constant (8 hr.). The solution was neutralized ($BaCO_3$) and evaporated to a sirup which was extracted once with methanol to remove a small amount of inorganic matter. A mixture of the methylated sugars (0.353 g.) was dissolved in butanone–water azeotrope (2 ml.) containing a few drops of methanol and added to the top of a cellulose–hydrocellulose column (40 × 2.8 cm. i.d.). Two drops of Sudan IV was added to mark the front and the column developed with butanone–water azeotrope. The column was jacketed at 30° and the front time was 3.5 hr. with a rate of flow of 25 ml./hr. Tubes 1 (from the dye)–50 were collected every 15 min. and thereafter at 30-min. intervals, with the results shown in Table III.

TABLE III

SEPARATION OF NEUTRAL SUGARS

| Tube number | Component number | Identity |
|---|---|---|
| 3-11 | 1 | 2,3,5-Tri-*O*-methyl-L-arabinose |
| | | 2,3,4-Tri-*O*-methyl-D-xylose |
| 13-27 | 2 | 2,3-Di-*O*-methyl-D-xylose |
| 60-85 | 3 | 2- and 3-*O*-methyl-D-xylose |

**Component 1.**—The sirup (40.3 mg.), which had a very slight positive rotation, was shown readily by paper chromatography (butanone–water) to be a mixture. Using the values $[\alpha]D$ −38.5° (*c* 1 in methanol) for 2,3,5-tri-*O*-methyl-L-arabinose and $[\alpha]D$ 18.5° (*c* 1 in methanol) for 2,3,4-tri-*O*-methyl-D-xylose, it was concluded from the rotation of the sirup that there were present *ca.* 13 mg. of the arabinose derivative and 27 mg. of the xylose derivative.

When the sirup was dissolved in methanol containing 1% HCl, the solution became strongly positive in rotation and reached a constant value in 3.5 hr. After neutralization ($Ag_2CO_3$) the mixture of neutral sugar and furanoside was separated on the cellulose-hydrocellulose column. The neutral sugar was detected with *p*-anisidine spray in tubes 10-21 (10 min. fractions) and the furanoside in tubes 1–8 (positive Molisch and negative *p*-anisidine).

**Component 1a. 2,3,5-Tri-*O*-methyl-L-arabinose.**—The sirup obtained in tubes 1–8 was hydrolyzed with sulfuric acid and on chromatographic examination it was shown to consist of a single component and to behave in the same way as an authentic sample of 2,3,5-tri-*O*-methyl-L-arabinose.

**Component 1b. 2,3,4-Tri-*O*-methyl-D-xylose.**—The sirup from tubes 10–21 (20 mg.) partly crystallized on seeding and was characterized as the crystalline 2,3,4-tri-*O*-methyl-N-phenyl-D-xylosylamine, m.p. and mixed m.p. 98–100°.

**Component 2. 2,3-Di-*O*-methyl-D-xylose.**—This component (256 mg.) crystallized on seeding and after recrystallization had m.p. and mixed m.p. 75–77°.

**Component 3. Mixture of 2- and 3-*O*-Methyl-D-xyloses.**—The sirup (36 mg.) had $[\alpha]^{23}D$ +19.8° and was shown by paper chromatography for 20 hr. in butanone–water to be a mixture of monomethylxyloses. From tubes 60–62 and 81–85 it was possible to obtain chromatographically pure samples corresponding to 3- and 2-*O*-methyl-D-xylose, respectively, but not in sufficient quantity to prepare any crystalline derivatives. From the rotation of the sirup it was judged to contain *ca.* 78% 3-*O*-methyl-D-xylose and 22% 2-*O*-methyl-D-xylose.

**Acknowledgment.**—The authors are grateful to the National Research Council of Canada for continued financial support and to Dr. J. K. N. Jones F.R.S. for the gift of crystalline 2,3-di-*O*-methyl-D-xylose.

VANCOUVER, B. C., CANADA

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[CONTRIBUTION FROM THE MERCK, SHARP AND DOHME RESEARCH LABORATORIES]

# Alkylated Adrenal Hormones. The Synthesis of 5-Methylated Pregnanes

BY JOHN H. FRIED, GLEN E. ARTH AND LEWIS H. SARETT

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The synthesis of 5-methylpregnane-11β,17α,21-triol-3,20-dione acetate and 5-methyl-1-pregnene-11β,17α,21-triol-3,20-dione acetate *via* angular methylation of a suitably protected 6-ketone II is described.

Although there is no evidence that allo-dihydrohydrocortisone exhibits anti-inflammatory activity when administered systemically to animals, local activity has been demonstrated with this compound.[1] The possibility that the lack of systemic activity could be due to rapid reduction of the 3-ketone function, prompted us to prepare the sterically hindered 5-methyl analog. This paper describes the synthesis of 5-methylpregnane-11β,17α,21-triol-3,20-dione 21-acetate and 5-methyl-1-pregnene-11β,17α,21-triol-3,20-dione 21-acetate. Chuman[2] has described the preparation of 5α-methylcholestane-3β,6β-diol by reaction of cholesteryl-β-oxide and methylmagnesium iodide. Attempts to utilize this reaction with 17α,20,20,21-bismethylenedioxy-3-ethylenedioxy-5,6β-oxidopregnane-11β-ol (I) did not give the desired 5α-methyl product but a compound of unknown constitution.

However, 17α,20,20,21-bismethylenedioxy-3-ethylenedioxy-allo-pregnane-6,11-dione (II), recently reported,[3] appeared to be a suitable starting material for the projected synthesis. Although II possesses carbonyl functions at C-6 and C-11, selective alkylation of the 6-ketone was judged to be the more likely possibility due to the relatively unreactive character of saturated 11-ketosteroids[4a]; furthermore, on the basis of the stabilities[4b] of the enolates involved and in the absence of over-riding steric effects, preferential methylation of II at C-5 appeared to be indicated.[5] The two possible enolic forms of the C-6 ketone have double bonds between carbons five and six and six and seven. Turner[6] has shown that in the cholestane series the former is *ca.* 1.5 kcal. more stable than the latter. This is in agreement with the initial formation of a C-5 substituted bromide as the result of bromination of 6-ketosteroids.[7]

Initial attempts to methylate II using either potassium *t*-butoxide in *t*-butyl alcohol or sodium hydride in benzene were unsuccessful; however, addi-

(1) J. L. Hollander, E. M. Brown, Jr., R. A. Jessar, L. Udell, N. Smukler and M. A. Bowie, *Ann. Rheumatic Diseases*, **13**, 297 (1954).

(2) M. Chuman, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **70**, 253 (1949).

(3) J. H. Fried, G. E. Arth and L. H. Sarett, THIS JOURNAL, **81**, 1235 (1959).

(4) (a) Private communication from Dr. R. R. Beyler; *cf.*, however, R. R. H. Jones, G. D. Meakins and J. S. Stephenson, *J. Chem. Soc.*, 2156 (1958), for the methylation of unsaturated 11-ketosteroids; (b) *cf.* H. M. R. Cardwell, *ibid.*, 2442 (1951).

(5) *Cf.* D. A. Peak and R. Robinson, *ibid.*, 1581 (1937).

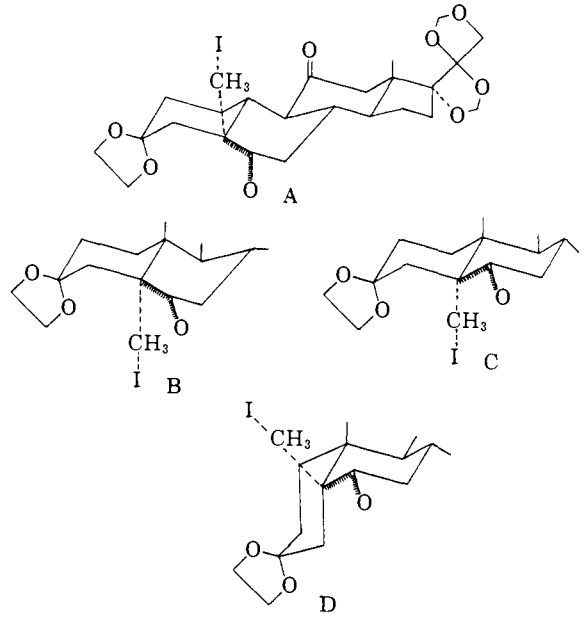
(6) R. B. Turner, W. R. Meador and R. R. Winkler, THIS JOURNAL, **79**, 4122 (1957).

(7) I. M. Heilbron, E. R. H. Jones and F. S. Spring, *J. Chem. Soc.*, 801 (1937).

tion of methyl iodide to a refluxing suspension of sodium hydride in a solution of II in xylene afforded 5-methyl-17$\alpha$,20,20,21-bismethylenedioxy-3-ethylenedioxypregnane-6,11-dione (III) in about 37% yield. The 5$\beta$-methylated product was the only monoalkylated component present as shown by chromatographic separation of the crude product. The reaction can therefore be considered stereospecific. The remainder of the material consisted of recovered II (21%) and mixtures of what appeared on n.m.r. evidence to be polymethylated products. The structure[8] assigned to III is consistent with infrared, analytical and n.m.r. data, the latter particularly significant in that a signal indicative of one additional quaternary C–$CH_3$ group was clearly evident.

The stereochemistry of the newly introduced methyl group was not ascertained at this stage of the synthesis, but the A/B ring juncture was later shown to be *cis* by rotational dispersion studies carried out with compound VI.[9]

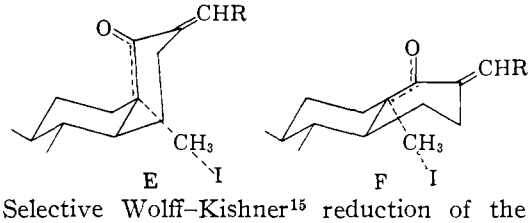
The steric consequences of the alkylation can be considered to depend upon the geometry of the transition state involved.[10] The four most likely possibilities are represented by the expressions A through D. Although the considerations expressed by A-D are extreme, they are nevertheless useful for purposes of discussion; A and B resemble the enol form of the starting material while C and D resemble the keto form of the starting material. A comparison of calculated conformational interactions present in A and B indicates that B is de-



stabilized relative to A by an energy difference at least as great as one 1:3 oxygen–methyl plus one 1:3 hydrogen–methyl interaction.[11] A similar comparison between C and D indicates approximately equivalent conformational interactions; however, D will be of greater energy content, since C is stabilized by $\sigma$–$\pi$ orbital interactions between C-5 and the adjacent carbonyl. Eliminating the two less stable transition states from further consideration, the remaining choice is between A leading to an A/B *cis* and C leading to an A/B *trans* product. From a conformational viewpoint A is the more stable by an energy difference at least as great as one 1:3 methyl–oxygen and one 1:3 methyl–hydrogen interaction. From an electronic viewpoint, however, a greater degree of electron delocalization and maximum bonding is possible with C thus lowering the energy content of this transition state. This factor has been termed stereoelectronic control and is discussed in greater detail by Corey[12a,b] as applied to the ketonization-enolization reaction.

The formation of a 5$\beta$-methylated steroid as the result of alkylation of II indicates that in this case the steric advantages[13] inherent in A outweigh any electronic advantages of C. On the other hand, it would not seem unreasonable to assume that stereoelectronic control favoring transition state C should become more important as the electron demand of the reagent increases while the electron supply decreases. The initial product of bromination of 3$\beta$-acetoxycholestane-6-one, the 5$\alpha$-brominated product,[7,12b] is an example of this latter possibility.

Although the over-all steric result of methylation of II is similar to that reported by Johnson[14] for the angular methylation of furfurylidene derivatives such as $\alpha$-decalone and 18-nor-D-homoepiandrosterone tetrahydropyranyl ether an important difference should be noted. By analogy with A-D four transition states appear most likely for this reaction. Of these E and F leading to a C/D *cis* product are favored on the basis of calculated conformational interactions. Electronically both E and the corresponding transition state leading to the C/D *trans* product are able to engage in $\sigma$–$\pi$ orbital overlap. Thus there is no disparity between steric and electronic effects as in the case of the methylation of II.



Selective Wolff–Kishner[15] reduction of the 5-methyl-6,11-dione III afforded the 6-desoxy compound IV.

This compound on reduction with lithium aluminum hydride in refluxing tetrahydrofuran yielded

(8) The alternative C-9 methylated structure was ruled out since attempts to methylate 17$\alpha$,20,20,21-bismethylenedioxy-3-ethylenedioxy-5-pregene-11-one[3] under somewhat more strenuous conditions afforded less than 15% of a mixture of alkylated products.

(9) Kindly measured by Professor C. Djerassi and Robert R. Engle at Wayne State University, Detroit, Mich.

(10) It should be noted that the subsequent discussion dealing with conformational interactions and transition states must of necessity be qualitative in nature.

(11) For purposes of this discussion a 1:2 methyl–methyl interaction is considered equivalent to a 1:3 methyl–hydrogen interaction.

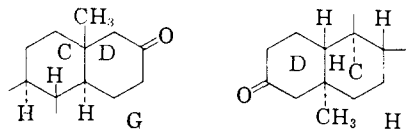
(12) (a) E. J. Corey and R. A. Sneen, THIS JOURNAL, **78**, 6269 (1956); (b) **76**, 175 (1954).

(13) *Cf.* H. E. Zimmerman, *J. Org. Chem.*, **20**, 549 (1955); THIS JOURNAL, **78**, 1168 (1956).

(14) W. S. Johnson, *ibid.*, **78**, 6278 (1956), and subsequent papers in this issue. The C/D *cis* product predominated by a ratio of 2 to 4:1 for the cases cited in this series.

(15) Huang-Minlon, *ibid.*, **71**, 3301 (1949).

5-methyl-17$\alpha$,20,20,21-bis-methylenedioxy-3-ethylenedioxypregnane-11$\beta$-ol (V). Dioxolane cleavage was carried out with *p*-toluenesulfonic acid in acetone to give 5-methyl-17$\alpha$,20,20,21-bismethylenedioxypregnane-11$\beta$-ol-3-one (VI). The rotational dispersion curve of compound VI exhibited a negative Cotton effect characteristic of A/B *cis* steroids.[16] The possibility that the observed result was only due to inversion of the sign of the Cotton effect in an A/B *trans*-steroid caused by the introduction of methyl at C-5 could be ruled out on the basis of the inferential argument cited below. Djerassi[16,17a,b] has shown the shape of the rotational dispersion curve of a 3-keto steroid to be independent of skeletal changes in rings C, D or the side chain,[17c] and the presence or absence of the angular methyl at C-10. Thus the mirror image (H) of a D-homo-17-ketone (G) should be a good prototype of a 5$\alpha$-methyl-3-ketosteroid. The rotational dispersion curve of G has been measured[18] and found to bear a mirror image relationship to 3-keto A/B *trans*-steroids. Introduction of an angular methyl at C-5 is thus shown not to influence the sign of the Cotton effect of 3-keto steroids.




Removal of the bismethylenedioxy protecting[3,19] group with 60% formic acid followed by acetylation afforded 5-methylpregnane-11$\beta$,17$\alpha$,21-triol-3,20-dione 21-acetate (VIII) along with considerable amounts of a dehydration product, presumably the corresponding $\Delta^{9(11)}$-compound.

Introduction of the C-1 double bond into VI was carried out by a bromination–dehydrobromination sequence. Addition of bromine[20] to VI afforded a crude bromination product that could be dehydrobrominated with lithium chloride in dimethylformamide[21] to yield VII in *ca.* 30% yield. Even though bromine migration from C-4 to C-2 during dehydrohalogenation cannot be ruled out, the experiment does at least suggest bromination at C-2, an unexpected result with an A/B *cis*-steroid. Since bromination is an enol-controlled process,[22] conformational factors[23] due to the introduction of the new angular methyl group may be influencing the direction of enolization. Similarly, Mazur[24] has recently described the monomethylation of 7-dehydrocholestane-3-one at C-4 presumably due to enolization of the A/B *trans*-steroid toward C-4 rather than C-2.[24]

Hydrolysis[3,19] of the BMD-protecting group in VII with 60% aqueous formic acid and then acetylation yielded 5-methyl-1-pregnene-11$\beta$,17$\alpha$,21-triol-3,20-dione 21-acetate (IX). Compounds VIII and IX were evaluated by Dr. R. H. Silber in the Merck Institute for Therapeutic Research and found to be inactive in the liver glycogen[25] and systemic granuloma assays.[26]

## Experimental[27]

**17$\alpha$,20,20,21-Bismethylenedioxy-3-ethylenedioxy-5,6$\beta$-oxidopregnane-11$\beta$-ol (I).**—To a solution of 4.0 g. of 17$\alpha$,20,20,21-bis-methylenedioxy-3-ethylenedioxy-5,6$\beta$-oxidopregnane-11$\beta$-one[3] in 170 ml. of tetrahydrofuran was added 4.0 g. of sodium borohydride in 50 ml. of water. The two-phase system was stirred 4.5 hours at room temperature and subsequently allowed to stand in the refrigerator overnight. The reaction mixture was poured into aqueous sodium dihydrogen phosphate and the tetrahydrofuran removed *in vacuo*. The aqueous suspension was extracted with chloroform and the chloroform layer dried and concentrated. Crystallization from benzene afforded 3.2 g., 80%, of I, m.p. 247–256°. Two recrystallization from benzene provided the analytical sample of 17$\alpha$,20,20,21-bismethylenedioxy-3-ethylenedioxy-5,6$\beta$-oxidopregnane-11$\beta$-ol, m.p. 258–261°, $[\alpha]_D$ −53°. Calcd. for $C_{25}H_{36}O_8$: C, 64.63; H, 7.81. Found: C, 64.83; H, 7.70.

**Reaction of 17$\alpha$,20,20,21-bismethylenedioxy-3-ethylene dioxy-5,6$\beta$-oxidopregnane-11$\beta$-ol (I) with Methylmagnesium Iodide.**[2]—A solution of methylmagnesium iodide was prepared from 72 mg. of magnesium, 1 ml. of methyl iodide and 10 ml. of ether. The centrifuged reagent was added to a dry solution of 245 mg. of I in 50 ml. of benzene. About 10 ml. of solvent was removed by distillation and the cloudy reaction mixture refluxed for 4 hours and allowed to stir overnight. The benzene suspension was washed with water and separated. The organic layer was dried and concentrated *in vacuo*. The crude product, 250 mg., was chromatographed on 10 g. of acid-washed alumina. Elution with chloroform–ether 2:3 to 9:1 afforded 175 mg. of a crystalline product, m.p. 190–200°. Two crystallizations from methanol gave a sample for analysis, m.p. 202–206°, $[\alpha]_D$ −75°; n.m.r. indicates the presence of BMD; loss of dioxolane; infrared spectrum: $\lambda_{max}^{Nujol}$ 2.85 9.16 $\mu$. Found: C, 65.70, 65.77; H, 8.77, 8.57. Starting material was recovered on attempted acetylation with acetic anhydride in pyridine.

**5-Methyl-17$\alpha$,20,20,21-bismethylenedioxy-3-ethylenedioxypregnane-6,11-dione (III).**—A solution containing 3.01 g. of 17$\alpha$,20,20,21-bismethylenedioxy-3-ethylenedioxypregnane-6,11-dione (II) in 55 cc. of xylene was dried azeotropically. Powdered sodium hydride, 0.90 g., and *t*-butyl alcohol, 0.10 ml., was added and the resulting suspension refluxed for one hour. The yellow suspension was cooled, and 8 ml. of methyl iodide added, with a refluxing period of 20 hours. The suspended solids were separated by centrifugation and the xylene layer washed with water, dried over sodium sulfate and concentrated *in vacuo*. The crude product was crystallized twice from methanol yielding 0.80 g. of methylated product, m.p. 272–277°. The analytical sample of 5-methyl-17$\alpha$,20,20,21-bismethylenedioxy-3-ethylenedioxypregnane-6,11-dione was prepared from methanol, m.p. 272–277°, $[\alpha]_D$ −93°; infrared spectrum, $\lambda_{max}^{CHCl_3}$ 5.86–5.89 m$\mu$; n.m.r., three single methyl resonances. Calcd. for $C_{26}H_{36}O_6$: C, 65.53; H, 7.61. Found: C, 65.61; H, 7.55. Combined mother liquors were adsorbed on 150 g. of acid-washed alumina (Merck) and

(16) C. Djerassi and W. Closson, THIS JOURNAL, **78**, 3761 (1956).

(17) (a) C. Djerassi, R. Riniker and B. Riniker, *ibid.*, **78**, 6362 (1956); (b) C. Djerassi, O. Halpern, V. Halpern and B. Riniker, *ibid.*, **80**, 4001 (1958); (c) any possible influence of the BMD on the sign of the Cotton effect can be ruled out since the model compound of known stereochemistry 17$\alpha$,20,20,21-bismethylendioxy-*allo*-pregnane-11$\beta$-ol-3-one (kindly furnished by Dr. D. Hoff of this Laboratory), exhibited a positive Cotton effect characteristic of A/B *trans* steroids.[16]

(18) Reference 17b footnote 43.

(19) R. E. Beyler, R. M. Moriarty, Frances Hoffman and L. H. Sarett, THIS JOURNAL, **80**, 1517 (1958).

(20) G. R. Krsek, U. S. Patent 2,732,385.

(21) R. P. Holysz, THIS JOURNAL, **75**, 4432 (1953).

(22) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940.

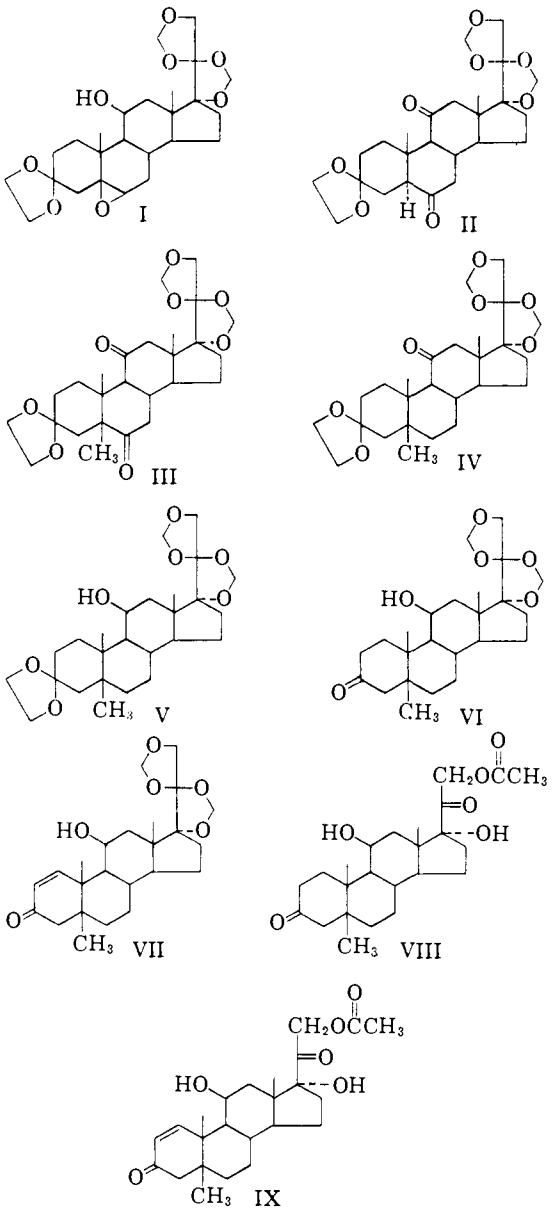
(23) *Cf.* D. H. R. Barton, A. J. Head and P. J. May, *J. Chem. Soc.*, 935 (1957).

(24) Y. Mazur and F. Sondheimer, THIS JOURNAL, **80**, 6296 (1958).

(25) R. M. Reinecke and E. C. Kendall, *Endocrinol.*, **31**, 573 (1942).

(26) R. Meier, W. Schuler and P. Desaulles, *Experientia*, **6**, 469 (1950). Compound VIII was administered subcutaneously; compound IX was administered orally.

(27) Melting points were determined on a Kofler micro hot-stage and are corrected. Rotations were determined at 24° in chloroform at concn. = 10 mg./ml., unless otherwise noted. We wish to thank Mr. R. Boos and his associates for microanalyses, Mr. J. Wittick and associates for the ultraviolet absorption spectra, Mr. R. Walker and Mr. N. Allen for the infrared spectra and Dr. N. R. Trenner and Mr. B. Arison for the nuclear magnetic resonance spectra herein reported.



eluted with benzene to yield initially oily fractions and subsequently crystalline material. The crystalline material was combined and crystallized twice from methanol to yield an additional 0.35 g. of III, a total of 1.15 g., 37%. Further elution with chloroform–benzene, 2:8, afforded *ca.* 21% of recovered starting material. Further attempts to separate the non-crystalline components obtained from the column did not yield additional monomethylated products. Careful rechromatography of fractions less polar than III on acid-washed alumina (200:1) yielded non-crystalline tetramethylated products as judged by n.m.r. in addition to small amounts of III. A similar column on the mother liquors of III and components more polar than III afforded II, III and non-crystalline tetramethylated products.

**5-Methyl-17α,20,20,21-bismethylenedioxy-3-ethylenedioxypregnane-11-one (IV).**—A mixture consisting of 4.6 g. of III, 460 ml. of redistilled diethylene glycol, 46 ml. of 85% hydrazine hydrate and 32 g. of potassium hydroxide pellets was refluxed 1.75 hours at 170°. The pot temperature was raised to 215–225° by removing an aqueous fraction by distillation, and maintained there for 4 hours.[15] The reaction mixture was allowed to cool overnight and extracted with ether. The ether layer was washed with water, dried and concentrated *in vacuo*. Crystallization from methanol afforded 3.5 g., 75%, of the 6-desoxy compound, m.p. 215–225°. The analytical sample of 5-methyl-17α,20,20,21-bismethylenedioxy-3-ethylenedioxypregnane-11-one was obtained by two crystallizations from methanol, m.p. 222–228°, $[\alpha]D$ −47°. Calcd. for $C_{26}H_{38}O_7$: C, 67.51; H, 8.28. Found: C, 67.37; H, 8.05.

**5-Methyl-17α,20,20,21-bismethylenedioxy-3-ethylenedioxypregnane-11β-ol (V).**—A solution of 180 mg. of IV, m.p. 215–225°, in 5 ml. of benzene was dried azeotropically; 30 ml. of dry tetrahydrofuran and 280 mg. of lithium aluminum hydride were added and the suspension refluxed two hours and subsequently allowed to stir overnight. Excess reagent was destroyed by the cautious addition of ethyl acetate. The suspension was filtered after the addition of 4 ml. of water, the filter-cake was washed with chloroform and the organic phase concentrated *in vacuo*. Trituration of the residue with ether afforded 130 mg. of product, m.p. 200–220°. The analytical sample of 5-methyl-17α,20,20,-21-bismethylenedioxy-3-ethylenedioxypregnane-11β-ol was obtained from methanol, m.p. 220–225°, $[\alpha]D$ −38°. Calcd. for $C_{26}H_{40}O_7$: C, 67.21; H, 8.68. Found: C, 66.83; H, 8.58.

**5-Methyl-17α,20,20,21-bismethylenedioxypregnane-11β-ol-3-one (VI).**—A solution of 2.30 g. of V, 0.20 g. of *p*-toluenesulfonic acid and 200 ml. of acetone was allowed to stand at 25° overnight. The solution was diluted with water, extracted with chloroform and the organic layer dried over sodium sulfate and concentrated *in vacuo*. The residue crystallized from methanol afforded 1.40 g. of product, m.p. 238–245°. The analytical sample of 5-methyl-17α,20,20,21-bis-methylenedioxypregnane-11β-ol-3-one was obtained from methanol, m.p. 244–249°; $[\alpha]D$ −51°, $[\alpha]^{27}_{400}$ −112°, $[\alpha]_{350}$ −207°, $[\alpha]_{312.5}$ −506°, $[\alpha]_{310}$ −337°, $[\alpha]_{305}$ −325°, $[\alpha]_{300}$ −398°, $[\alpha]_{290}$ −165°, $[\alpha]_{285}$ −49° (*c* 0.067, dioxane[9]). Calcd. for $C_{24}H_{36}O_6$: C, 68.54; H, 8.63. Found: C, 68.60; H, 8.53.

**5-Methyl-17α,20,20,21-bismethylenedioxy-1-pregnene-11β-ol-3-one (VII).**—A solution of 400 mg. of VI and 250 mg. of *p*-toluenesulfonic acid in 10 cc. of acetic acid was brominated at 20° over a 15-min. period with a solution containing 153 mg. of bromine and 88 mg. of sodium acetate in 4 ml. of acetic acid.[20] The solution turned light yellow, but the color was discharged on adding 2.9 g. of sodium acetate in 6 ml. of water. The reaction mixture was diluted with ice-water, allowed to stand 0.5 hour and filtered to yield 0.46 g. of crude bromide. Several crystallizations from methanol afforded 40 mg. of a monobromide, dec. 210–215°; the infrared (KBr) carbonyl of this product showed absorption at 5.78 μ. Calcd.: Br, 16.02. Found: Br, 16.12. The crude product above combined with 0.21 g. from a similar run, a total of 0.67 g., was heated at 100° with 0.67 g. of lithium chloride and 12 cc. of dimethylformamide for 2.3 hours.[21] The cooled reaction mixture was poured into water, extracted with chloroform and the organic phase was dried over sodium sulfate and concentrated *in vacuo*. The crude product was adsorbed on 60 g. of acid-washed alumina. The fractions 4–6, a total of 220 mg., eluted with ether to chloroform–ether, were combined. The infrared spectrum of this product showed the presence of some saturated carbonyl containing compound and it was therefore rechromatographed on 26 g. of acid-washed alumina. Elution with ether–petroleum ether 7:3 afforded 193 mg. of the 1-dehydro compound. Crystallization from methanol and recrystallization from benzene yielded the analytical sample of 5-methyl-17α,20,20,21-bismethylenedioxy-1-pregnene-11β-ol-3-one, m.p. 238–242°, $[\alpha]^{27}D$ +13° (*c* 0.5 $CHCl_3$); $\lambda_{max}^{methanol}$ 235 mμ, *E* 6790. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 69.11; H, 8.35.

**5-Methylpregnane-11β,17α,21-triol-3,20-dione Acetate (VIII).**—A suspension of 250 mg. of VI in 50 ml. of 60% aqueous formic acid[3,19] was heated inside a steam-cone for 20 min. in a nitrogen atmosphere. The cooled solution was diluted with ice-water and extracted with chloroform. The chloroform layer was washed with aqueous sodium bicarbonate solution, dried and concentrated *in vacuo*. The crude product dissolved in 10 ml. of methanol was allowed to stand 15 min. at 25° with 0.15 ml. of 1 *N* methanolic sodium methoxide to cleave any formate esters. The solution was neutralized with acetic acid and diluted with ice-water. The product was extracted into chloroform and the chloroform layer dried and concentrated *in vacuo*. The crude product was acetylated with acetic anhydride in pyridine under standard conditions. Two crystallizations from methanol afforded 60 mg. of an anhydro compound, m.p. 215–223°, presumably 5-methyl-9(11)-pregnene-17α,21-diol-3,-

20-dione 21-acetate. The analytical sample was crystallized from benzene, m.p. 222–229°, $[\alpha]D$ +61°; $\lambda_{max}^{KBr}$ 2.93, 3.31, sh.5.75, 5.81, sh.5.87, sh.5.93, 7.90, 8.10 $\mu$. Calcd. for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.15; H, 9.00. Chromatography of the mother liquors on 7.0 g. of acid-washed alumina (Merck) and elution with chloroform–ether 3:7 and 4:6 afforded additional anhydro product (13 mg.). Chloroform–ether 6:4 and 7:3 eluted 60 mg. of crystalline product, m.p. 190–200°. Rechromatography of the latter fraction on 5.0 g. of acid-washed alumina and elution with chloroform–ether 4:6 afforded 26 mg. of 5-methylpregnane-11$\beta$,17$\alpha$,21-triol-3,20-dione 21-acetate, m.p. 205–211°, $[\alpha]D$ +78°, after three crystallizations from benzene; $\lambda_{max}^{KBr}$ 2.92, sh.5.75, 5.81–5.86, sh.5.90, 7.88, 8.08 $\mu$. Calcd. for $C_{24}H_{36}O_6$: C, 68.54; H, 8.63. Found: C, 67.76; H, 8.49.

**5-Methyl-1-pregnene-11$\beta$,17$\alpha$,21-triol-3,20-dione Acetate (IX).**—The cleavage of the bismethylenedioxy protecting group and acetylation of 200 mg. of VI was carried out as described above. The crude product was chromatographed on 17 g. of acid-washed alumina. Elution with ether afforded 22 mg. of recovered starting material. Elution with chloroform–ether 7:3 to chloroform afforded 101 mg. of material, m.p. 180–215°, which on rechromatography and then two crystallizations from benzene yielded the analytical sample of 5-methyl-1-pregnene-11$\beta$,17$\alpha$,21-triol-3,20-dione acetate, m.p. 209–215°, $[\alpha]D$ +140°; $\lambda_{max}^{KBr}$ 2.93, sh.5.73, 5.80, 6.02, sh.6.17, 7.91, 8.13 $\mu$; $\lambda_{max}^{methanol}$ 233 m$\mu$, $E$ 6,900. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 69.10; H, 8.39.

RAHWAY, N. J.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY, HARVARD UNIVERSITY]

# Origin of Ketone 104 and Isolation of a Companion Acid[1]

BY LOUIS F. FIESER, WEI-YUAN HUANG[2a] AND TOSHIO GOTO[2b]

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Ketone 104 is shown to be derived from cholesterol and not a companion, and analysis of the infrared and nuclear magnetic resonance spectra indicate that it is a spiroketal or spiroacetal. Synthetic 4,5-secocholestane-(3$\alpha$,5$\alpha$)(3$\beta$,4)-dioxide (**5**) is not identical with desoxoketone 104 but is similar in showing very strong infrared bands in the fingerprint region. Dichromate oxidation of cholesterol at 100° destroys other neutral products and affords ketone 104 in 4% yield. Oxidation at 121° leads to the easily isolated duoannelic acid (**8**). Another oxidation procedure affords crystalline Butenandt acid (**7**) in 12% yield.

Ketone 104, one of several products resulting on oxidation of commercial cholesterol with sodium dichromate in benzene–acetic acid,[3] has previously been characterized as a somewhat hindered ketone of the formula $C_{27}H_{44}O_3$ probably containing two oxidic bridges.[3,4] Because of the low yield (about 1%) and the high oxygen content, we at first thought it possible that the substance arises from an oxygen-rich companion rather than from cholesterol itself. However, a search for such a precursor proved fruitless[5] and we can now present evidence that cholesterol is the actual precursor. In view of later developments the experiments will not be recorded in detail but are summarized as follows. First a procedure was developed for oxidation of a 300–400-mg. sample, chromatography of the neutral fraction, removal of cholestanone (from cholestanol, present as a companion) and $\Delta^4$-cholestene-3,6-dione by Girard separation (usually repeated), conversion of ketone 104 to the 2,4-dinitrophenylhydrazone, and determination of the yield by spectrophotometry based upon the following constants: derivative, $E_{342}$ = 17,500, $E_{357.5}$ = 21,400; reagent: $E_{342}$ = 14,400, $E_{357.5}$ = 10,800. Typical results for oxidation of two samples of cholesterol purified through the dibromide and of unpurified commercial cholesterol were: yield of ketone 104: 1.19, 1.12 and 1.16%. Then $\Delta^4$-cholestene-3,6-dione was purified by the highly selective process of extraction from ligroin with Claisen alkali as the enolate and transformed into $\Delta^5$-cholestene-3$\beta$-ol. This sample on oxidation by the analytical procedure afforded ketone 104 in the same yield as obtained from other samples. In further confirmation of the point, we now report oxidation of methyl 3$\beta$-hydroxy-$\Delta^5$-cholenate to a dioxidic ketone fully analogous to ketone 104.

As previously reported,[4] the infrared spectrum of ketone 104 is characterized by four extremely strong bands in the fingerprint region. Drs. M. E. Wall and C. R. Eddy kindly examined the infrared region and noted a significant analogy to the sapogenins. Whereas ordinary steroids show absorption bands in the fingerprint region of molar absorptivities seldom exceeding 30 liters per mole per centimeter,[6] sapogenins are exceptional in having several sharp bands in this region with molar absorptivities[7] up to 422 l./mole$^{-1}$/cm.$^{-1}$. These bands are attributable to the spiroketal system in rings E and F, since opening of this ring system is attended with marked decrease in absorption in the fingerprint region.[7]

CHARACTERISTIC BANDS OF KETONE 104[a]

| Wave length, $\mu$ | Wave no., cm.$^{-1}$ | Molar absorptivity, l./mole$^{-1}$/cm.$^{-1}$ |
|---|---|---|
| 11.08 | 904 | 445 |
| 10.02 | 998 | 565 |
| 9.81 | 1019 | 604 |
| 8.97 | 1114 | 572 |

[a] Measurements by Dr. Eddy.

The oxidation product is clearly not a spiroketal of the sapogenin type, since it is very resistant to

(1) The Editors kindly consented to a trial in this and a few papers to follow of having formula numbers set in boldface arabic type as a means of obviating the many disadvantages of roman numerals.—L. F. FIESER.

(2) (a) Work done as postdoctoral fellow in 1954–1955; (b) Recipient of a Fulbright travel grant on leave from Nagoya University, Nagoya, Japan.

(3) L. F. Fieser, THIS JOURNAL, **75**, 4395 (1953).

(4) L. F. Fieser and B. K. Bhattacharyya, *ibid.*, **75**, 4418 (1953).

(5) L. F. Fieser, W.-Y. Huang and B. K. Bhattacharyya, *J. Org. Chem.*, **22**, 1380 (1957).

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