crystallization from hot CCl_4 gave 3.65 g. (96%) melting at 108.5–110.5°.

Anal. Calcd. for $C_8H_9ClIO_3$: C, 30.57; H, 2.55; I, 40.45; Cl, 11.15. Found: C, 30.79; H, 2.73; I, 40.62; Cl, 10.95.

γ-Lactone of 3-Hydroxy-4-iodo-1-carboxy-6-hydroxymethylcyclohexane (XIX).—Following the method of Brown and Chaiken[12] with some modification, a three-necked flask fitted with a water condenser and stirrer and containing 25 ml. of purified diglyme was heated to 40°. To this was added 0.3 g. (0.008 mole) of sodium borohydride and the temperature was raised to 60°. The iodolactone acid chloride (4.0 g., 0.0127 mole) in 25 ml. of diglyme was slowly added over a 0.75-hr. period. The reaction mixture turned an opaque orange. Stirring and heating were continued for 3 hr., and then the mixture was cooled slowly overnight. The reaction was then poured on a 1:1 mixture of ice–HCl and stirred for 1 hr. The red solution was extracted with $CHCl_3$. The $CHCl_3$ layer was treated with 20% $NaHCO_3$, $NaHSO_3$, and water, respectively. The yellow $CHCl_3$ layer was then dried over $MgSO_4$, filtered, and concentrated. The residual liquid was vacuum distilled using a water bath at 50° to remove the diglyme. The remaining light brown oil (0.09 g.) precipitated 0.04 g. (1.1%) of product after dilution with $CHCl_3$ and standing several days. A melting point of 124–126° was obtained using a Kofler block. The infrared spectra (KBr) indicated –OH and 5-membered lactone at 2.95 and 5.69 μ, respectively.

Anal. Calcd. for $C_8H_{11}IO_3$: C, 34.04; H, 3.90; I, 45.04. Found: C, 34.20; H, 3.82; I, 45.23.

(12) W. G. Brown and S. W. Chaiken, *J. Am. Chem. Soc.*, **71**, 122 (1949).

The Configuration at C-20 of 11-Oxygenated 3α,20-Dihydroxy-5β-pregnan-21-oic Acids[1]

VERNON R. MATTOX AND WILEY VRIEZE

Section of Biochemistry, Mayo Clinic and Mayo Foundation, Rochester, Minnesota

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The C-20 configuration in a pair of epimeric 3α,20-diacetoxy-11-oxo-5β-pregnan-21-oic acids (m.p. 199–200° and 261.5–262°) was determined by correlation with the configuration in 3α,20β,21-triacetoxy-5β-pregnan-11-one. 3α,20β-Diacetoxy-11-oxo-5β-pregnan-21-al was prepared by ozonization of the corresponding 21-benzylidene derivative. Reduction of the 3α,20β-diacetoxy-11-oxo-5β-pregnan-21-al at C-21 followed by acetylation gave 3α,20β,21-triacetoxy-5β-pregnan-11-one and established the 20β-configuration in the aldehyde. Oxidation of the aldehyde with potassium permanganate produced 3α,20β-diacetoxy-11-oxo-5β-pregnan-21-oic acid which was identical with the 3α,20-diacetoxy-11-oxo-5β-pregnan-21-oic acid of m.p. 199–200°. In the 20-hydroxypregnan-21-oic derivatives, C-20 configuration was established in another manner. Lithium aluminum hydride reduction of both 3α,20β,21-trihydroxy-5β-pregnan-11-one and methyl 3α,20-dihydroxy-11-oxo-5β-pregnan-21-oate (of the same configuration at C-20 as the 3α,20-diacetoxy-11-oxo-5β-pregnan-21-oic acid of m.p. 199–200°) gave the same product: 5β-pregnane-3α,11β,20β,21-tetrol.

When the 17β-steroidal glyoxal I (Fig. 1) is treated with alkali and the product is acetylated, two substances (II and III), which are isomeric at C-20, are formed.[2] We wished to determine the C-20 configuration of these compounds and their derivatives. The optical rotatory values of the hydroxyl compounds and their acetates were determined, and the data were correlated[2] according to procedures used by Fieser and Fieser[3,4] and by Sarett[5] for assigning C-20 configuration to steroids. There were reasons to suspect[2] that the C-20 configuration indicated for substances II and III by these procedures was wrong. Consequently, the transformations outlined in Fig. 2 have been performed in order to establish unequivocally the C-20 configuration in these epimeric 20-hydroxypregnan-21-oic acids.

Oliveto, *et al.*,[6] reduced the 20-keto group of the benzylidene (IV) and obtained a 20-hydroxyl derivative which was tentatively assigned the β-configuration on the basis that metal hydride reduction of 20-keto steroids usually gives predominantly 20β-hydroxyl derivatives.

We reduced several samples of this benzylidene (IV) under conditions similar to those described by the Schering group.[6] If the solution was agitated, reduction at C-20 was complete within 1 hr. Chromatography of the crystalline product on paper and examination of the chromatogram after treatment with 4% phosphomolybdic acid in absolute ethanol[7] revealed the presence of two substances (R_f 0.63 and 0.54). The starting material IV has an R_f of 0.81. There was considerable variation in the proportions of the compound with R_f 0.63 (the 20β-hydroxyl steroid V) and the one with R_f 0.54 (presumably the 20-epimer of V) obtained in several experiments in which the procedure was not altered significantly. Separation of the C-20 epimers by crystallization was difficult, both with the dihydroxyl compounds and with their diacetyl derivatives. Only the 20β-epimer was obtained in chromatographically pure form.

The diacetate VI of the 20β-epimer, obtained by acetylation of V, had physical constants in good agreement with those of the compound prepared by Oliveto, *et al.* An attempt to cleave the double bond of the acetylated benzylidene (VI) with osmium tetroxide–periodic acid[8] to obtain the aldehyde was not successful. However, the aldehyde VII was obtained in over 90% yield by ozonization of VI in chloroform–methanol at −20°. The melting points of samples of the aldehyde varied from about 90 to 125°, although the samples had identical paper chromatographic mobilities and infrared spectra.

Reduction of the aldehyde VII with hydrogen in the presence of Adams' platinum oxide and ferrous sulfate[9] proceeded readily and hydrogen uptake stopped after 1 molar equiv. had been absorbed. The corresponding

(1) This investigation was supported in part by Grant A-5452 from the National Institutes of Health, Public Health Service.

(2) L. Lewbart, and V. R. Mattox, *J. Org. Chem.*, **28**, 1779 (1963).

(3) L. F. Fieser and M. Fieser, *Experientia*, **4**, 285 (1948).

(4) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 612.

(5) L. H. Sarett, *J. Am. Chem. Soc.*, **71**, 1175 (1949).

(6) E. P. Oliveto, C. Gerold, and E. B. Hershberg, *ibid.*, **76**, 6111 (1954).

(7) M. L. Lewbart and J. J. Schneider, *Nature*, **176**, 1175 (1955).

(8) R. Pappo, D. S. Allen, Jr., R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, **21**, 478 (1956).

(9) R. Adams and B. S. Garvey, *J. Am. Chem. Soc.*, **48**, 477 (1926).

21-hydroxyl derivative (VIII) was obtained in good yield. Acetylation of VIII gave a product (IX) which was shown by a mixture melting point determination and by comparison of infrared spectra to be 3α,20β,21-triacetoxy-5β-pregnan-11-one.[10] This triacetate IX was obtained also by potassium borohydride reduction of the aldehyde VII followed by acetylation. The triacetate IX has been prepared by Sarett[10] and its configuration at C-20 has been correlated with that of a considerable number of other 11-keto steroids which have hydroxyl groups at C-3,20,21, at C-3,17,20,21, at C-3,17,20, and at C-3,20. Thus, it follows that compounds V–VIII of Fig. 2 have the oxygen function at C-20 in the β-configuration since, during the conversion of V to IX, the asymmetry at C-20 was not disturbed.

Saponification of VIII yielded a derivative with the same physical constants as those reported for 3α,20β,21-trihydroxy-5β-pregnan-11-one[10] (X).

Chromic acid oxidation of the 21-hydroxyl group in VIII gave an acid (XI) which was shown by mixture melting point determination and comparison of infrared spectra to be identical with the 3α,20-diacetoxy-11-oxo-5β-pregnan-21-oic acid[2] of m.p. 199–200°, $[\alpha]_D$ +41°. Furthermore, the same acid (XI) was obtained by oxidation of the 21-aldehyde VII with potassium permanganate in acetone. The methyl ester XII, prepared by treatment of XI with diazomethane, was identical with the methyl 3α,20-diacetoxy-11-oxo-5β-pregnan-21-oate[2] with m.p. 204–205°, $[\alpha]_D$ +33°. Thus, since no change in configuration at C-20 should occur during oxidation of the 21-hydroxyl compound VIII or the 21-aldehyde VII to the corresponding acid XI, substances XI and XII must have 20β-acetoxyl groups.

It was possible to correlate C-20 configuration in the 20-hydroxypregnan-21-oic acid derivatives and 3α,20β,-21-triacetoxy-5β-pregnan-11-one (IX) in another manner. The triolone X, with the same C-20 configuration as IX, and methyl 3α,20-dihydroxy-11-oxo-5β-pregnan-21-oate (XIII), with the same C-20 configuration as XI, had been prepared. Lithium aluminum hydride reduction of both the triolone X and the 20-hydroxyl pregnanoic ester XIII gave the same product: 5β-pregnane-3α,11β,20β,21-tetrol (XIV). Since it is known that lithium aluminum hydride reduction of an α-hydroxyl ester does not invert[11] the configuration of the α-substituent, these transformations demonstrate that X and XIII had identical C-20 configurations. The assignment of configuration to several pairs of epimeric 20-hydroxypregnan-21-oic acids[2] is based on these results.

The finding that the acetoxyl group at C-20 in the 3α,20-diacetoxy-11-oxo-5β-pregnan-21-oic acid of m.p. 199–200° (XI) is β-oriented is of considerable interest because, on the basis of acetylation increments of optical rotation as applied previously, the configuration was expected to be 20α. In previous studies on a number of pairs of steroids with an α-hydrogen atom at C-17 and either no substitution at C-21 or a hydroxyl or acetoxyl group at this position, rotations of the 20β-acetoxyl derivatives were larger than those of the 20α-acetoxyl epimers. In addition, acetylation increments of the 20β-hydroxyl derivatives were uniformly larger than those of the 20α-hydroxyl epimers. In a comparison of several pairs of such compounds, no exception to these rules was found.[4]

In correlating the optical rotatory data on the derivatives of the 20-hydroxypregnan-21-oic acids, six pairs of 20-acetoxyl epimers were examined and in all cases the rotations of the 20α-acetoxyl compounds were larger than those of the 20β-epimers.[2] This difference must be related to the carboxyl function of the molecule since

(10) L. H. Sarett, *J. Am. Chem. Soc.*, **71**, 1165 (1949).
(11) D. S. Noyce and D. B. Denney, *ibid.*, **72**, 5743 (1950).

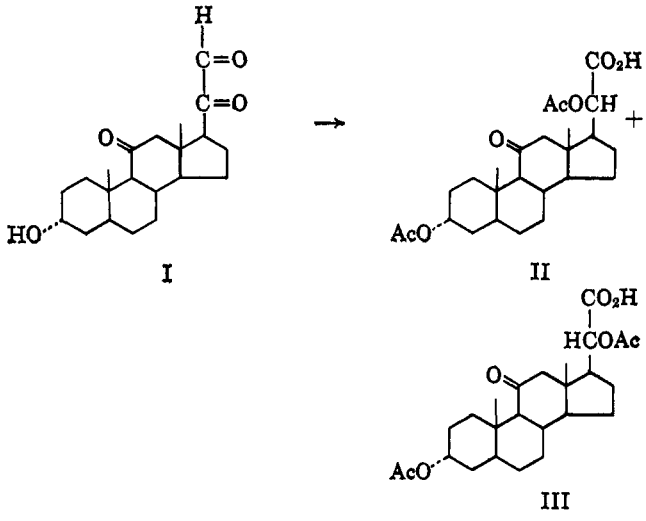

Figure 1.

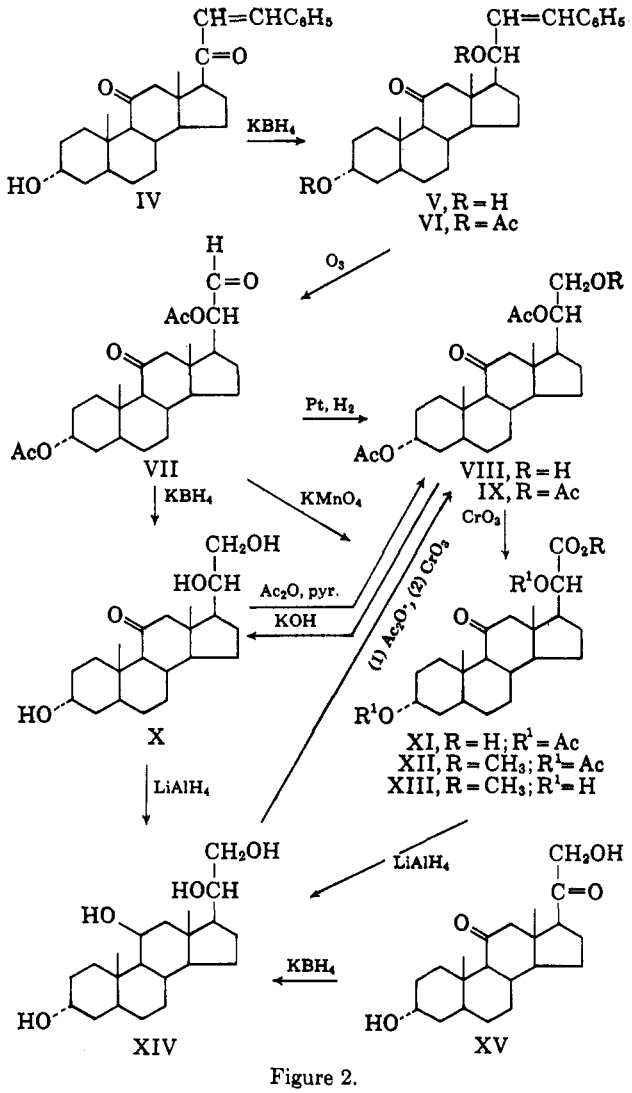

Figure 2.

this moiety of the compounds represents the only portion which is different from the instances in which the generalization is valid. The relationship of optical activity to the polarizability of groups attached to the asymmetric center, as discussed by Brewster,[12] may offer an explanation of the anomalous rotatory behavior of the epimeric 20-hydroxypregnan-21-oic acids after acetylation.

Experimental[13]

21-Benzylidene-3α,20β-dihydroxy-5β-pregnan-11-one (V) from IV.—To a suspension of 2.00 g. of 21-benzylidene-3α-hydroxy-5β-pregnane-11,20-dione in 75 ml. of methanol was added 2.0 g. of KBH_4 in 7.5 ml. of water. The mixture was shaken by hand every 5 min. for 45 min. and then shaken mechanically for 15 min. The mixture was concentrated *in vacuo* to about 15 ml. and diluted with 100 ml. of water, and 50 ml. of 1 *N* hydrochloric acid was added slowly. The precipitate was collected and dissolved in chloroform and this solution was washed with water and taken to dryness *in vacuo*. After recrystallization once from aqueous methanol and then three times from benzene, 876 mg. (44%) of product, m.p. 201–201.5°, was obtained. Paper chromatography with isooctane–toluene–methanol–water (225:275:400:100) revealed only one compound: R_f 0.63 (in cruder fractions a substance with R_f 0.54, presumably the 20α-epimer, was present), λ_{max}^{MeOH} 252 mμ (ε 21,100), [α]D +13 ±2° ($CHCl_3$); lit.[6] m.p. 191–193°, λ_{max}^{EtOH} 254 mμ (ε 20,700), [α]D +3.8° ($CHCl_3$).

Anal. Calcd. for $C_{28}H_{38}O_3$: C, 79.58; H, 9.06. Found: C, 79.36; H, 9.27.

21-Benzylidene-3α,20β-diacetoxy-5β-pregnan-11-one (VI) from V.—Acetylation of 710 mg. of 21-benzylidene-3α,20β-dihydroxy-5β-pregnan-11-one in 5.0 ml. each of pyridine and acetic anhydride for 18 hr. at room temperature and crystallization of the product from benzene–methanol gave the diacetate VI (94%): m.p. 192–194° (further recrystallization raised the melting point to 196.5–197°), λ_{max}^{MeOH} 253 mμ (ε 22,300), [α]D +15 ± 2° ($CHCl_3$); lit.[6] m.p. 199–201°, [α]D +11.8° ($CHCl_3$). On paper impregnated with 30% kerosene in acetone and developed with ethanol–water (2:1) saturated with kerosene, only one substance was detectable by examination over 254-mμ illumination or by drying and treating with alcoholic 4% phosphomolybdic acid. The chromatographic mobilities and the infrared spectra of this compound and of a sample of the 21-benzylidene-3α,20β-diacetoxy-5β-pregnan-11-one[14] described by Oliveto, *et al.*,[6] were identical.

Anal. Calcd. for $C_{32}H_{42}O_5$: C, 75.85; H, 8.36. Found: C, 76.04; H. 8.38.

3α,20β-Diacetoxy-11-oxo-5β-pregnan-21-al (VII) from VI.—Two molar equivalents of ozone were passed into a solution of 1.19 g. of 21-benzylidene-3α,20β-diacetoxy-5β-pregnan-11-one in 10 ml. each of chloroform and methanol at −20° during 35 min. While the solution was still at −20°, 4.0 g. of zinc dust and then 8 ml. of 95% acetic acid were added. The flask was shaken continuously for 5 min., after which peroxides were not detectable with KI–starch paper. The zinc was filtered off and washed with 50 ml. of ethyl acetate; to the combined filtrate and washings 50 ml. of water was added. The organic phase was separated and the aqueous phase was washed with two 25-ml. portions of ethyl acetate. The combined ethyl acetate extract was washed with an excess of concentrated sodium bicarbonate and then twice with water and concentrated *in vacuo* almost to dryness. To remove benzaldehyde, the residue was dissolved in about 10 ml. of acetone, 30 ml. of water was added, and the solution was concentrated *in vacuo* to about 10 ml. An additional 15 ml. of acetone and 40 ml. of water were added, and the solution was concentrated to about 20 ml. to give well-formed crystals which had no odor of benzaldehyde. The product, dried to constant weight at 55°, weighed 987 mg. and melted at 103–109°. The extinction at 253 mμ indicated the presence of less than 0.4% of starting material. Paper chromatography with isooctane–methanol–water (5:4:1) followed by treatment with phosphomolybdic acid gave only one spot, R_f 0.13. Melting points of different preparations, crystallized from acetone–water, varied from 82–89° to 121–124° for samples indistinguishable by chromatographic mobilities and by infrared spectra. The product is hygroscopic. A sample which had been dried and subsequently exposed to the atmosphere lost 2.7% when redried *in vacuo* at 60° for 24 hr. The optical rotation, [α]D +69 ± 2° (CH_3OH), and analysis were obtained immediately after the sample had been dried.

Anal. Calcd. for $C_{25}H_{36}O_6 \cdot 0.5H_2O$: C, 68.00; H, 8.45. Found: C, 68.02; H, 8.54.

The 21-(2,4-Dinitrophenylhydrazone) of 3α,20β-Diacetoxy-11-oxo-5β-pregnan-21-al (VII).—A solution of 45 mg. of aldehyde VII and 22 mg. of 2,4-dinitrophenylhydrazine in 5 ml. of acetic acid stood at room temperature 30 min. and then was diluted with water. The product was crystallized from methanol: m.p. 215–216° dec., $\lambda_{max1}^{CHCl_3}$ 261 mμ (ε 10,900), $\lambda_{max2}^{CHCl_3}$ 351 mμ (ε 22,200).

Anal. Calcd. for $C_{31}H_{40}N_4O_9$: N, 9.15. Found: N, 9.42.

3α,20β-Diacetoxy-21-hydroxy-5β-pregnan-11-one (VIII) from VII.—A solution of 100 mg. of 3α,20β-diacetoxy-11-oxo-5β-pregnan-21-al in 12 ml. of glacial acetic acid which contained 0.10 ml. of freshly prepared aqueous 0.10 *M* ferrous sulfate and 25 mg of $PtO_2 \cdot H_2O$ absorbed 1.0 molar equiv. of hydrogen (in excess o that required for the $PtO_2 \cdot H_2O$) in 20 min. and hydrogen uptake ceased. The platinum was filtered off, the solvent was removed *in vacuo*, and crystals (47 mg., m.p. 137–138.5°) were obtained from methanol. Additional product (23 mg., m.p. 134–135°) was obtained from ether. A sample, purified from ether, partially melted at 137–140°, recrystallized, and then melted at 163–165°, [α]D +80 ± 2° (CH_3OH).

Anal. Calcd. for $C_{25}H_{38}O_6 \cdot 0.5H_2O$: C, 67.69; H, 8.86. Found: C, 67.17; H, 8.67.

3α,20β,21-Triacetoxy-5β-pregnan-11-one (IX) from VIII.—Acetylation of 143 mg. of 3α,20β-diacetoxy-21-hydroxy-5β-pregnan-11-one in 3.0 ml. each of pyridine and acetic anhydride at room temperature for 1.5 hr. and crystallization from ether–isooctane gave a product (71 mg., m.p. 159.5–160°; 36 mg., m.p. 158.5–159°) which did not depress the melting point of 3α,20β,21-triacetoxy-5β-pregnan-11-one[15] (m.p. 158.5–159°): [α]D +77 ± 2° (acetone), lit.[10] [α]D +78 ± 2° (acetone). The infrared spectra in chloroform of this compound and of the 3α,20β,21-triacetoxy-5β-pregnan-11-one[10] supplied by Sarett were identical.

3α,20β,21-Triacetoxy-5β-pregnan-20-one (IX) from VII.—Reduction of 35 mg. of 3α,20β-diacetoxy-11-oxo-5β-pregnan-21-al in 2.0 ml. of methanol with 20 mg. of KBH_4 in 0.2 ml. of water during 4.5 hr. at room temperature followed by acetylation of the product and crystallization gave 3α,20β,21-triacetoxy-5β-pregnan-11-one, m.p. 153–155°. After recrystallization from ether, the product, 5.2 mg., m.p. 155.5–157°, had an infrared spectrum identical with that of the product prepared by catalytic reduction and acetylation of VII.

3α,20β,21-Triacetoxy-5β-pregnan-11-one (IX) from XIV. Acetylation.—A solution of 200 mg. of 5β-pregnane-3α,11β,20β,-21-tetrol in 1.7 ml. each of acetic anhydride and pyridine stood at room temperature for 18 hr. Ice was added, the product was extracted with chloroform, and the solution was washed successively with dilute hydrochloric acid and 5% sodium bicarbonate solution and taken to dryness.

Oxidation.—The residue in 3.0 ml. of acetic acid, maintained at 15°, was mixed with 15 ml. of 1% CrO_3 in acetic acid–water (99:1) which had been precooled to 15°. After 10 min. water was added and the product was extracted with chloroform and crystallized from acetone–isooctane; the yield was 234 mg. (86%), m.p. 156–158°. After recrystallization the product melted at 159–160°. It did not depress the melting point of the triacetoxy ketone (IX) which had been prepared by acetylation of VIII; the infrared spectra of these two samples of IX were identical.

3α,20β,21-Trihydroxy-5β-pregnan-11-one (X) from VIII.—To 125 mg. of 3α,20β-diacetoxy-21-hydroxy-5β-pregnan-11-one in 1.62 ml. of methanol was added 0.38 ml. of 4 *N* methanolic potassium hydroxide; the solution was refluxed 10 min., diluted with 1 ml. of water, and refluxed 5 min. The solution was diluted to turbidity with water and allowed to cool; the resultant crystals (78 mg., 78%, m.p. 231–233°) were collected and washed. The recrystallized product had m.p. 233–234°, [α]D +50 ± 2° (alcohol); lit.[10] m.p. 235°, [α]D +53° (alcohol).

3α,20β-Diacetoxy-11-oxo-5β-pregnan-21-oic Acid (XI) from VII.—A mixture of 48 mg. of potassium permanganate, 44 mg. of 3α,20β-diacetoxy-11-oxo-5β-pregnan-21-al and 10 ml. of acetone

(12) J. H. Brewster, *J. Am Chem. Soc.*, **81**, 5475 (1959).

(13) Analyses were by Mr. J. F. Alicino, Metuchen, N. J.

(14) Kindly supplied by Dr. E. P. Oliveto.

(15) Obtained through the courtesy of Dr. L. H. Sarett.

was shaken mechanically for 4 hr. at room temperature. Water (10 ml.), ethyl acetate (10 ml.), and hydrochloric acid (2 ml., 1 *N*) were added, and the mixture was shaken vigorously and filtered through a pad of infusorial earth. The organic phase was washed with water and taken to dryness *in vacuo*, and crystals (31 mg., m.p. 190–195°) were obtained from acetone. Recrystallization from acetone gave 9.1 mg. of product which melted at 196–197.5° and did not depress the melting point of samples of XI which had been prepared from VIII and from I.[2] The infrared spectra of the three samples of XI were identical.

3α,20β-Diacetoxy-11-oxo-5β-pregnan-21-oic Acid (XI) from VIII.—To a solution of 50 mg. of 3α,20β-diacetoxy-21-hydroxy-5β-pregnan-11-one in 5 ml. of acetic acid was added 0.11 ml. of 5 *M* chromic acid in water at room temperature. After 1.5 hr., water was added, the solution was extracted with ethyl acetate, and the organic phase was washed with water and taken to dryness *in vacuo*. Crystals (16 mg., m.p. 196.5–198°; 20 mg., m.p. 192–194.5°) were obtained from acetone. The recrystallized product melted at 198.5–200.5° and did not depress the melting point of the 3α,20-diacetoxy-11-oxo-5β-pregnan-21-oic acid[2] (m.p. 199–200°, $[\alpha]_D$ +41°) which was derived from 3α,-21,21-trihydroxy-5β-pregnane-11,20-dione (the hydrate of I) by treatment with alkali. Furthermore, the infrared spectra of the two diacetoxy acids were identical.

Methyl 3α,20β-Diacetoxy-11-oxo-5β-pregnan-21-oate (XII) from XI.—Treatment of 3α,20β-diacetoxy-11-oxo-5β-pregnan-21-oic acid (derived from VIII) with diazomethane yielded the ester XII, m.p. 200–202°, which did not depress the melting point of methyl 3α,20β-diacetoxy-11-oxo-5β-pregnan-21-oate,[2] m.p. 204–205°. Their infrared spectra were identical.

5β-Pregnane-3α,11β,20β,21-tetrol (XIV) from X.—To 98 mg. of 3α,20β,21-trihydroxy-5β-pregnan-11-one (X) in 5.0 ml. of tetrahydrofuran was added 190 mg. of lithium aluminum hydride in 25 ml. of the same solvent. The solution was refluxed for 30 min. and cooled and the excess $LiAlH_4$ was decomposed with ethyl acetate. The solution was acidified with hydrochloric acid and extracted with ethyl acetate. The extract was washed, the solvent was removed, and crystals (52 mg., m.p. 198–200°) were obtained from acetone. A purified sample had m.p. 207–207.5°, $[\alpha]_D$ +43 ± 2° (CH_3OH); lit.[16] m.p. 203–204°, $[\alpha]_D$ +53° (CH_3OH). This product did not depress the melting point of the tetrol (XIV) prepared by reduction of methyl 3α,20β-dihydroxy-11-oxo-5β-pregnan-21-oate with $LiAlH_4$. The infrared spectra of these two samples of tetrol were identical.

Anal. Calcd. for $C_{21}H_{36}O_4$: C, 71.55; H, 10.29. Found: C, 71.05; H, 10.18.

5β-Pregnane-3α,11β,20β,21-tetrol[17] (XIV) from XIII.—A solution of 190 mg. of methyl 3α,20β-dihydroxy-11-oxo-5β-pregnan-21-oate[2] (m.p. 204–205°) in 5 ml. of tetrahydrofuran (distilled from $LiAlH_4$) was mixed with 190 mg. of $LiAlH_4$ dissolved in 20 ml. of tetrahydrofuran. The mixture was refluxed 30 min. and cooled. The excess of $LiAlH_4$ was decomposed with ethyl acetate. A small volume of concentrated Na_2SO_4 was added and then 12 g. of solid Na_2SO_4 was added. The precipitate was filtered off and washed repeatedly with tetrahydrofuran. The combined filtrate and washings were taken to dryness *in vacuo* and crystals (20 mg., m.p. 197–199°) were obtained from acetone. The product appeared to be homogeneous on chromatography in formamide–chloroform and in toluene–ethyl acetate–methanol–water (16:4:10:10); it migrated at the same rate as 5β-pregnane-3α,11β,20β,21-tetrol and in the latter system, R_f 0.33. After recrystallization from methyl ethyl ketone, the product had m.p. 208.5–209° and it did not depress the melting point of 5β-pregnane-3α,11β,20β,21-tetrol which was derived from X. The infrared spectra of the two samples of XIV were identical.

5β-Pregnane-3α,11β,20β,21-tetrol (XIV) from XV.—To a solution of 1.74 g. of 3α,21-dihydroxy-5β-pregnane-11,20-dione[18] (XV) in 75 ml. of methanol was added 2.0 g. of potassium borohydride in 7.5 ml. of water at room temperature. After 48 hr. the solution was concentrated *in vacuo* to remove most of the methanol, water was added, and the solution was extracted with ethyl acetate. The extract was washed with dilute hydrochloric acid, sodium bicarbonate solution, and water and then taken to dryness. The residue gave 1.42 g. of crude product, m.p. 190–194°, from acetone. During chromatography in isooctane–*t*-butyl alcohol–water (50:25:45), R_f of XIV was 0.62; a minor constituent migrated with R_f 0.56. By recrystallization from methyl ethyl ketone, 527 mg. (30%) of chromatographically pure tetrol (XIV), m.p. 209–209.5°, $[\alpha]_D$ +41 ± 2° (CH_3OH), was obtained.

(16) M. Harnick, *Steroids*, **2**, 485 (1963).

(17) We are indebted to Dr. Marvin L. Lewbart for performing this reduction.

(18) M. L. Lewbart, and V. R. Mattox, *J. Org. Chem.*, **28**, 2001 (1963).

The Synthesis of 3-Alkoxy-*cis*-2-*trans*-4-unsaturated Acids[1]

EDWARD E. SMISSMAN AND A. NELSON VOLDENG

Department of Pharmaceutical Chemistry, University of Kansas, Lawrence, Kansas

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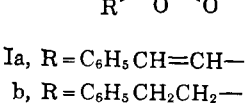
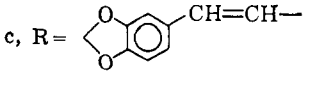
Ethyl β-methoxy-*cis*-crotonate and ethyl β-ethoxy-*cis*-crotonate were conveniently prepared in high yield. The reaction of various aldehydes with these crotonates yielded the corresponding 3-alkoxy-*cis*-2-*trans*-4-unsaturated acids. The ultraviolet and nuclear magnetic resonance spectra of these compounds are discussed.

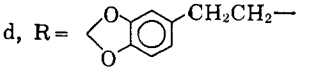
To prepare various constituents of *Piper methysticum* Forst. many workers have utilized the Reformatsky reaction. Kostermans[2] reported the synthesis of *dl*-kawain (Ia) by a condensation of ethyl α-bromo-β-methoxycrotonate and cinnamaldehyde in a yield of less than 10%. Viswanathan and Swaminathan[3] were able to prepare *dl*-dihydrokawain (Ib) in an 8.6% yield by a condensation of ethyl α-bromo-β-methoxycrotonate with hydrocinnamaldehyde. Klohs and coworkers[4] prepared *dl*-methysticin (Ic) in a 38% yield in an analogous manner. Reduction of the racemate Ic



Ia, R = $C_6H_5CH{=}CH-$

b, R = $C_6H_5CH_2CH_2-$





afforded *dl*-dihydromethysticin (Id).[4] The preparation of the bromocrotonate is lengthy and the over-all yield is low.

The approach to the synthesis of dihydrokawain (Ib) and analogs reported herein was essentially a three-step

(1) Taken from the dissertation presented by A. N. Voldeng, Jan., 1964, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Ph.D. degree.

(2) D. G. F. R. Kostermans, *Rec. trav. chim.*, **70**, 79 (1951).

(3) K. Viswanathan and S. Swaminathan, *Proc. Indian Acad. Sci.*, **52A**, 63 (1960).

(4) M. W. Klohs, F. Keller, and R. E. Williams, *J. Org. Chem.*, **24**, 1829 (1959).