassium carbonate in 3 cc. of 80% aqueous methanol was allowed to stand at room temperature overnight. Water was added to the reaction mixture, the methanol was distilled and the organic material was extracted with chloroform. After drying, concentration and crystallization from ether, there was obtained 102 mg. of crystals melting at 144–149°. One recrystallization from ether gave XIII as platelets, m.p. 147–150°.

2β,4b-Dimethyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,-10,10aβ-dodecahydrophenanthrene-1,4-dione (XIII).—A solution of 185 mg. of 2β,4b-dimethyl-7-ethylenedioxy-1,2,-3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4β-ol-1-one (VIII) in 2 cc. of pyridine was oxidized with the complex prepared from 185 mg. of chromium trioxide in 2 cc. of pyridine at room temperature for six hours. The addition of water followed by extraction with ether, washing, drying and concentration gave 175 mg. (95%) of crystalline product. Recrystallization from ether gave XIII as platelets, m.p. 149–151° (λ_{max} 5.83 μ).

Anal. Found: C, 71.04; C, 8.08.

4b-Methyl-2-carbomethoxy-7-ethylenedioxy-1,2,3,4,4aα,-4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-1,4-dione (X).—One gram of finely ground sodium hydride was suspended in 40 cc. of anhydrous ether and to this suspension was added 5.0 g. of 4b-methyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-1,4-dione (IX), 30 cc. of methyl carbonate and 0.2 cc. of methanol. The mixture was stirred for 16 hours, cooled to about 10°, and to it was added, with rapid stirring, 50 cc. of water, and then 50 cc. of ether. The aqueous layer was separated, and the ethereal layer was extracted once with water and once with cold 1 *N* aqueous potassium hydroxide. The combined aqueous extracts were acidified with excess solid sodium dihydrogen phosphate and extracted thoroughly with chloroform. Evaporation of the combined chloroform extracts yielded a residue of 5.2 g. of crude crystalline enol. Recrystallization from ethanol afforded 4.0 g. (67%) of X, m.p. 148–149° (λ_{max} 259 mμ, E_{mol} 6750). The infrared absorption spectrum showed maxima at 5.81 μ (CO) and 6.05 μ ($COCHCO_2CH_3$).

Anal. Calcd. for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.76; H, 6.89.

2,4b-Dimethyl-2-carbomethoxy-7-ethylenedioxy-1,2,3,4,-4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-1,4-dione (XIII).—A solution of 3.4 g. of 4b-methyl-2-carbomethoxy-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-1,4-dione (X) and 30 cc. of methyl iodide in 130 cc. of acetone in which was suspended 6.1 g. of anhydrous potassium carbonate was stirred overnight. The solvent was evaporated *in vacuo* without warming, and the residual paste was extracted with benzene. Evaporation of the benzene gave 3.6 g. of amorphous residue, which when crystallized from ether, deposited 2.4 g. (66%) of XII (isomer a), m.p. 121–124°, infrared absorption spectrum maxima at 5.70 μ (CO_2CH_3) and 5.82 μ (CO).

Anal. Calcd. for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23. Found: C, 66.44; H, 7.14.

Evaporation of the mother liquors and crystallization of the residue from ethanol gave 0.7 g. (20%) of XII (isomer b), m.p. 153–156°, infrared absorption spectrum maxima at 5.75 μ (CO_2CH_3) and 5.84 μ (CO).

Anal. Found: C, 66.51; H, 7.27.

It was found in subsequent experiments that chromatography of the crude methylation product over acid-washed alumina provided a more convenient separation of XIIa and XIIb.

Hydrolysis and Decarboxylation of XII.—A solution of 29.5 g. of 2,4b-dimethyl-2-carbomethoxy-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-1,4-dione (XIIa), m.p. 121–124°, in 126 cc. of 20% aqueous potassium bicarbonate and 420 cc. of methanol was heated under reflux for three hours. The methanol was evaporated under reduced pressure and, after about 200 cc. had been removed, crystals separated. The distillation was continued until a total of approximately 300 cc. had been distilled. The crystals were separated by filtration and washed with water. The dried product, essentially one isomer, XIV, weighed 16.1 g. (64.5%) and melted at 133–135° with preliminary softening at 122°. The aqueous mother liquors were extracted twice with a 1:1 ether–benzene mixture. The extracts were evaporated to an oil (5.5 g.) which in 50 cc. of ether deposited 1.9 g. (7.8%) of crude XIII, m.p. 135–145°. Two recrystallizations from ether gave the pure epimeric monomethyl diketone XIII, m.p. and mixed m.p. 149–151°. This isomer was the major product when potassium carbonate was substituted for the potassium bicarbonate.

By a similar treatment with potassium bicarbonate, the hydrolysis of 1.00 g. of XIIb, m.p. 150–155°, gave 370 mg. of XIV, m.p. 128–131°.

4b-Methyl-2-acetyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,-7,8,10,10aβ-dodecahydrophenanthrene-1,4-dione (XI).—To 590 mg. (0.011 mole) of baked sodium methoxide (heated one hour at 200° and 0.03 mm.) under nitrogen were added 1.50 g. (0.00516 mole) of IX in 10 cc. of dry benzene and 1.53 g. (0.0206 mole) of methyl acetate. The reaction vessel was stoppered and the mixture was stirred at room temperature overnight. Ice-water and ether were added to the orange salt suspension and after thorough mixing the aqueous layer was rapidly withdrawn and neutralized with excess cold sodium dihydrogen phosphate solution. The organic layer was extracted with 10 cc. of cold 0.5 *N* potassium hydroxide which was combined with the acid phosphate solution. The enolic product was extracted with chloroform and, after drying, concentration and crystallization from acetone amounted to 1.00 g. (58.5%), m.p. 173–176°. A sample recrystallized from acetone melted at 176–177°, λ_{max} 288 mμ, E_{mol} 9,130.

Anal. Calcd. for $C_{19}H_{24}O_5$: C, 68.65; H, 7.28. Found: C, 68.82; H, 7.17.

2,4b-Dimethyl-2-acetyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-1,4-dione (XV).—To a suspension of 400 mg. of anhydrous potassium carbonate in 6 cc. of acetone was added 200 mg. of XI and 0.5 cc. of methyl iodide. The reaction mixture was stirred at room temperature overnight. The volatile materials were removed *in vacuo* and the solid residue was triturated thoroughly with benzene. Filtration and evaporation of the benzene afforded 200 mg. (96%) of crystalline product. Recrystallization from acetone gave a sample melting at 200–203°.

Anal. Calcd. for $C_{20}H_{28}O_5$: C, 69.34; H, 7.57. Found: C, 69.58; H, 7.65.

Alkaline Cleavage of 2,4b-Dimethyl-2-acetyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-1,4-dione.—A solution containing 130 mg. of the methyl acetyl diketone (XV) and 420 mg. of potassium carbonate in 6 cc. of 50% aqueous methanol was boiled for three hours. Methanol was removed *in vacuo* and the product was collected in chloroform. Drying and concentration gave a residue (85 mg.) which crystallized from ether; m.p. 112–140°. Three recrystallizations from ether gave XIII; m.p. and mixed m.p. 149–151°.

Chromium Trioxide–Pyridine Oxidation of 2,4b-Dimethyl-2-acetyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4β-ol-1-one (IV).—A solution of 300 mg. of IV in 3 cc. of pyridine was combined with 300 mg. of chromium trioxide in 3 cc. of pyridine. After stand-

ing at room temperature overnight, the reaction mixture was poured into water and extracted with benzene. The benzene solution was washed with water, dried and concentrated. Crystallization from acetone gave 251 mg. (83%) of 2,4b-dimethyl-2-acetyl-7-ethylenedioxy-1,2,3,4,4aα,4b,-5,6,7,8,10,10aβ-dodecahydrophenanthrene-1,4-dione (XV), melting at 195–202°. Mixture melting point and infrared spectra established identity with the material prepared by methylation of XI.

RAHWAY, NEW JERSEY

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, COLLEGE OF AGRICULTURE, AND THE DEPARTMENT OF CHEMISTRY COLLEGE OF LETTERS AND SCIENCE, UNIVERSITY OF WISCONSIN]

Separation and Tentative Identification of Two New Sterols from Oats[1]

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Two new sterols and β-sitosterol were isolated from oats by a chromatographic separation of the azoyl esters. The upper zone sterol was a Δ^7-stigmastadiene-3β-ol with the most probable location of the second double bond at the 11(12)-position. The middle zone sterol appeared to be $\Delta^{5,11}$-stigmastadiene-3β-ol. Oat oil sterols contain 11–14% of the Δ^7 sterol, 32–35% of $\Delta^{5,11}$-stigmastadiene-3β-ol, 53–56% of β-sitosterol, and 0.4% of a $\Delta^{5,7}$-sterol.

Δ^7-Cholestenol is a minor constituent of commercial cholesterol[3] and a major constituent of rat skin.[4] The present study shows that a Δ^7-sterol occurs in substantial amounts in oats along with a new Δ^5-sterol. Crude oat sterols resemble the sterols from skin in that they react rapidly with the modified Liebermann–Burchard reagent (Fig. 1) in contrast to pure cholesterol[5,6] or β-sitosterol,[6] which develop a maximum color only after prolonged contact with the reagent.

Experimental[7]

Preparation of Crude Sterols.—Six hundred pounds of ground whole oats were extracted with petroleum ether, and a dark, viscous, tubid oil was obtained in 3% yield. On the addition of 5 volumes of acetone, a voluminous precipitate formed, and the clear solution of the oil was decanted from the residue after settling. The clear oil was saponified with alcoholic KOH under N_2 and in the presence of pyrogallol, and the unsaponifiable matter, 2.5% of the oil, was taken up in a minimum amount of boiling petroleum ether, and stored at 0° for several days. The colorless precipitate representing 24.5% of the original non-saponifiable fraction was stirred in chloroform or carbon tetrachloride and the poorly soluble *n*-aliphatic alcohols filtered off. The solution yielded crude sterols, m.p. 130–133°. Purified *via* the digitonide,[4] the sterol mixture melted at 137.5°, and showed maxima in alcohol at 265, 271.5, 281 and 293 mμ. The intensities of these bands indicated the presence of 0.41% of a $\Delta^{5,7}$-sterol.

Chromatography.—Azoyl esters were prepared by refluxing 1.0 g. of dry crude sterol and 0.9 g. of *p*-phenylazobenzoyl chloride with 10 ml. of pyridine for two hours. The mixture was chilled, precipitated with cold water, filtered and thoroughly washed with water. The dry mixed esters were taken up in 20 ml. of warm benzene, filtered to remove most of the pyridinium salt, and 180 ml. of petroleum ether (Skellysolve C) added to the filtered solution. The best esterification achieved was 65%.

A Zechmeister column, 7.6 cm. inside diameter, was treated with silicone oil[4,8] and prepared by packing a slurry of two parts of silicic acid[9] and one part of Celite 503 in petroleum ether under pressure. Without pressure the flow rate through the column was 5–6 ml. per minute. The esters were adsorbed on the first cm. of the column and a 3:1 Skelly C–benzene mixture was then passed through the column until the esters moved about 2 cm. The developer was gradually changed to 5.5:1 Skelly C–benzene and the column was run for 44 hours without further attention. The descending order of the bands and the amounts of ester recovered in a typical run were: 1 cm., pyridinium salt; 23 cm., space; 2 cm., "upper zone" ester (62 mg.); 1.5 cm., space; 4 cm., "middle zone" ester (132 mg.); 4 cm., space; 6 cm., "lower zone" ester (224 mg.); 7 cm., space; filtrate, *n*-aliphatic ester (114 mg.). Unesterified sterol from the top of the column brought the total recovery to 95%.

Properties of the Azoyl Esters.—The upper zone ester melted at 209° after two crystallizations from benzene–ethyl alcohol. These crystallizations resulted in a negligible loss of material and the melting point was unchanged on further recrystallizations from benzene.

Anal. Calcd. for $C_{42}H_{56}O_2N_2$: C, 81.30; H, 9.03. Found: C, 81.02; H, 9.12.

The middle zone ester was rechromatographed and the extremities of the zone discarded. After two crystallizations from benzene–ethyl alcohol the ester melted at 191°. The lower zone ester melted at 181°. Neither melting point was changed by further crystallization.

In the hydrolysis of these esters 4% KOH[4] caused considerable discoloration of the upper and middle zone sterols although the lower zone ester hydrolyzed satisfactorily. An empirical mixture which gave complete hydrolysis of many azoyl esters without discoloration was 3 ml. of 8% KOH in 70% ethanol, 7 ml. of ethanol, 2 ml. of water and 5 ml. of benzene for each 150 mg. of azoyl ester. Hydrolysis was continued on the steam-bath until solution was complete, one hour usually being sufficient. More benzene was added for very insoluble esters.

Upper Zone Sterol.—Hydrolysis of the azoyl ester yielded long needles on crystallization from methanol, m.p. 145°. The sterol contained 2.7% of a $\Delta^{5,7}$-sterol as measured by the ultraviolet spectrum. The sterol gave a Liebermann–Burchard reaction similar to that of the Δ^7-sterols[5,6] (Fig. 1), $[\alpha]^{28}D$ +8.75 ± 2° (30 mg. in 2.5 ml., corrected for 7-dehydrostigmasterol). The sterol could be precipitated by digitonin.

Anal. Calcd. for $C_{29}H_{48}O$: C, 84.40; H, 11.73. Found: C, 84.37; H, 11.85.

Derivatives.—The acetate of the upper zone sterol crystallized from ethanol in plates, m.p. 155°, $[\alpha]^{29}D$ +7.0 ± 2° (24 mg. in 2.5 ml., corrected for 7-dehydrostigmasterol).

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(2) Shell Oil Company Fellow, 1951–1952.

(3) L. F. Fieser, THIS JOURNAL, **73**, 5007 (1951).

(4) D. R. Idler and C. A. Baumann, *J. Biol. Chem.*, **195**, 623 (1952).

(5) P. R. Moore and C. A. Baumann, *ibid.*, **195**, 615 (1952).

(6) (a) D. R. Idler and C. A. Baumann, *ibid.*, in press; (b) summary given at the A.C.S. Meeting, Milwaukee, Wis., April, 1952.

(7) Melting points are corrected. All solutions for rotations were prepared in 2.5 ml. of chloroform solution, and the measurements made with a Schmidt and Haensch polarimeter No. 52-b with monochromator. Ultraviolet absorption spectra were taken of ethanol solutions. We are indebted to C. H. Schroeder of the Department of Biochemistry for the carbon and hydrogen analyses.

(8) General Electric Company "dri film" 9987.

(9) Analytical grade specially prepared for chromatography by the method of Ramsay and Patterson. Mallinckrodt Chemical Works.