points within the range 95–110°. These fractions were combined and hydrolyzed, giving 1.32 g. of 3(α),6(α)-dihydroxycholanic acid, m. p. 203–206°. Recrystallization from aqueous methanol gave fine needles melting sharply at 205°, $[\alpha]^{20}$D + 37.2 ± 3° (methanol). Mixed melting point with hyodesoxycholic acid 175–180°.

Anal. Calcd. for $C_{24}H_{40}O_4$: C, 73.43; H, 10.27. Found[12]: C, 73.88; H, 10.35. The methyl ester[6] crystallized from a mixture of ether and petroleum solvent (b. p. 69°) melted at 112–114° and showed $[\alpha]^{20}$D + 35.1 ± 3° (methanol).

B. To a solution of 1.90 g. of methyl 3(α)-acetoxy-6-ketocholanate in 100 ml. of methanol was added 5 g. of Raney nickel catalyst and the mixture was shaken four hours at a hydrogen pressure of about 50 lb. The solution was filtered from the catalyst and the ester was hydrolyzed with sodium hydroxide. Acidification of the hot solution yielded 1.44 g. (85%) of 3(α),6(α)-dihydroxycholanic acid, m. p. 202.5–204.5°; mixed melting point with hyodesoxycholic acid, 173–182°.

Methyl 3(α),6(α)-Diacetoxycholanate.—3(α),6(α)-Dihydroxycholanic acid (1.37 g.) was esterified with diazomethane in ether. The crude ester was acetylated by refluxing for one hour with 10 ml. of acetic anhydride. It was then poured into water, the gum dissolved in benzene, and washed with dilute sodium carbonate and then with water. After removal of the solvent it was crystallized from aqueous methanol giving 1.14 g. (67%) of needles, m. p. 106–108°. A mixture with methyl 3(α),6(β)-diacetoxycholanate (m. p. 98–100°) melted at 88–94°; $[\alpha]^{24}$D + 26.6 ± 3°.

Anal. Calcd. for $C_{29}H_{46}O_6$: C, 70.98; H, 9.45. Found[10]: C, 70.60; H, 9.36.

Rearrangement of Methyl 3(α)-Acetoxy-6-ketocholanate on Fisher Alumina.—A sample of methyl 3(α)-acetoxy-6-ketocholanate (m. p. 155–157°) was dissolved in a small volume of benzene and the solution was poured over a column of Fisher adsorption alumina (80–200 mesh). Elution with benzene and then with benzene-ether, gave solutions which left, when the solvent was evaporated, crystalline residues melting in the range of 168–174°. Recrystallization from aqueous methanol gave needles, m. p. 179–182°. The rotation was negative and the mixed m. p. with methyl 3(α)-acetoxy-6-keto-*allo*-cholanate[14] (m. p. 179–181°) prepared from 3-hydroxy-6-keto-*allo*-cholanic acid[5,14] showed no depression. Methyl 3-acetoxy-6-keto-*allo*-cholanate showed $[\alpha]^{20}$D − 18.3 ± 3° (benzene).

A sample of the alumina was washed with 10% methanolic acetic acid, then repeatedly with water and reactivated at 200–230°. A sample of methyl 3(α)-acetoxy-6-ketocholanate chromatographed on it as described above gave several fractions; the first to come off proved to be unchanged and 3(α)-acetoxy-6-ketocholanate and the last was the *allo* form.

Summary

1. 3-Keto-6(β)-hydroxycholanic acid has been prepared by the partial hydrolysis of methyl 3(α),6(β)-diacetoxycholanate, followed by oxidation and saponification.

2. This was characterized by converting it to the known 6-keto-*allo*-cholanic acid by a Wolff–Kishner reduction, followed by oxidation and rearrangement.

3. Methyl 3(α)-hydroxy-6-ketocholanate was prepared by partial oxidation of methyl hyodesoxycholate and several derivatives were made.

4. Methyl 3(α)-acetoxy-6(α)-hydroxycholanate was obtained by the hydrogenation of methyl 3(α)-acetoxy-6-ketocholanate and several derivatives were prepared.

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(14) Fernholz, *Z. physiol. Chem.*, **232**, 202 (1935).

KANSAS CITY, MISSOURI RECEIVED MAY 23, 1946

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF GEORGE A. BREON & CO.]

Degradation of Hyodesoxycholic Acid

BY ROBERT BRUCE MOFFETT, JAMES E. STAFFORD, JACOB LINSK* AND WILLARD M. HOEHN

Several workers[1] have reported the degradation of hyodesoxycholic acid by the Barbier–Wieland method. In this work we have repeated the degradation by the procedure of Hoehn and Mason.[2] Several intermediates, hitherto unreported, were isolated and we have found melting points and rotations of several other compounds at variance with those reported previously.

We have also applied to the degradation of hyodesoxycholic acid the recently reported method which Miescher and co-workers[3] used for the degradation of several bile acids. By this method the diphenylethylene derivative of a bile acid is brominated with N-bromosuccinimide followed by dehydrobromination with dimethylaniline and oxidation with chromic acid to the corresponding pregnan-20-one.

By both methods of degradation the same compound, 3(α),6(β)-diacetoxypregnan-20-one, was obtained, m. p. 131–133°, $[\alpha]^{24}$D + 53 ± 3° (in dioxane). Marker and Krueger[1b] report a compound melting at 100° (no rotation given) to have this structure. Hydrolysis of this acetate gave pregnan-3(α),6(β)-diol-20-one; m. p. 187–190°, $[\alpha]^{26}$D + 61.8 ±3° (in methanol). Kimura and Sugiyama[1a] report a compound melting at 198° with $[\alpha]$D + 6.52° (in alcohol) to have this structure. It seems certain that our pregnan-3,6-diol-20-one and acetate are not identical with the compounds previously reported; and, in view of the fact that we obtained the same acetate by two different methods, great doubt is cast on the structure of the previously reported compounds.

Numerous attempts to remove one of the ace-

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* Present address: Ohio State University, Columbus, Ohio.

(1) (a) Kimura and Sugiyama, *J. Biochem.* (Japan), **29**, 409 (1939); (b) Marker and Krueger, THIS JOURNAL, **62**, 79 (1940); (c) Marker and Lawson, U. S. Patents: 2,337,563; 2,337,564; and 2,366,204.

(2) Hoehn and Mason, THIS JOURNAL, **60**, 1493 (1038).

(3) (a) Meystre, Frey, Wettstein and Miescher, *Helv. Chim. Acta*, **27**, 1815 (1944); (b) Meystre, Ehmann, Neher and Miescher, *ibid.*, **28**, 1252 (1945); (c) Meystre and Miescher, *ibid.*, **28**, 1497 (1945); (d) Meystre and Miescher, *ibid.*, **29**, 33 (1946).

tiate groups from the diacetate of methyl-*bis-nor*-hyodesoxycholate and from 3(α),6(β)-diacetoxypregnan-20-one by partial saponification failed. In every case both acetate groups were hydrolyzed even when a great deficiency of alkali was used.

Intermediates in the Barbier–Wieland degradation hitherto unreported are: 3(α),6(β)-dihydroxy-*nor*-cholanyldiphenylcarbinol, and 3(α),6(β)-dihydroxy (and diacetoxy)-*bis-nor*-(and *ter-nor*)-çholanyldiphenylethylenes. Other new derivatives are: methyl dehydro-*nor*-(and *bis-nor*)-hyodesoxycholates, methyl 3(α),6(β)-diacetoxy-*bis-nor*-cholanate and pregnan-3,6,20-trione. Bromination of this last compound gave 4-bromopregnan-3,6,20-trione which was converted to 6-ketoprogesterone[4] by the action of boiling pyridine. Treatment of pregnan-3,6,20-trione with either mineral acid or alkali converted it to *allo*-pregnan-3,6,20-trione, m. p. 227–230.5°. This appears to be the same compound, m. p. 226.5–230°, prepared by Ehrenstein and Stevens[5] by the hydrolysis of 6-acetoxy-progesterone.

Experimental

3(α),6(β)-Dihydroxy-*nor*-cholanyldiphenylcarbinol.—A solution of 1 kg. of methyl hyodesoxycholate in 12 liters of hot toluene was added to a solution containing 39 moles of phenylmagnesium bromide in 7 liters of dry ether. The ether was distilled off during the addition and the reaction mixture was refluxed overnight. The mixture was worked up in the usual way giving 1035 g. of crude carbinol. A sample of the carbinol was recrystallized twice from benzene and melted at 203–205° $[\alpha]^{24}\mathrm{D}$ + 12.2 ± 3° (dioxane).

Anal. Calcd. for $C_{36}H_{50}O_3 \cdot 0.5H_2O$[6]: C, 80.10; H, 9.52. Found[7]: C, 80.54; H, 9.53.

3(α),6(β)-Dihydroxy-*bis-nor*-cholanyldiphenylethylene.—(a) Five grams of the crude carbinol in a mixture of 100 ml. of acetic acid and 5 ml. of acetic anhydride was refluxed for four hours. The solution was concentrated and poured into cold water. The suspended solid was coagulated by warming and dissolved in 300 ml. of methanol. Twelve grams of sodium hydroxide in 20 ml. of water was added and the solution was refluxed one hour, filtered and diluted with water, giving 4.7 g. of solid, m. p. 181–183°. Recrystallization from 80% methanol gave needles, m. p. 184–186° $[\alpha]^{27}\mathrm{D}$ + 31.1 ± 3° (dioxane).

Anal. Calcd. for $C_{36}H_{48}O_2$: C, 84.34; H, 9.44. Found[7]: C, 84.25; H, 9.77.

(b) One gram of carbinol (m. p. 202–204°) was dissolved in 80 ml. of toluene containing 1 ml. of concentrated hydrochloric acid. The solution was refluxed for fifteen hours and then concentrated. The solid residue was crystallized from aqueous methanol giving 0.83 g. of needles, m. p. 181–184°. A mixed melting point with a sample of the above gave no depression.

3(α),6(β)-Diacetoxy-*bis-nor*-cholanyldiphenylethylene.—A solution of 68.7 g. of the above dihydroxyethylene in 300 ml. of acetic acid and 36 ml. of acetic anhydride was refluxed for three and one-half hours, cooled, filtered and concentrated *in vacuo*. Petroleum solvent (b. p. 100°) was added and distilled off under reduced pressure to remove the last traces of acetic anhydride. The residue was crystallized from carbon tetrachloride from which it separated with 31% of solvent of crystallization which could only be removed by fusion; weight 82.5 g., m. p. 80–92°. A sample of the glass remaining after drying *in vacuo* at 100° was crystallized first from acetone and then from methanol giving white crystals, m. p. 121.5–124°, $[\alpha]^{29}\mathrm{D}$ + 44.1 ± 3° (dioxane).

Anal. Calcd. for $C_{40}H_{52}O_4$: C, 80.47; H, 8.72. Found[8]: C, 80.59; H, 8.79.

***nor*-Hyodesoxycholic Acid and Methyl Ester.**—The crude diacetoxyethylene from 1025 g. of crude carbinol was oxidized in the usual way.[2] The acid fraction was separated giving 420 g. (57.4%) of solid melting at 190–197°. This was converted to the methyl ester with methanol and sulfuric acid. When crystallized from benzene, it contained one molecule of benzene of crystallization, m. p. 94–97°. Removal of the benzene of crystallization at 90° *in vacuo* and recrystallization from ethyl acetate gave methyl *nor*-hyodesoxycholate melting at 116–117°[9] $[\alpha]^{26}\mathrm{D}$ + 21.4 ± 3° (dioxane).

A sample hydrolyzed back to *nor*-hyodesoxycholic acid and recrystallized from ethyl acetate melted at 217.5–219°,[10] $[\alpha]^{22}\mathrm{D}$ + 9.5 ± 3° (methanol).

Methyl Dehydro-*nor*-hyodesoxycholate.—Ten grams of methyl *nor*-hyodesoxycholate was dissolved in 100 ml. of acetic acid and 4 g. of chromium trioxide in 4 ml. of water and 10 ml. of acetic acid was added at 30°. After one hour at the same temperature the solution was slowly diluted with water. Scratching induced crystallization. The product was filtered and washed well with water: yield 7.4 g.; m. p. 156–158.5°. Two recrystallizations from 80% methanol raised the m. p. to 164–165°, $[\alpha]^{21}\mathrm{D}$ − 62.3 ± 3° (methanol).

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found[7]: C, 73.90; H, 9.44.

3(α),6(β)-Dihydroxy-*bis-nor*-cholanyldiphenylcarbinol.—A solution of 5 g. (0.105 mole) of methyl *nor*-hyodesoxycholate in ether was added to 1.68 moles of phenylmagnesium bromide in ether, and the reaction mixture was decomposed with ice and ammonium chloride. The solution was washed with water, concentrated and the residue was hydrolyzed with methanolic alkali to remove any unchanged ester. The benzene solution of the carbinol was washed with water and concentrated, giving a precipitate which was filtered and washed with benzene; yield 74%, m. p. 214–218°. Two recrystallizations from aqueous methanol gave a crystalline product melting at 226–227.5°,[11] $[\alpha]^{25}\mathrm{D}$ + 13.5 ± 3° (dioxane).

3(α),6(β)-Dihydroxy-*ter-nor*-cholanyldiphenylethylene.—Five grams of the crude carbinol was dehydrated and the amorphous product hydrolyzed as described for the *bis-nor*-ethylene. The dihydroxyethylene was obtained sa a granular precipitate in theoretical yield, m. p. 190–200°. Treatment with hot ether followed by three crystallizations from aqueous methanol gave needles, m. p. 233–234.5°, $[\alpha]^{23}\mathrm{D}$ + 88.3 ± 3° (dioxane).

Anal. Calcd. for $C_{35}H_{46}O_2$: C, 84.28; H, 9.30. Found[8]: C, 84.24; H, 9.26.

Diacetate.—A sample of the dihydroxyethylene was acetylated with acetic anhydride. The product crystallized from aqueous methanol giving needles, m. p. 170–173°; $[\alpha]^{23}\mathrm{D}$ + 75.8 ± 3° (dioxane).

Anal. Calcd. for $C_{39}H_{50}O_4$: C, 80.37; H, 8.65. Found[8]: C, 80.38; H, 8.60.

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(4) Ehrenstein, *J. Org. Chem.*, **4**, 517 (1939).

(5) Ehrenstein and Stevens, *J. Org. Chem.*, **5**, 318 (1940).

(6) When a sample of the carbinol was heated above its melting point for thirty minutes, in an oil-bath maintained at 220–230° and then dried at 100° and 0.7 mm. for thirty minutes, the sample lost 1.86% in weight. Calcd. for one-half molecule of water of crystallization: 1.67%. The resinous material was recrystallized from benzene to give a 66% yield of carbinol, m. p. 198–202°. The material in the mother liquor showed $[\alpha]^{23}\mathrm{D}$ approximately 15°.

(7) C and H analyses by Arlington Laboratories, Fairfax, Virginia.

(8) Analysis by Micro-Tech Laboratories, Skokie, Illinois.

(9) Kimura and Sugiyama, ref. 1a, report m. p. 115° (from ethyl acetate); Marker and Krueger, ref. 1b, report m. p. 95° (from benzene).

(10) Kimura and Sugiyama, ref. 1a, report m. p. 209° $[\alpha]^{20}\mathrm{D}$ +6.32°; Marker and Krueger, ref. 1b, report m. p. 198°.

(11) Marker and Krueger, ref 1b, report m. p. 222°.

***bis-nor*-Hyodesoxycholic Acid.**—Methyl *nor*-hyodesoxycholate (519 g., 1.1 moles) was dissolved in ether and added to 17.5 moles of phenylmagnesium bromide in ether. The ether was distilled off and replaced with toluene. The degradation was carried out as described for methyl hyodesoxycholate. No attempt was made to isolate any intermediates. The yield of *bis-nor*-hyodesoxycholic acid melting at 225–232° was 161 g. (41%). When 50 g. of crude carbinol was worked up, the yield of *bis-nor*-hyodesoxycholic acid melting at 237–243° was 19.4 g. (55%). Crystallization from ethyl acetate gave a product melting at 249–250.5°,[12] $[\alpha]^{23}\text{D}$ − 12.6 ± 3° (methanol). Calcd. for $C_{22}H_{36}O_4$: neut. equiv., 364.5; Found: neut. equiv., 363.6.

Methyl *bis-nor*-Hyodesoxycholate.—This was prepared from *bis-nor*-hyodesoxycholic acid with methanol and sulfuric acid. Recrystallized from benzene it melted at 155.5–156.5°. A sample dried at 100° and 0.5 mm. for one and one-half hours lost 17.4% in weight. Calcd. for one molecule of benzene of crystallization: 17.3%. The melting point of the dried sample was 156–156.5°,[13] $[\alpha]^{26}\text{D}$ 0 ± 3° (dioxane).

Methyl 3(α),6(β)-Diacetoxy-*bis-nor*-cholanate.—Methyl *bis-nor*-hyodesoxycholate (6.33 g.) was dissolved in 15 ml. of acetic anhydride and the solution was warmed on the steam-bath for two hours. Water was added to decompose the excess anhydride. Further dilution induced crystallization in needles. These were filtered and washed with water; yield 6.41 g., m. p. 180–183°. Recrystallization from 170 ml. of 90% methanol gave 5.7 g. (88%) of long needles, m. p. 183–185°, $[\alpha]^{22}\text{D}$ + 9.3 ± 3° (ethanol).

Anal. Calcd. for $C_{27}H_{42}O_8$: C, 70.10; H, 9.15. Found[7]: C, 70.36; H, 9.29.

Methyl Dehydro-*bis-nor*-hyodesoxycholate.—Methyl *bis-nor*-hyodesoxycholate (0.757 g.) was oxidized in 10 ml. of acetic acid with 1 g. of chromium trioxide. After one hour at room temperature the solution was diluted with water. The crystalline precipitate was filtered and washed with water; yield 0.58 g. (94%), m. p. 170–173°. Recrystallization from ethyl acetate plus petroleum solvent (b. p. 69°) gave glistening needles, m. p. 174–176°, $[\alpha]^{22}\text{D}$ − 78.2 ± 3° (methanol).

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 73.75; H, 9.15. Found[7]: C, 73.78; H, 9.14.

Attempted Partial Saponification of Methyl 3(α),6(β)-Diacetoxy-*bis-nor*-cholanate.—Numerous attempts under a variety of conditions were made to remove one acetate group from this ester by treatment with 0.1 *N* alcoholic potassium hydroxide or methanolic hydrogen chloride. In all cases both acetate groups were removed and methyl *bis-nor*-hyodesoxycholate was recovered in 64–86% yield.

3(α),6(β)-Diacetoxypregnan-20-one by Barbier–Wieland Degradation.—The degradation of methyl-*bis-nor*-hyodesoxycholate was carried out in the usual way.[2] The carbinol and ethylene could not be crystallized. The ethylene was ozonized in acetic acid solution containing a little acetic anhydride. Ten-gram portions of the ethylene were ozonized with an excess of ozone at 10–15°. The ozonized fractions were combined in a flask containing zinc dust and water. After standing overnight the solution was filtered from the zinc and concentrated. Benzene was added and the benzene solution was washed with water, dilute sodium hydroxide and then with water until neutral. A ketone separation was carried out with Girard's reagent.[14] After hydrolysis the ketone fraction was taken into ether. The solution was washed until neutral, dried, and concentrated. The viscous residue crystallized slowly from aqueous methanol in rosets of needles; yield 23.1 g. (24.9% based on 101.4 g. methyl *bis-nor*-hyodesoxycholate), m. p. 112.5–117°. A sample recrystallized three times from aqueous methanol melted at 130.5–132°,[15] $[\alpha]^{30}\text{D}$ + 48.9 ± 3° (dioxane). For carbon and hydrogen analysis see the following preparation.

3(α),6(β)-Diacetoxy-pregnan-20-one by Miescher's N-Bromosuccinimide Degradation.—To a solution of 54.2 g. of 3(α),6(β)-diacetoxy-*bis-nor*-cholanyldiphenylethylene in 800 ml. of carbon tetrachloride was added 17.8 g. of N-bromosuccinimide.[16] The flask was illuminated with a 150 watt reflector flood light and heated to reflux for fifteen minutes. After cooling the succinimide and excess N-bromosuccinimide were removed by filtration. To this solution was added 81 ml. of dimethylaniline, the carbon tetrachloride was distilled off, and the residue was heated at reflux temperature for ten minutes. After cooling 300 ml. of 10% hydrochloric acid was added and the mixture was shaken with ether and benzene. The ether–benzene layer was separated, washed with water, and dried over sodium sulfate. The solvent was removed and the residue was reacetylated by refluxing for two hours with 100 ml. of acetic acid and 25 ml. of acetic anhydride. After removing the solvent *in vacuo* a residue of 62 g. was obtained.

The crude 1-(3,6-diacetoxy-*etio*-cholanyl)-1-methyl-4,4-diphenyl-1,3-butadiene in 125 ml. of acetic acid, 125 ml. of chloroform and 25 ml. of water was oxidized at 0 to 23° with 40 g. of chromium trioxide in 130 ml. of water and 640 ml. of acetic acid. The excess oxidizing agent was destroyed with sulfur dioxide and the solvent was removed *in vacuo*. The residue was shaken with water and extracted with a mixture of chloroform and ether which was washed with 5% sodium carbonate solution, then with water and dried over sodium sulfate. Removal of the solvent left 57 g. of residue which was subjected to a ketone separation with Girard's Reagent "P".[14] The ketone-containing fraction weighed 14 g. and was crystallized from methanol containing a little water giving material melting at 120–122°. Chromatographic adsorption on alumina[17] gave a fraction which after crystallization from petroleum solvent (b. p. 69°) and then from methanol melted at 131–133°. A mixed melting point with the compound from the Barbier–Wieland degradation above gave no depression; $[\alpha]^{24}\text{D}$ + 53 ± 3° (dioxane).

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.73; H, 9.14. Found[8]: C, 71.80; H, 9.24.

Pregnan-3(α),6(β)-diol-20-one.—Five-tenths of a gram of the diacetate was hydrolyzed by warming in 2 *N* methanolic sodium hydroxide for fifteen minutes. The hydrolysis product was taken into ether and the solution was washed until neutral with water. After drying and concentrating the residue was crystallized from benzene, from which it separated with one molecule of solvent; yield 0.36 g. (73%), m. p. 102–106°. After recrystallization from benzene and drying in high vacuum (first at 80° then at 100°) the m. p. was 187–190°.[18] The compound showed no change in melting point when recrystallized from ethyl acetate; $[\alpha]^{26}\text{D}$ + 69.6 ± 3° (dried sample in dioxane), $[\alpha]^{26}\text{D}$ + 61.8 ± 3° (methanol).

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.26. Found[7]: C, 75.29; H, 9.96.

Pregnan-3,6,20-trione.—A solution of 1.77 g. of pregnan-3(α),6(β)-diol-20-one in 35 ml. of acetic acid was oxidized with 1.5 g. of chromium trioxide in 3 ml. of water and 10 ml. acetic acid. After standing one hour at 30° the reaction mixture was taken to benzene. The solution was washed with dilute sodium hydroxide and then with water until

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(12) Kimura and Sugiyama, ref. 1a, report m. p. 238°, $[\alpha]^{20}\text{D}$ − 12.9°; Marker and Krueger, ref. 1b, report m. p. 240°.

(13) Kimura and Sugiyama, ref. 1a, report m. p. 137° from ethyl acetate. Marker and Krueger, ref. 1b, report m. p. 146° (diazomethane plus ether).

(14) Girard and Sandulesco, *Helv. Chim. Acta*, **19**, 1095 (1936); Moffett and Hoehn, THIS JOURNAL, **66**, 2098 (1944).

(15) Marker and Krueger, ref. 1b, report m. p. 100° after crystallization from ether–pentane.

(16) Ziegler, Späth, Schumann and Winkelmann, *Ann.*, **551**, 80 (1942).

(17) Fisher Adsorption Alumina (80–200 mesh) was washed with dilute methanolic acetic acid then repeatedly with methanol and dried at 200° for four hours.

(18) Kimura and Sugiyama, ref. 1a, report a m. p. of 198° (after crystallization from ethyl acetate) and $[\alpha]\text{D}$ +6.52° (in alcohol).

neutral. The benzene solution was dried and concentrated. The crystalline residue was recrystallized from benzene-ether and washed on the filter with ether, yield 1.28 g., m. p. 177–180°. An additional 0.17 g. was obtained from the mother liquor (total 83%). Recrystallization from the same solvent raised the m. p. to 189–190.5°, $[\alpha]^{27}\text{D}$ −46.5 ± 3° (dioxane).

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found[8]: C, 76.01; H, 9.06.

***allo*-Pregnan-3,6,20-trione.**—A solution of 200 mg. of pregnan-3,6,20-trione in 5 ml. of acetic acid and 0.5 ml. of concentrated hydrochloric acid was heated one hour on the steam-bath, diluted with water and the precipitate filtered. A light yellow solid (130 mg.) was obtained, m. p. 213–223°. Recrystallization from acetone–ether raised the m. p. to 223–227°. In another experiment 140 mg. of the triketone gave 50 mg. of the *allo* compound, m. p. 227–230.5°,[5] $[\alpha]^{23}\text{D}$ + 52.9 ± 3° (dioxane).

4-Bromo-pregnan-3,6,20-trione.—To a solution of 660 mg. of pregnan-3,6,20-trione in 10 ml. of acetic acid, 0.23 ml. of 0.499 *N* bromine in acetic acid was added at room temperature. After shaking for two minutes the bromine color disappeared. The solution was cooled to 15° and the remainder of the bromine solution (total 8.0 ml.) was added dropwise with swirling during fifteen minutes. The solution was kept cold for an additional five minutes and then diluted with water. The suspension was chilled, filtered, washed with water, and dried in a vacuum desiccator. The substance was rubbed with warm dry ether, filtered and dried; yield 570 mg. (69.5%), m. p. 132–132.5° (dec.), $[\alpha]^{28}\text{D}$ + 25.9 ± 3° (dioxane).

Anal. Calcd. for $C_{21}H_{29}O_3Br$: Br, 19.52. Found[19]: Br, 20.25.

6-Ketoprogesterone.—A solution of 440 mg. of the bromo compound in 2 ml. of dry pyridine was refluxed for two hours, cooled and taken into ether. The ether solution was washed with dilute hydrochloric acid and then with water. The ether was distilled leaving a crystalline residue which was recrystallized from acetone–ether giving 13 mg. of material, m. p. 185–187°.[4]

Summary

1. Hyodesoxycholic acid has been degraded by two methods to pregnan-3(α),6(β)-diol-20-one.

2. Several previously unreported intermediates were isolated, and the physical constants of some other compounds were found to be at variance with those previously reported.

3. Pregnan-3,6,20-trione (a) was converted to 6-ketoprogesterone by bromination and dehydrobromination; and (b) was rearranged by acid or alkali to *allo*-pregnan-3,6,20-trione.

(19) Analysis by Charlotte Hart in this Laboratory.

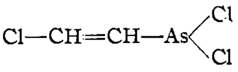
KANSAS CITY, MISSOURI RECEIVED MAY 23, 1946

[CONTRIBUTION FROM THE C. W. S. TECHNICAL COMMAND, EDGEWOOD ARSENAL]

Some Organic Arsenicals Containing the Arsenic–Sulfur Linkage[1]

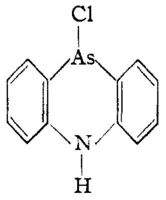
BY WALTER H. C. RUEGGEBERG,[2] ABRAM GINSBURG[3] AND WALTER A. COOK[4]

In the production of certain chemical warfare agents such as lewisite (β-chlorovinyl-dichloroarsine, I) and adamsite (10-chloro-5,10-dihydrophenarsazine, II), arsenic trichloride is used as one of the basic raw materials.



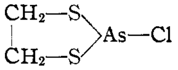
$Cl-CH=CH-AsCl_2$

I

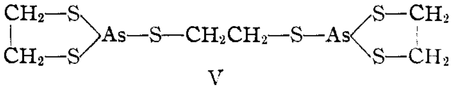


II

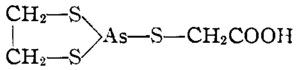
The end of the war left considerable stores of all three of these materials and it appeared of interest to convert them to relatively non-toxic substances which might find peace-time applications. To this end the substances shown below were prepared, among others, and their toxicities investigated. Since these all contain the As–S linkage, they may be considered to be derivatives of thioarsenious acid.[5]



III



V



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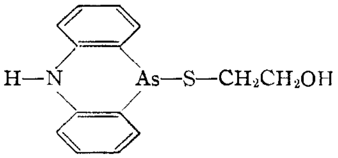

VII

Experimental

2-Chloro-4,5-dihydro-1,3,2-dithiarsenole (III).—This substance was obtained by allowing ethanedithiol to react with arsenic trichloride in carbon tetrachloride at room temperature. To a solution of 200 g. (1.1 mole) of arsenic trichloride in 250 cc. of carbon tetrachloride was added dropwise 94 g. (1 mole) of ethanedithiol. The liberation of hydrogen chloride was almost instantaneous accompanied by self-cooling of the reaction mixture. After standing an hour, the mixture was chilled in a Dry Ice chest and the crystalline product thus obtained was filtered off with suction and air-dried: yield, 90% or higher.

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(1) Published with the permission of the Chief, Chemical Warfare Service.

(2) Captain, C. W. S., Army of the United States.

(3) Technician, 3rd grade, Army of the United States.

(4) Present address: University of Akron, Akron 4, Ohio.

(5) The reaction between mercaptans and lewisite constitutes the basis of the chemistry of BAL (see Waters and Stock, *Science*, **102**, 601 (1945)). Since BAL was studied by other investigators prior to the work here described, the reactions of lewisite with mercaptans will not be discussed in this publication.