complexes of the amides with boron trifluoride. This is in agreement with the work of Bowlus and Nieuwland on acetamide.[3]

No method was devised for the purification of the complexes. The reaction products were very hygroscopic and were immediately decomposed by water. Tetrahydrofuran and ethanol reacted rapidly with the complexes, yielding precipitates of ammonium fluoborate.

The compounds did not possess sufficient thermal stability to allow high vacuum distillation or sublimation. The complex with formamide decomposed on warming in vacuum, with evolution of carbon monoxide and hydrogen cyanide, which gases were identified by their infrared spectra. Ammonium fluoborate was one of the solid reaction products, but since the solid reaction product was very soluble in water no boron nitride was considered to be formed.

Anal. Calcd. for NH_4BF_4: HBF_4, 83.44. Found: HBF_4, 83.89.

The complex of acetamide with boron trifluoride began to decompose in vacuum at about 90°, with liberation of a small amount of acetic acid. At 130–140° and 0.1 mm. a yellow viscous oil distilled over. Efforts to purify and characterize this oil were not successful. The boron present in the oil was in the form of a fluoborate salt.

(3) H. Bowlus and J. A. Nieuwland, THIS JOURNAL, **53**, 3835 (1931).

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Some Amides of Piperazines

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Since 1,4-bis-(benzenesulfonyl)-piperazine[1] exhibited marked activity in inhibiting growth of tubercle bacillus in serum, twelve new amides of piperazines were synthesized for testing against this organism. These compounds were prepared by modifications of the method of Pollard and Adelson.[2] Anhydrous piperazines were used; anhydrous sodium carbonate was added; and propanol-2 or benzene was employed as a reaction solvent instead of ether. Data concerning these compounds are given in Table I.

TABLE I

DATA CONCERNING SOME AMIDES OF PIPERAZINES

Compound, piperazine	Crystallized from	Yield, % purified product	M.p., °C. (cor.)	Nitrogen, % Calcd.	Found
1-(*p*-Chlorobenzoyl)-4-phenyl	Methanol	29.2	119–121	9.32	9.24
1-(*o*-Chlorobenzoyl)-4-phenyl	Methanol	22.5	109–111	9.32	9.17
1-(*m*-Nitrobenzenesulfonyl)-4-phenyl	Formamide	43.2	153–154	12.10	12.29
1-(*p*-Bromobenzenesulfonyl)-4-phenyl	Methanol	38.6	180–182	7.35	7.35
1,4-Bis-(*p*-chlorobenzoyl)	Propanol-2	36.0	238.8–239.8	7.71	7.75
1,4-Bis-(*p*-toluenesulfonyl)	Boiling dioxane	42.0	295.3–296.3	7.11	7.09
1,4-Bis-(*o*-chlorobenzoyl)	Methanol	22.9	214–215.5	7.71	7.71
1,4-Bis-(*m*-nitrobenzenesulfonyl)	Formamide	34.4	262–264	12.28	12.14
1,4-Bis-(*p*-chlorobenzoyl)-2,5-dimethyl	Chlorobenzene	38.2	288–289	7.16	6.93
1,4-Bis-(*o*-chlorobenzoyl)-2,5-dimethyl	Formamide	48.2	296–298	7.16	7.15
1,4-Bis-(*m*-nitrobenzenesulfonyl)-2,5-dimethyl	Formamide	48.5	249–250	11.57	11.25
1,4-Bis-(*p*-bromobenzenesulfonyl)-2,5-dimethyl	Formamide	51.5	262–263	5.07	5.21

These new amides were ineffective against tubercle bacillus.

The authors express their sincere appreciation for the *in vitro* tuberculostatic testing of these compounds. The tests were performed in the laboratory of Dr. Guy P. Youmans, Department of Bacteriology, Northwestern University Medical School, and made available by arrangement with Parke, Davis and Company.

(1) M. E. Smith and C. B. Pollard, THIS JOURNAL, **63**, 630 (1941).
(2) C. B. Pollard and D. E. Adelson, *ibid.*, **56**, 150 (1934).

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Homologs of Some Steroid Hormones

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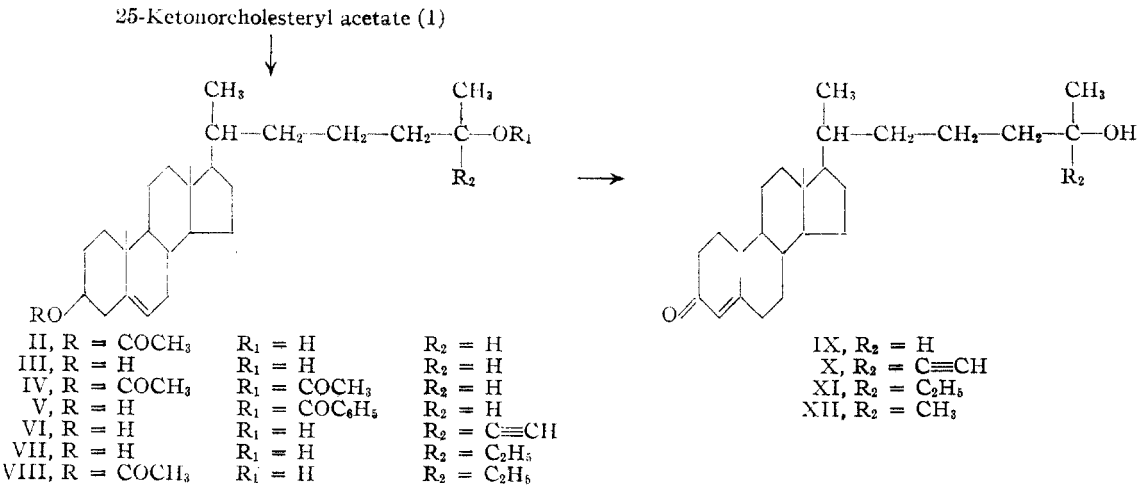
In connection with other work in progress in these laboratories, some homologs of testosterone and one homolog of ethinyltestosterone were prepared. These new steroids in which the hydroxyl is at C_{25} instead of C_{17} possess no androgenic activity. These compounds were synthesized from 25-ketonorcholesteryl acetate (I), a by-product of the oxidation of cholesteryl acetate dibromide.[1]

25-Hydroxy-Δ^4-norcholestene-3-one (IX) was obtained using a procedure similar to that described for the synthesis of testosterone.[2] 25-Ketonorcholesteryl acetate (I) was reduced to the diol monoacetate (II); this was then benzoylated and the resulting 3-acetate-25-benzoate partially hydrolyzed to give 25-benzoxynorcholesterol (V). Oxidation by a modification of the method of Oppenauer[3] followed by hydrolysis produced the ketone (IX).

25-Ethinyl-Δ^4-norcholestene-25-ol-3-one (X) was prepared by the ethynation of I with potassium acetylide to give the 25-ethinyl derivative (VI) followed by Oppenauer oxidation. The reaction of ethylmagnesium iodide with I yielded 26-methyl-25-hydroxycholesterol (VII). Both VII and 25-hydroxycholesterol[4] were oxidized to XI and XII, respectively. A derivative of IX, 25-chloro-Δ^4-norcholestene-3-one (XV), was also prepared in which the hydroxyl at C_{25} was replaced with chlorine.

(1) L. Ruzicka and W. H. Fischer, *Helv. Chim. Acta*, **20**, 1291 (1937).
(2) L. Ruzicka, A. Wettstein and H. Kägi, *ibid.*, **18**, 1478 (1935).
(3) R. V. Oppenauer, *Rec. trav. chim.*, **56**, 137 (1937).
(4) A. I. Ryer, W. H. Gebert and N. M. Murrill, THIS JOURNAL, **72**, 4247 (1950).



Experimental[5]

25-Hydroxynorcholesteryl Acetate (II).—To 40 g. of 25-ketonorcholesteryl acetate (I) [m.p. 138.1–139.6°, $[\alpha]^{23}D$ −37.8° (2% in $CHCl_3$)] dissolved in 300 ml. of benzene was added Raney nickel catalyst (prepared from 90 g. of Raney nickel catalyst powder)[6] suspended in 100 ml. of methyl alcohol. The suspension was reduced with hydrogen for ten hours at 20 lb. pressure. The reaction mixture was filtered, the filtrate concentrated to dryness and the residue recrystallized from methanol to give 35 g. of II melting at 117–129°, $[\alpha]^{19}D$ −40.8° (2% in $CHCl_3$). Repeated recrystallizations from various solvents did not change the melting point.

Anal. Calcd. for $C_{28}H_{46}O_3$: C, 78.09; H, 10.77. Found: C, 78.08; H, 10.94.

25-Hydroxynorcholesterol (III).—The diol acetate (II) was hydrolyzed by refluxing with aqueous methanolic potassium carbonate solution for two hours. The crude product, after successive recrystallizations from acetone, benzene and ethyl acetate, melted at 158–168°, $[\alpha]^{20}D$ −36.9° (2% in $CHCl_3$).

Anal. Calcd. for $C_{26}H_{44}O_2$: C, 80.35; H, 11.41. Found: C, 80.10; H, 11.20.

25-Acetoxynorcholesteryl Acetate (IV).—The diol (III) was acetylated by refluxing with acetic anhydride for five hours. The crude product was recrystallized from methanol to give IV (needles), m.p. 85.6–86.6°, $[\alpha]^{23}D$ −37.8° (2% in $CHCl_3$).

Anal. Calcd. for $C_{30}H_{48}O_4$: C, 76.22; H, 10.23. Found: C, 76.15; H, 10.35.

25-Benzoxynorcholesterol (V).—25-Hydroxynorcholesteryl acetate (II) was benzoylated by treating with benzoyl chloride in a mixture of dry dioxane and dry pyridine at 11° and allowing the reaction mixture to stand overnight at room temperature.

A 15-g. portion of the crude 3-acetate-25-benzoate (melting at 83–90°) was added to a solution of 1.50 g. of potassium hydroxide in 900 ml. of methanol and the mixture stirred for 33 hours at 15–20°. The solution was poured into water, filtered and washed neutral with water to give 11.3 g. of crude 25-benzoate (V), m.p. 63.8–65.7°. After two recrystallizations from methanol, the product was dried in a vacuum oven at 64° for six hours to give 10.0 g. of V, m.p. 79.5–81.2°, $[\alpha]^{22}D$ −29.7° (2% in $CHCl_3$).

Anal. Calcd. for $C_{33}H_{48}O_3$: C, 80.44; H, 9.82. Found: C, 80.71; H, 9.45.

25-Hydroxy-Δ^4-norcholestene-3-one (IX).—Δ^5-Norcholestene-3β,25-diol-25-benzoate (8.0 g.) was oxidized by the procedure described for the oxidation of Δ^5-pregnene-3β,21-diol-20-one.[7] The crude product was hydrolyzed by refluxing with methanolic potassium hydroxide for two hours. After several recrystallizations from methanol and acetone, 3.2 g. of IX (flat needles) were obtained, m.p. 154.4–155.5°, $[\alpha]^{22}D$ +90.9° (2% in $CHCl_3$).

Anal. Calcd. for $C_{26}H_{42}O_2$: C, 80.77; H, 10.95. Found: C, 80.52; H, 11.25.

25-Ethinyl-Δ^5-norcholestene-3β,25-diol (VI).—Acetylene was passed into a solution of 108 g. of potassium in 6.0 liters of liquid ammonia until the blue color disappeared. A solution containing 200 g. of 25-ketonorcholesteryl acetate (I) dissolved in 1800 ml. of dry pyridine was then added dropwise. The reaction mixture was allowed to stand at room temperature until the ammonia had evaporated. Water (600 ml.) was added and the mixture heated at 85° for 30 minutes. After pouring into water, the precipitate was filtered and washed until neutral. The crude product (194.5 g.), melting at 167.2–170.2°, was recrystallized from ethyl acetate to give 147.4 g. of VI (needles), m.p. 170.0–173.4°. The analytical sample melted at 175.6–177.4°, $[\alpha]^{22.5}D$ −37.2° (2% in $CHCl_3$).

Anal. Calcd. for $C_{28}H_{44}O_2$: C, 81.49; H, 10.75. Found: C, 81.40; H, 10.63.

25-Ethinyl-Δ^4-norcholestene-25-ol-3-one (X).—25-Ethinyl-Δ^5-norcholestene-3β,25-diol (VI) (20 g.) was oxidized by the procedure used for the preparation of 25-hydroxy-Δ^4-norcholestene-3-one (IX). The crude product (11.0 g.) was recrystallized successively from ethyl acetate and methanol to give X (needles) melting at 172.4–173.2°, $[\alpha]^{23}D$ +87.2° (2% in $CHCl_3$).

Anal. Calcd. for $C_{28}H_{42}O_2$: C, 81.89; H, 10.31. Found: C, 81.68; H, 10.14.

26-Methyl-Δ^5-cholestene-3β,25-diol (VII).—A solution of 100 g. of 25-ketonorcholesteryl acetate in 640 ml. of thiophene-free benzene was added to a Grignard solution prepared from 28.4 g. of magnesium, 364 g. of freshly distilled ethyl iodide and 670 ml. of anhydrous ethyl ether. The mixture was refluxed for four hours and allowed to stand overnight. After cooling, the mixture was decomposed by the addition of ice-water and dilute acetic acid, and then steam distilled until no more oil passed over. The product was filtered and dried, yielding 98.9 g., m.p. 151.4–157.0°. A 10.0-g. portion of the crude product was recrystallized successively from acetone and ethyl acetate to give 6.6 g. of VII (fine needles) melting at 154.2–158.4°, $[\alpha]^{20}D$ −35.7° (2% in $CHCl_3$).

Anal. Calcd. for $C_{28}H_{48}O_2$: C, 80.71; H, 11.61. Found: C, 80.66; H, 11.31.

26-Methyl-Δ^5-cholestene-3β,25-diol-3-acetate (VIII).—The diol (VII) was monoacetylated by warming with dry pyridine and acetic anhydride for one hour at 60°. The crude product was recrystallized from methanol and ethyl acetate to give VIII as needles melting at 111.2–111.6°, $[\alpha]^{23}D$ −39.5° (2% in $CHCl_3$).

Anal. Calcd. for $C_{30}H_{50}O_3$: C, 78.55; H, 10.99. Found: C, 78.22; H, 10.66.

26-Methyl-Δ^4-cholestene-25-ol-3-one (XI).—The diol (VII) (20 g.) was oxidized by the procedure used for the preparation of 25-hydroxy-Δ^4-norcholestene-3-one (IX).

(5) All melting points are corrected. Microanalyses and microrotations by Edwin Conner and staff of these laboratories.

(6) R. Mozingo, *Org. Syntheses*, **21**, 15 (1941).

(7) "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 235.

The crude product (13.8 g., m.p. 123.6–126.5°) was recrystallized several times from methanol and acetone to give XI, m.p. 124.5–127.2°, $[\alpha]^{21}D$ +82.0° (2% in $CHCl_3$).

Anal. Calcd. for $C_{28}H_{46}O_2$: C, 81.10; H, 11.18. Found: C, 81.07; H, 10.92.

25-Hydroxy-Δ⁴-cholestene-3-one (XII).—25-Hydroxycholesterol[4] (25 g.) was oxidized by the procedure used for the preparation of 25-hydroxy-Δ⁴-norcholestene-3-one (IX). The crude product (20.5 g., m.p. 145.2–146.4°) was recrystallized from acetone and methanol to give XII (plates) melting 147.8–148.4°, $[\alpha]^{20}D$ +88.4° (2% in $CHCl_3$).

Anal. Calcd. for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.80; H, 11.00.

25-Chloro-Δ⁵-norcholestene-3β-ol-acetate (XIII).—To a solution of 40 g. of 25-hydroxynorcholesteryl acetate (II) in 1200 ml. of dry pyridine was added 40 ml. of freshly distilled phosphorus oxychloride. The mixture was refluxed for 0.5 hour, cooled to 10° and poured into a mixture of ice and water. The precipitated product was filtered and washed neutral with water. The dried crude product was dissolved in hot benzene and filtered to remove a brown insoluble substance. The filtrate, after treatment with decolorizing charcoal, was concentrated to dryness and the residue recrystallized from methanol and acetone to give 20.7 g. of XIII (needles), m.p. 116.2–117.0°, $[\alpha]^{23}D$ −35.4° (2% in $CHCl_3$).

Anal. Calcd. for $C_{28}H_{45}O_2Cl$: C, 74.88; H, 10.10; Cl, 7.89. Found: C, 74.71; H, 10.32; Cl, 8.44.

25-Chloro-Δ⁵-norcholestene-3β-ol (XIV).—A solution of 15 g. of the 25-chloroacetate (XIII) was hydrolyzed by refluxing for two hours with ethanolic potassium hydroxide. The crude product (13.5 g.), after recrystallization from methanol and from acetone, gave XIV (fine needles) melting at 132.0–133.0°, $[\alpha]^{29}D$ −38.6° (2% in $CHCl_3$).

Anal. Calcd. for $C_{26}H_{43}OCl$: C, 76.71; H, 10.65; Cl, 8.71. Found: C, 76.92; H, 10.24; Cl, 8.38.

25-Chloro-Δ⁴-norcholestene-3-one (XV).—A 10.5-g. sample of 25-chloro-5-norcholestene-3β-ol (XIV) was oxidized by the procedure used for the preparation of 25-hydroxy-Δ⁴-norcholestene-3-one (IX). The crude product (8.0 g.), after successive recrystallizations from methanol and acetone, gave XV (needles) melting at 119.0–119.9°, $[\alpha]^{20}D$ +101.6° (2% in $CHCl_3$).

Anal. Calcd. for $C_{26}H_{41}OCl$: C, 77.09; H, 10.20, Cl, 8.75. Found: C, 77.05; H, 9.97; Cl, 9.04.

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3α-Carboxylic Acids of 5-Sitostene and Stigmastane

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Previous work has dealt with the introduction of the carboxylic acid group in the 3α-position of the 5-cholestene, cholestane and 5-androstene nuclei.[1,2] The present work deals with the insertion of the carboxylic acid group at the 3α-positions of 5-sitostene and stigmastane nuclei.

Sitosteryl chloride was prepared in good yield by treatment of β-sitosterol with thionyl chloride. A high melting side product has been isolated in this preparation. Conversion to sitosterylmagnesium chloride followed by carbonation yields 5-sitostene-3α-carboxylic acid which has been characterized by transformation to its methyl ester. β-Sitosteryl is a probable by-product from the preparation of the Grignard reagent. Catalytic low pressure hydrogenation of the 5-sitostene-3α-carboxylic acid gives the stigmastane-3-carboxylic acid which is characterized through its methyl ester.

The low pressure hydrogenations of 5-cholestene-3α-carboxylic acid and 5-sitostene-3α-carboxylic acid catalyzed by platinum oxide are interesting because of the completeness of the reaction; *i.e.*, the resulting acids do not give a Liebermann–Burchard reaction nor a yellow color with tetranitromethane. In this Laboratory similarly hydrogenated products of cholesteryl chloride, cholesteryl acetate and cholesterol all give positive Liebermann–Burchard reactions and yellow coloration with tetranitromethane, indicating small amounts of unsaturated materials in the product.

Experimental[3]

3α-Chloro-5-sitostene.—Purified β-sitosterol[4] was converted to the chloro compound as described by Shoppee.[5] In some of these preparations of sitosteryl chloride, a petroleum ether-insoluble substance was isolated and is presumably bis-sitosteryl sulfite.[6] Recrystallization of this material from ethyl ether gave colorless crystals, m.p. 197–200°, $[\alpha]^{25}D$ −29.4°, *c* 1.175 in chloroform, Rast molecular weight was abnormally high (1.1×10^3), Liebermann–Burchard reaction was positive, bromine in carbon tetrachloride was absorbed, alkaline or acid hydrolysis in ethanol gives β-sitosterol, m.p. 140–141°, $[\alpha]^{25}D$ −34°, *c* 1.69 in chloroform.

5-Sitostene-3α-carboxylic Acid.—Methylmagnesium iodide was prepared from 6.0 (42.3 mmoles) of methyl iodide and 3.0 g. (123 mg. atoms) of magnesium in 50 ml. of dry ethyl ether. To this there was added 15.7 g. (36.2 mmoles) of sitosteryl chloride in 50 ml. of dry ether. The solution was then refluxed for 48 hours under the usual conditions; carbon dioxide gas at 1 atm. was passed into the reaction mixture at room temperature for 40 hours. The entire reaction mixture was poured onto 500 ml. of 1:5 hydrochloric acid and stirred well. The two layers were transferred to a separatory funnel and *ca.* 200 ml. of ether added. After separation of the acid layer, an ether-insoluble fraction, 1.76 g., m.p. > 270° dec., was filtered from the ether. The ether layer was then extracted alternately with 10% sodium hydroxide and water to yield the sodium 5-sitostene-3-carboxylate in the aqueous layer; the remainder of the sodium salt was secured by filtration of the ether layer in which it was suspended. The solid salt was added to the aqueous layer which was acidified with hydrochloric acid to congo red and allowed to stand overnight on the steam-bath prior to filtration, which gave 7.5 g. of the crude acid, m.p. 195–202°. This was taken up in *ca.* 200 ml. of refluxing benzene and crystallization was allowed to proceed during slow evaporation of the solvent to yield 5-sitostene-3α-carboxylic acid as colorless platelets, m.p. 206–208°, $[\alpha]^{24}D$ −15.1°, *c* 1.79 in chloroform.

Anal. Calcd. for $C_{30}H_{50}O_2$: C, 81.39; H, 11.39. Found: C, 81.39, 81.18; H, 11.18, 11.31.

Crystallization of the high melting side product from benzene gave colorless crystals, m.p. 302–306°. This probably is bisitosteryl which was formed in the same manner as bicholesteryl.[2]

3α-Carbomethoxy-5-sitostene.—To 100 ml. of absolute methanol containing 2 ml. of concd. sulfuric acid there was added 0.690 g. of 5-sitostene-3α-carboxylic acid. The solution was heated at reflux temperature for 3 hours and then poured onto *ca.* 100 g. of ice. The insoluble ester was filtered and washed well with cold water until neutral to litmus. It was then taken up in 60 ml. of hot methanol and upon standing 0.575 g. of colorless platelets were secured, m.p. 85°, $[\alpha]^{22}D$ −19.4°, *c* 2.78 in chloroform.

Anal. Calcd. for $C_{31}H_{52}O_2$: C, 81.52; H, 11.48. Found: C, 81.7; H, 11.40.

(1) The 3α-designation is based upon the work of R. H. Baker and Q. R. Petersen, THIS JOURNAL, **73**, 4080 (1951).

(2) R. E. Marker, T. S. Oakwood and H. M. Crooks, *ibid.*, **58**, 481 (1936); R. H. Baker and E. N. Squire, *ibid.*, **70**, 1487 (1948); R. H. Baker and E. N Squire, *ibid.*, **71**, 1383 (1949).

(3) Microanalyses by Dr. Carl Tiedke.

(4) We are indebted to Dr. Howard L. Gerhardt of the Pittsburgh Paint and Glass Co. for supplying the β-sitosterol.

(5) C. W. Shoppee, *J. Chem. Soc.*, 1043 (1947).

(6) *Cf.* bis-cholestenyl sulfite, P. J. Daughensbaugh and J. B. Allison, THIS JOURNAL, **51**, 3665 (1929).