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Sterols. IV. Δ^{20}-Pregnenes from *bisnor*-Steroid Acids

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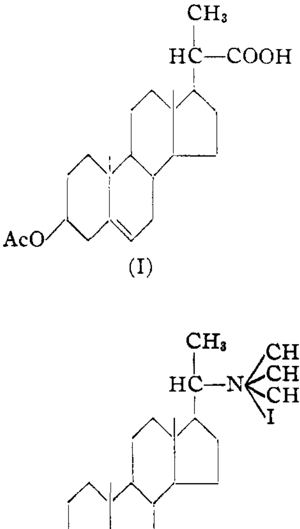
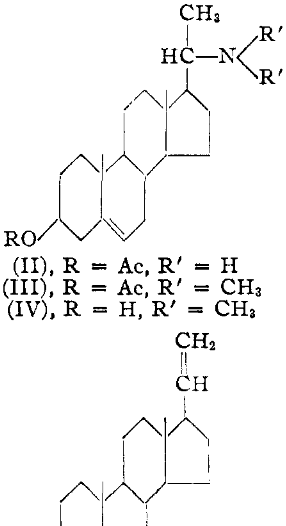
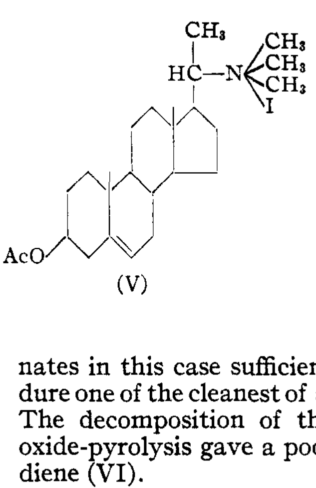
Intensive studies in these Laboratories over the past few years have resulted in making 3-acetoxy-5-*bisnor*-cholenic acid a relatively cheap and useful raw material for the synthesis of most of the major steroid hormones. This communication presents one of the promising and convenient methods for degrading this acid to key intermediates in such a synthetic approach. The emphasis in this particular investigation centers upon the Δ^{20}-pregnenes prepared from 3-acetoxy-5-*bisnor*-cholenic acid and analogous steroid acids. The ease of preparation and the excellent yields encountered make the Δ^{20}-pregnenes focal points of interest in the general picture involving degradation and synthesis of physiologically active steroids.



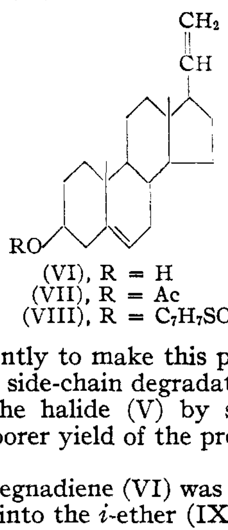
(I)



(II), R = Ac, R′ = H
(III), R = Ac, R′ = CH_3
(IV), R = H, R′ = CH_3



(V)



(VI), R = H
(VII), R = Ac
(VIII), R = $C_7H_7SO_2$

3-Acetoxy-5-*bisnor*-cholenic acid (I) was converted to 3-acetoxy-20-amino-5-pregnene (II) in practically quantitative yield *via* the acid chloride by the Curtius method.[1] Methylation of the 20-amine (II) with formic acid and formaldehyde[2] gave 3-acetoxy-20-dimethylamino-5-pregnene (III) and this compound reacted smoothly with methyl iodide to yield the desired quaternary halide (V). All steps to this point gave yields which were excellent. Decomposition of the ammonium iodide (V) by treatment with potassium hydroxide in ethylene glycol solution afforded 3-hydroxy-5,20-pregnadiene (VI) in only 65% yield, but the major portion of the remaining 35% was recovered as the 3-hydroxy-20-dimethylamine (IV). Thus this reaction, too, in the end, becomes nearly quantitative. Of the two competing reactions involved in the degradation of the quaternary base, namely, the loss of trimethylamine and the loss of methyl alcohol, the former predominates in this case sufficiently to make this procedure one of the cleanest of side-chain degradations. The decomposition of the halide (V) by silver oxide-pyrolysis gave a poorer yield of the pregnadiene (VI).

The structure of the pregnadiene (VI) was demonstrated by conversion into the *i*-ether (IX) followed by oxidation with potassium permanganate in pyridine and subsequent "rearrangement" and esterification with acidulated methanol to yield methyl 3-methoxy-5-*etio*-cholenate (X) identical with the compound prepared from 3-hydroxy-5-*etio*-cholenic acid. Oxidation of 3-hydroxy-5,20-pregnadiene (VI) offers the first authentic and clean-cut preparation of 3-keto-4,20-pregnadiene

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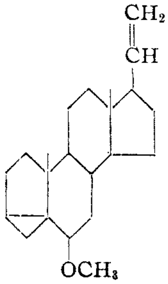
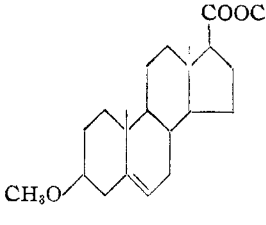
[1] Bochmühl, Ehrhart and Ruschig, U. S. Patent 2,108,646; Ruschig, *Med. u. Chem.*, **4**, 327 (1942) (*C. A.*, **38**, 4954 (1944)).

[2] Clarke, Gillespie and Weisshaus, THIS JOURNAL, **55**, 4571 (1933).

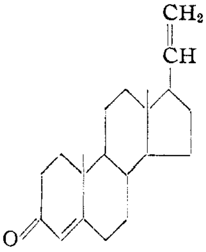
(XI). This material melted at 126.5° and gave a good yield of 3-keto-4-*etio*-cholenic acid (XII) upon mild treatment with ozone. The structure of the pregnadiene is, therefore, indisputably established.



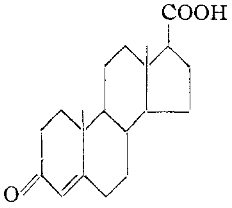
(IX)



(X)



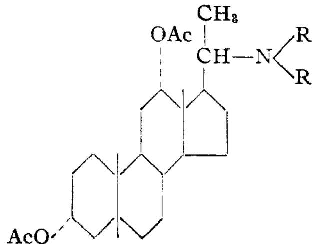
(XI)



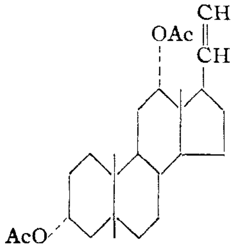
(XII)

Ruzicka and co-workers[3a] posed the possibility that their substance of melting point 132–133°, prepared by the reduction of 3,17-dihydroxy-17-ethynyl-5-androstene with sodium in ethanol–xylene, might have the structure of our pregnadiene (VI). These authors, however, in a later communication,[3b] presented satisfactory proof that their compound did not possess the first proposed structure but was instead the 3-hydroxy-5,17-pregnadiene.

The application of the above-described degradative scheme to 3(α),12(α)-diacetoxy-*bisnor*-cholanic acid afforded equally as facile a route to 3(α),12(α)-diacetoxy-20-pregnene (XV) *via* the amino-pregnane derivatives (XIII) and (XIV). Oxidation of this pregnene gave a good yield of 3(α),12(α)-diacetoxy-*etio*-cholanic acid.



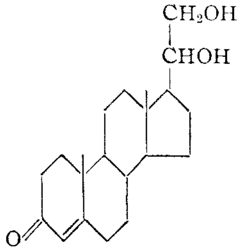
(XIII), R = H
(XIV), R = CH_3



(XV)

This preparation of *etio*-acids from *bisnor*-acids *via* the Δ^{20}-pregnenes constitutes, in our opinion, the most satisfactory route to *etio*-acids yet proposed. The preparation of 3-acetoxy-5-*etio*-cholenic acid by Steiger and Reichstein[4] gave, according to these investigators, only a 9.0% yield based upon 3-hydroxy-5-*bisnor*-cholenic acid. Hoehn and Mason[5] prepared 3(α),12(α)-dihydroxy-*etio*-cholanic acid in 14.5–17% yield by an improved procedure from 3(α),12(α)-dihydroxy-*bisnor*-cholanic acid. Our preparation gives a minimum yield of 33% of 3-keto-4-*etio*-cholenic acid based on the 3-acetoxy-5-*bisnor*-cholenic acid. Thus the Δ^{20}-pregnenes occupy a significant role in the classical route to the cortical hormones.

The Δ^{20}-pregnenes offer other interesting approaches to the typical ketol structure of the cortical hormones. The pregnadiene (XI) underwent hydroxylation with osmium tetroxide giving both of the expected diastereoisomeric 20,21-diols (XVI) which have been separated and characterized. One diol melted at 168°, $[\alpha]^{27}_D + 98°$, and the other melted at 194°, $[\alpha]^{35}_D + 97°$. The first of these agrees in its properties with the so-called "α-form" of the diol which Steiger and Reichstein[6] prepared from desoxycorticosterone. These workers, however, apparently did not have the β-modification in pure form as they give a melting point of 185° and indicate that they had too little material for analysis and complete characterization. These diols and their derivatives offer attractive routes to the cortical hormones[7] and we shall report more in detail later upon this phase of the investigation.



(XVI)

Experimental[8,9]

3-Acetoxy-20-amino-5-pregnene (II).—In a flask protected with a calcium chloride tube, a suspension of 50.0 g. of 3-acetoxy-5-*bisnor*-cholenic acid in 1000 ml. of anhydrous ether was treated with 29 ml. of freshly distilled thionyl chloride. After the addition of a few drops of 10% pyridine in benzene, the mixture was swirled occasionally. The acid dissolved within one-half hour. After two hours, the solvent was removed *in vacuo* with gentle warming. To remove the last traces of thionyl chloride, the residue was dissolved successively in several small portions of dry benzene and this solvent was removed *in vacuo*. The acid chloride remained as a white, crystalline cake.

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[3] (a) Ruzicka, Goldberg and Hardegger, *Helv. Chim. Acta*, **22**, 1294 (1939); (b) Ruzicka, Goldberg and Hardegger, *ibid.*, **25**, 1297 (1942).

[4] Steiger and Reichstein, *Helv. Chim. Acta*, **20**, 1040 (1937).

[5] Hoehn and Mason, This Journal, **60**, 1493 (1938).

[6] Steiger and Reichstein, *Helv. Chim. Acta*, **21**, 171 (1938).

[7] *Cf.* Sarett, *J. Biol. Chem.*, **162**, 601 (1946); This Journal, **68**, 2478 (1946).

[8] The carbon-hydrogen analyses were performed by Mr. C. W. Beazley of the Micro-Tech Laboratories, Skokie, Illinois.

[9] We are indebted to Miss Isabelle Ryden of this Laboratory for certain technical assistance.

The acid chloride was dissolved in 900 ml. of acetone and chilled in an ice-bath to 10°. A solution of 16.0 g. of sodium azide in 75 ml. of water was then added dropwise, with mechanical stirring, at such a rate that the temperature of the solution was maintained at 10–13°. After fifteen minutes of stirring, 1000 ml. of ice-cold water was added and the white crystalline azide was filtered. The moist cake which weighed 160 g. was added to a mixture of 1000 ml. of glacial acetic acid and 142 ml. of water. The mixture was warmed on a steam-bath with swirling. At about 38° nitrogen was evolved and the azide went into solution. After heating for one hour at 60–65°, the solution was steam distilled (about 2–3 l. of distillate). To the residual mixture, while still hot, a solution of 80 g. of sodium hydroxide in 300 ml. of water was added portionwise with good agitation. Upon cooling, the 3-acetoxy-20-amino-5-pregnene acetate formed needle-like crystals. The mass was filtered, washed with a small quantity of cold water and dried. The acetate weighed 51.7 g. (96%) and melted at 200–205° after softening slightly at about 185°. This material which contains a small quantity of sodium acetate is of sufficient purity for further experimentation.

A 5.0-g. sample of the acetate was dissolved in a small amount of methanol and treated with dilute sodium carbonate solution. After addition of ether, the ethereal solution was washed with water (it was necessary to add a small amount of methanol from time to time to solubilize the amine which is only moderately soluble in ether) and dried. The solid remaining after removal of ether was dissolved in hot methanol, filtered, and precipitated by the cautious addition of water. It was recrystallized several times from a concentrated methanol solution—white silky needles resulted, m. p. 116–120° (loss of solvent).

A convenient derivative for this amine was the benzal derivative, 3-hydroxy-20-benzaldimino-5-pregnene. For preparation, the 20-amine described above was hydrolyzed with 2% methanolic potassium hydroxide and this solution was treated with benzaldehyde. The benzal compound crystallized readily in the form of glistening plates. For analysis it was recrystallized from benzene–methanol, m. p. 191°.

Anal. Calcd. for $C_{28}H_{39}ON$: C, 82.90; H, 9.69. Found: C, 82.57; H, 9.31.

3-Acetoxy-20-dimethylamino-5-pregnene (III).—A solution of 20.5 g. of 3-acetoxy-20-amino-5-pregnene acetate in 17.8 g. of 90% formic acid and 13.2 g. of 35% aqueous formaldehyde was heated on a steam-bath under reflux for five hours. At the outset the evolution of carbon dioxide was vigorous but this subsided to a slow steady rate. The mixture was diluted with water and extracted with ether after the addition of dilute hydrochloric acid. The aqueous layer containing suspended insoluble hydrochloride was separated and combined with the water washings of the ethereal layer. The aqueous mixture was made alkaline with dilute sodium hydroxide and extracted well with ether. The ether solution was washed with water and dried. Upon removal of solvent, there remained 17.8 g. (92%) of a white, crystalline residue melting at 155–175°, which was sufficiently pure for the preparation of (V). For analysis, however, several recrystallizations from a small volume of ether gave glistening plates which melted at 184.5–187.5°; $[\alpha]^{34}_{\mathrm{D}}$ $-50 \pm 1°$ (77.2 mg. made up to 5 ml. with chloroform, α $-0.77°$, l, 1 dm.).

Anal. Calcd. for $C_{25}H_{41}NO_2$: C, 77.47; H, 10.66. Found: C, 77.65; H, 10.76.

3-Hydroxy-20-dimethylamino-5-pregnene (IV).—A 1.94-g. sample of the 3-acetoxy-amine was dissolved in a solution of 0.5 g. of potassium hydroxide in 50 ml. of methanol and 10 ml. of benzene. This solution was refluxed for three hours. It was then diluted with water and extracted with ether. The water-washed ether solution was concentrated to a crystalline mass which was recrystallized from ether–petroleum ether (b. p. 35–60°). The product, 1.7 g. of white prisms, melted at 162–171°. Recrystallization from ether gave material melting at 169–170°; $[\alpha]^{33}_{\mathrm{D}}$ $-54 \pm 2°$ (23.3 mg. made up to 5 ml. with chloroform, α $-0.25°$, l, 1 dm.).

Anal. Calcd. for $C_{23}H_{39}ON$: C, 79.94; H, 11.37. Found: C, 80.17; H, 11.08.

3-Acetoxy-5-*ternor*-cholenyltrimethylammonium Iodide (V).—Ten and four-tenths grams of the crude 3-acetoxy-dimethylamine was dissolved in 40 ml. of warm benzene, chilled and treated with 6 ml. of methyl iodide. The solution was refluxed for two hours. During this period a heavy crop of crystalline material separated. The mixture was slurried with ether, filtered, and the solid washed with ether. The mother liquor was concentrated to remove ether and was retreated with methyl iodide in the same fashion to obtain a second crop of material. The total yield of white, crystalline quaternary iodide amounted to 12.7 g. (89.2%), m. p. 255–265°, dec. Recrystallization from methanol gave plates which decomposed at 270°.

Anal. Calcd. for $C_{26}H_{44}O_2NI$: C, 58.97; H, 8.38. Found: C, 58.75; H, 8.23.

The ammonium iodide can be converted to the quaternary base, **3-hydroxy-5-*ternor*-cholenyltrimethylammonium hydroxide** by treatment with moist silver oxide. In one experiment, a solution of 1.0 g. of the iodide in 10 ml. of methanol was shaken with the moist silver oxide prepared from 1.0 g. of silver nitrate. After three hours the solution was filtered and the oxide washed with methanol. No attempt was made to isolate the base; however, it was converted directly to the picrate by the addition of 1.0 g. of picric acid in methanol to the methanolic solution of the base. After concentration the picrate was crystallized from methanol–ether; 0.8 g. of orange prisms melting at 188–194°. Recrystallization from methanol raised the melting point to 192–194.5°.

Anal. Calcd. for $C_{30}H_{44}O_8N_4$: C, 61.20; H, 7.54. Found: C, 60.92; H, 7.35.

3-Hydroxy-5,20-pregnadiene (VI).—A solution of 7.2 g. of 3-acetoxy-5-*ternor*-cholenyltrimethylammonium iodide in a mixture of 14.0 g. of potassium hydroxide, 15 ml. of water and 55 ml. of ethylene glycol was boiled, allowing the water vapor to escape until the solution reached a temperature of about 135°. Then heating was continued under reflux. Slowly oil globules separated and trimethylamine was liberated. After six hours the mixture was chilled, diluted with water and extracted with ether. The ether solution was washed with water, dried and treated with glacial acetic acid until a slight excess was present. The mixture was chilled and the white solid was separated by filtration and washed with ether (saved for amine recovery). The ether filtrate was then washed with dilute alkali, water and dried. Upon concentration there remained 2.8 g. (approximately 65% discounting water of crystallization) of a crystalline, white solid which lost water at 110–120° and melted 130–133°. Several recrystallizations from methanol gave colorless plates which frothed at 125–127° and melted 138–139.5°. Upon standing exposed to the atmosphere these crystals became opaque and slowly disintegrated; $[\alpha]^{27}_{\mathrm{D}}$ $-85 \pm 1°$ (46.0 mg. made up to 5 ml. with chloroform, α $-0.78°$, l, 1 dm.). For analysis the product was dried for five hours at 1 mm. over boiling chloroform.

Anal. Calcd. for $C_{21}H_{32}O$: C, 83.95; H, 10.72. Found: C, 83.64; H, 11.00.

The solid acetate, 3-hydroxy-5-*ternor*-cholenyldimethylammonium acetate, which was recovered from the reaction mixture weighed 1.4 g. Accounting for this material which may be re-used, the yield of the pregnadiene is 90%.

Upon titration of the pregnadiene in chloroform solution with a solution of bromine in chloroform, this substance absorbed the equivalent of two moles of bromine per mole of compound without liberation of hydrogen bromide. The first mole was absorbed more rapidly than the second but no sharp end-point existed between the two.

Treatment of the 3-hydroxy-pregnadiene with acetic acid–acetic anhydride at steam-bath temperature for one hour afforded **3-acetoxy-5,20-pregnadiene (VII)**. This material after two recrystallizations from methanol existed as white prisms which melted at 132.5–135°. $[\alpha]^{37}\text{D}$ −76.8 ± 1° (62.5 mg. made up to 5 ml. with chloroform, α −0.96°, *l*, 1 dm.).

Anal. Calcd. for $C_{23}H_{34}O_2$: C, 80.64; H, 10.01. Found: C, 80.53; H, 9.94.

3-Hydroxy-5,20-pregnadiene has also been prepared by conversion of the quaternary iodide to the ammonium hydroxide with moist silver oxide and subsequent pyrolysis of the quaternary base. In one experiment, 1.5 g. of the iodide was treated in 50 ml. of methanol with moist silver oxide prepared from 7.5 g. of silver nitrate. After twelve hours the oxide was separated and the pale yellow filtrate was concentrated *in vacuo*. The residue was pyrolyzed at 210° for fifteen minutes at 1 mm. It was then dissolved in ether, washed with dilute hydrochloric acid and water and dried. The gum which remained after removal of ether was crystallized from petroleum ether (b. p. 35–60°); 0.2 g. of white solid melting at 134° after losing solvent at 113–116°. Decomposition of the quaternary base was also effected by refluxing it in methanolic potassium hydroxide solution. This procedure was also effective in converting the quaternary iodide directly into the diene without employing moist silver oxide for the preparation of the intermediate base. However, the last two methods gave erratic results especially when applied to larger batches. Substitution of ethanol for methanol did not alter the situation.

3-*p*-Toluenesulfonoxy-5,20-pregnadiene (VIII).—A 5.8-g. sample of the 3-hydroxy-diene was dissolved in 13 ml. of pyridine. By warming on the steam-bath, 5.8 g. of *p*-toluenesulfonyl chloride was dissolved in this solution. The mixture was allowed to stand overnight, then diluted with water and extracted with ether. The ether solution was washed successively with dilute hydrochloric acid, water, dilute sodium carbonate solution. The residue remaining after removal of ether from the dried solution was crystallized from ether–petroleum ether (b. p. 35–60°). There resulted 7.4 g. (84%) of white solid which melted at 94–97°. After one crystallization from benzene–petroleum ether and another from petroleum ether, the colorless needles melted at 93.5–96°: $[\alpha]^{26}\text{D}$ −65 ± 1° (65.0 mg. made up to 5 ml. with chloroform, α −0.84°, *l*, 1 dm.).

Anal. Calcd. for $C_{28}H_{38}O_3S$: C, 73.96; H, 8.42. Found: C, 74.14; H, 8.39.

6-Methoxy-Δ^{20}-*i*-pregnadiene (IX).—A mixture of 5.2 g. of the *p*-toluenesulfonoxy derivative and 150 ml. of methanol containing 10 g. of freshly-fused potassium acetate was refluxed for two hours and allowed to stand overnight. It was then diluted to about 1.5 liters with water and extracted with ether. The extract was washed with water, dilute sodium carbonate solution, water and dried. Upon concentration (finally *in vacuo*) there remained 3.8 g. of a pale yellow sirup. This was dissolved in 50 ml. of petroleum ether (b. p. 35–60°) and treated with 10 g. of activated alumina (Aluminum Ore Company; grade F, −80 mesh). After shaking intermittently for fifteen minutes, the alumina was separated by filtration and washed with 150 ml. of petroleum ether. The filtrate was concentrated *in vacuo* to 3.2 g. (88.5%) of a colorless sirup: $[\alpha]^{27}\text{D}$ +28.6 ± 2° (43.7 mg. made up to 5 ml. with chloroform, α +0.25, *l* 1 dm.).

Anal. Calcd. for $C_{22}H_{34}O$: C, 84.01; H, 10.91. Found: C, 83.65; H, 10.72.

Methyl 3-Methoxy-5-*etio*-cholenate (X).—To a stirred solution of 2.5 g. of 6-methoxy-Δ^{20}-*i*-pregnadiene in 50 ml. of pyridine and 5 ml. of water, 5.0 g. of powdered potassium permanganate was added portionwise over a period of three hours. The manganese dioxide was filtered and washed with pyridine and water. The filtrate which remained clear upon dilution with water was acidified with dilute acetic acid and extracted with ether. The ether solution was washed with cold dilute sulfuric acid, with water and dried. The sirup which remained upon removal of ether was dissolved in 50 ml. of methanol. Fifteen drops of concd. sulfuric acid was added and the solution was refluxed for three and one-half hours. Water was added cautiously to the chilled solution until crystallization began. After completion of crystallization, the white solid was filtered, washed with aqueous methanol and dried. The solid, 1.5 g., melted at 115–128°. Several recrystallizations from a concentrated methanol solution gave 1.0 g. of white needles melting at 133–134°, $[\alpha]^{38}\text{D}$ −23 ± 2° (44.3 mg. made up to 5 ml. with chloroform, α, −0.20°, *l*, 1 dm.).

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.25; H, 9.90. Found: C, 76.10; H, 9.71.

The constitution of this *etio*-ester was proven by an independent synthesis. 3-Acetoxy-5-*etio*-cholenic acid was converted to the acid chloride with thionyl chloride in dry ether. The acid chloride when refluxed in methanol for a short period gave methyl 3-hydroxy-5-*etio*-cholenate (m. p. 175–178°). The 3-*p*-toluenesulfonoxy derivative (m. p. 155–157.5°) was prepared from this ester. The former upon refluxing in methanol yielded, as indicated by mixed m. p., the same compound as described above, namely, methyl 3-methoxy-5-*etio*-cholenate.

3-Keto-4,20-pregnadiene (XI).—Nine grams of 3-hydroxy-5,20-pregnadiene was dissolved in a mixture of 100 ml. of toluene and 54 ml. of cyclohexanone and then a few ml. of toluene was distilled in order to remove traces of moisture. After the addition of 9.2 g. of aluminum isopropoxide in 60 ml. of hot toluene, the solution was refluxed for one hour. The solution was then chilled, diluted with dilute hydrochloric acid and extracted with ether. The extract was washed with water, concentrated and then steam distilled. The residue was taken up in ether, washed with water, dilute sodium hydroxide solution and water. The pale yellow, crystalline residue remaining after the removal of ether from the dried solution was recrystallized from a concentrated methanol solution. The product, 7.3 g. (81.6%) of pale yellow prisms, melted at 120–125°. This material is soluble in ether, acetone, methanol, hexane and petroleum ether (b. p. 35–60°). After it was recrystallized several times from a concentrated methanol solution, the diene, practically colorless prisms, melted at 123.5–126.5°: $[\alpha]^{39}\text{D}$ +106 ± 1° (82.5 mg. made up to 5 ml. with chloroform, α +1.75°, *l*, 1 dm.).

Anal. Calcd. for $C_{21}H_{30}O$: C, 84.52; H, 10.12. Found: C, 84.56; H, 10.13.

3-Keto-4,20-pregnadiene formed a white, crystalline semicarbazone which melted at 243–244°, dec., after recrystallization from chloroform–methanol.

Anal. Calcd. for $C_{22}H_{33}ON_3$: C, 74.32; H, 9.37. Found: C, 74.13; H, 9.20.

3-Keto-4-*etio*-cholenic Acid (XII).—A solution of 2.0 g. of 3-keto-4,20-pregnadiene in 60 ml. of chloroform was ozonized (4.5% O_3 by volume at 0.5 l./min.) for ten minutes at ice-bath temperature. The solution was then steam distilled and the residual waxy solid dissolved in ether. The ether solution was washed with water and then extracted with cold dilute sodium hydroxide solution. Upon acidification of the alkaline solution with dilute hydrochloric acid, a white, crystalline solid separated. The solid was filtered, washed with water and dried; 1.2 g. (56.6%), m. p. 235–250°. After recrystallization from acetone–hexane and from acetone, the acid melted at 250–255°. This material showed no depression in melting point when mixed with an authentic sample of 3-keto-4-*etio*-cholenic acid prepared by the oxidation of 3-hydroxy-5-*etio*-cholenic acid. Reozonization of the neutral fraction yielded an additional quantity of *etio*-acid.

3(α),12(α)-Diacetoxy-20-aminopregnane (XIII).—A solution of 7.2 g. of 3(α),12(α)-diacetoxy-*bisnor*-cholanic acid in 20 ml. of dry benzene and 40 ml. of dry ether was treated with 4.2 ml. of freshly-distilled thionyl chloride. After standing at room temperature for one hour and forty minutes, the solvent was removed *in vacuo* with gentle warming. The last traces of thionyl chloride were removed by sweeping out, *in vacuo*, with several small portions of benzene. At this stage the acid chloride, which had begun to crystallize, was dissolved in 130 ml. of acetone. The solution was chilled in an ice–salt-bath to 0–5° and treated dropwise, with mechanical agitation, over a period of ten minutes with a solution of 2.3 g. of sodium azide in 10 ml. of water. Sodium chloride separated. After an additional twenty minutes of stirring, 200 ml. of cold water was dribbled in with continued stirring. The crystalline azide (a sample of this material melted at 86–90°, dec.) was then filtered, washed with cold water and suspended in 130 ml. of 80% acetic acid. This mixture was heated to 50–60° and held there for one hour. The azide dissolved rapidly and then decomposed with evolution of nitrogen. The solution was filtered, steam distilled for thirty minutes, filtered again and made alkaline with cold dilute sodium carbonate solution. The amine was extracted with ether and washed with water. Upon removal of solvent *in vacuo* from the dried solution there remained 6.2 g. (96.7%) of yellow amorphous material. Attempts to crystallize this material have not been overly successful. A small sample when crystallized from ether and ether–petroleum ether (b. p. 35–60°) melted at 207–209° but was not analytically pure.

The crude amine readily gave an acetamide upon treatment with acetic anhydride in acetic acid; 800 mg. with 4 ml. of acetic acid and 2 ml. of acetic anhydride gave 910 mg. of amide melting at 210–220°. After several recrystallizations from aqueous methanol, it melted at 220–221°.

Anal. Calcd. for $C_{27}H_{43}O_5N$: C, 70.24; H, 9.60. Found: C, 70.14; H, 9.44.

A sample of the crude azide upon warming with ethanol formed the urethan. After several recrystallizations from aqueous ethanol, it melted at 172–173°.

Anal. Calcd. for $C_{28}H_{45}O_6N$: C, 68.39; H, 922. Found: C, 68.23; H, 9.23.

3(α),12(α)-Diacetoxy-20-dimethylaminopregnane (XIV).—A mixture of 5.2 g. of the crude 20-aminopregnane, 6 ml. of 90% formic acid and 4 ml. of 35% aqueous formaldehyde was heated on the steam-bath under reflux for four hours. The orange liquid was poured into cold dilute sodium hydroxide solution and extracted with ether. The ether solution was washed with water, dried and concentrated *in vacuo*. There remained 5.5 g. (99%) of an orange glass. This material when crystallized from petroleum ether (b. p. 35–60°) gave 3.0 g. of white solid, m. p. 115–125° (cloudy). The residue (2.5 g.) in the mother liquor was also reserved for further processing. Several recrystallizations of the solid material from petroleum ether gave small, white needles melting at 134–137°.

Anal. Calcd. for $C_{27}H_{45}O_4N$: C, 72.45; H, 10.14. Found: C, 72.71; H, 10.52.

From one run there was isolated a small portion of material melting at 167–174°. Several recrystallizations from acetone gave fine, white needles melting at 184–187.5°. This material analyzed for an acetoxy-hydroxy-20-dimethylaminopregnane.

Anal. Calcd. for $C_{25}H_{43}O_3N$: C, 74.03; H, 10.68. Found: C, 73.90; H, 10.57.

3(α),12(α)-Diacetoxy-20-pregnene (XV).—A 2.2-g. sample of the crystalline 20-dimethylaminopregnane was dissolved in 20 ml. of benzene, treated with 5 ml. of methyl iodide and refluxed for two hours. The solution was diluted with ether, chilled, and the solid material separated. After washing with petroleum ether (b. p. 35–60°), the dry, pale yellow crystalline quaternary iodide was dissolved in a mixture of 6 ml. of water and 30 ml. of ethylene glycol containing 6 g. of potassium hydroxide. The mixture was refluxed (temperature of boiling solution about 135°) for seven and one-half hours, diluted with water and extracted with ether. The ether solution was then washed with water, dilute hydrochloric acid, water and dried. Concentration of the solution gave a pale yellow glass. This was dissolved in 10 ml. of acetic acid–3 ml. of acetic anhydride and treated with 1 ml. of 5 *N* perchloric acid[10] in acetic acid at ice-bath temperature and then allowed to stand for thirty minutes. Upon dilution with water, a white crystalline solid separated. This was filtered, washed with water and dried; 1.5 g. (75.7%), m. p. 162–175°. Several recrystallizations from methanol gave large needle-like prisms which melted at 184–185°.[11] $[\alpha]^{37}D + 102 \pm 2°$ (60.9 mg. made up to 5 ml. with chloroform, α 1.24°, *l*, 1 dm.).

Anal. Calcd. for $C_{25}H_{38}O_4$: C, 74.58; H, 9.52. Found: C, 74.63; H, 9.73.

The non-crystalline fraction (2.5 g.) of the diacetoxy-20-dimethylaminopregnane, when treated as described above gave 1.4 g. (62.2%) of crystalline material melting at 162–175°. Recrystallization from methanol raised the melting point to 184–185°.

3-Keto-20,21-dihydroxy-4-pregnene (XVI).—A solution of 1.1 g. of 3-keto-4,20-pregnadiene in 20 ml. of anhydrous ether was added to a solution of 1.0 g. of osmium tetroxide in a like amount of ether. After twenty-two hours at room temperature, the brown solid was separated and washed with ether–petroleum ether (b. p. 35–60°). It was then suspended in 75 ml. of 95% ethanol to which 8 g. of sodium sulfite in 40 ml. of water was added. The mixture was refluxed for four hours and, while hot, filtered to remove the black solid. After washing the solid with hot ethanol, the filtrate was concentrated *in vacuo* to about 20 ml. Upon addition of water, a white solid separated. This was chilled, filtered, washed with water and dried; 0.9 g., m. p. 170–175° after shrinking at 150°. Recrystallization from anhydrous ether gave 0.6 g. of white solid which melted at 176–183°. Four recrystallizations from acetone gave fine, colorless prisms melting at 192.5–194.5°; $[\alpha]^{35}D + 97 \pm 1°$ (47.3 mg. made up to 5 ml. with chloroform, α + 0.92°, *l*, 1 dm.).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.87; H, 9.69. Found: C, 75.75; H, 9.85.

The residual material from the crystallization was chromatographed over 30 g. of activated alumina (Aluminum Ore Co. grade F, −80 mesh) in ether–methanol (9–1). The separation was not sharp, but an intermediate fraction eluted with ether–methanol (9–1) gave a small amount of white solid melting at 164–170° but softening at 140°. Several recrystallizations from acetone gave fine needles melting at 166–168°; $[\alpha]^{27}D + 98 \pm 1°$ (83.8 mg. made up to 5 ml. with chloroform, α, + 1.65°, *l*, 1 dm.). This material when mixed with a portion of the 192.5–194.5° material melted at 115°.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.87; H, 9.69. Found: C, 75.83; H, 9.87.

3(α),12(α)-Diacetoxy-*etio*-cholanic Acid.—A solution of 1.0 g. of 3(α),12(α)-diacetoxy-20-pregnene in 30 ml. of acetic acid was ozonized for thirty minutes (4.5–5% O_3 at 0.5 l./min.). The solution was then treated with zinc dust, warmed, filtered and steam distilled after the addition of a few ml. of 30% hydrogen peroxide. The residue was dissolved in ether and washed with water. The ether solution was then extracted with cold dilute sodium hydroxide solution. The neutral material remaining in the ether was retreated with ozone and worked for acidic material. Upon addition of dilute hydrochloric acid to the alkaline solution a solid separated. This was filtered, washed with water and dried. It was then acetylated in 8 ml. of acetic acid with 3 ml. of acetic anhydride employing 1 ml. of 5 *N* $HClO_4$ in acetic acid for catalyst.[10] The product was precipitated by addition of water and dried—0.7 g. (67%), m. p. 190–199°. After one recrystallization from ether–pentane the *etio*-acid melted at 195–199° (reported 196–198°[12]).

Summary

1. *bisnor*-Steroid acids have been degraded to Δ^{20}-pregnenes *via* the Curtius procedure to 20-

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[10] Whitman and Schwenk, THIS JOURNAL, **68**, 1865 (1946).

[11] This pregnene may be identical with the compound of m. p. 176–178.5° described by Brink, Clark and Wallis, *J. Biol. Chem.*, **162**, 695 (1946).

[12] Reichstein and von Arx, *Helv. Chim. Acta*, **23**, 747 (1940).

amino-derivatives, followed by Hofmann degradation.

2. Ozonization of 3-keto-4,20-pregnadiene constitutes a better route than any hitherto suggested to 3-keto-4-*etio*-cholenic acid. Likewise ozonization of 3(α),12(α)-diacetoxy-20-pregnene gave 3(α),-12(α)-diacetoxy-*etio*-cholanic acid in good yield.

3. Hydroxylation of 3-keto-4,20-pregnadiene gave the isomeric 20,21-diols which have been separated and characterized.

4. This degradation of *bisnor*-acids facilitates the preparation of compounds containing the ketol structure of the cortical hormones.

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[CONTRIBUTION FROM THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY, MELLON INSTITUTE]

Studies in the Quinoline Series. IX. The Mononitrophenyllepidylcarbinols and Related Compounds

BY R. STUART TIPSON AND ANNE FARLEY WALTON

In a recent communication,[1] methods were described for the preparation of the three mononitrophenylquinaldylcarbinols and certain of their derivatives. We now describe related work on the lepidyl isomers.

In an attempt to prepare *p*-nitrophenyllepidylcarbinol by Bulach's[2] method (used for the preparation, in good yield, of the corresponding quinaldyl compounds[1]) the yield was only 7% of the theoretical; this is in agreement with Eibner's work[3] showing that a methyl group at position 4 reacts less readily with aldehydes than one at position 2. However, on lengthening the reaction time to eight hours, and changing the method of isolating the product, the yields of the lepidylcarbinols were: *o*- and *p*-, 24%; *m*-, 19%. A lower yield of *m*-derivative had also been noted[1] in the quinaldyl series. The *o*- and *p*-derivatives were isolated directly; because of the greater solubility of the *m*-derivative, it was found more convenient to extract it as the hydrochloride and to reconvert the latter to the base.

When *two* moles of lepidine were used to one of aldehyde, the yield of *m*-carbinol (after eight hours at 120°) was increased to 24%, but for the *o*- and *p*- isomers there was no great improvement in yield of isolable product (presumably because these compounds were, to a somewhat greater extent, retained in solution in the excess lepidine, and the dissolved part could not be readily separated from it). Various attempts were made to increase the yield of *m*-derivative still further. It was found that heating the reaction mixture at 120° for twenty-four hours, or at 145° for eight hours, always gave a mixture of the carbinol and the corresponding *styryl* compound. Moreover, after cooling to room temperature, the reaction mixture was invariably found to be acid to litmus and it was concluded that this acid, presumably formed from the aldehyde during the reaction, had facilitated conversion of some of the carbinol to the styryl derivative. (The ability of acid to catalyze this dehydration has already been proved[1] for the corresponding quinaldyl carbinols.) It was therefore decided to add to the reaction mixture some substance which would neutralize acid as fast as it was formed. After examining the effect of a number of materials, anhydrous sodium carbonate was finally selected, and the reaction mixture was heated at 145° for twenty-four hours. At the end of this time, the reaction mixture was still alkaline to litmus, and *no* styryl derivative had formed, but the yield obtained (33%), though higher, was scarcely increased enough to warrant using this method.

Just as for the three quinaldyl isomers, we find the three nitrophenyllepidylcarbinols exhibit two melting points, depending on whether heated rapidly or slowly. On cooling until crystallized and remelting, the melting point is found to be lower in each case, presumably owing to partial conversion to the corresponding styryl derivative on heating. The carbinols were transformed to their monohydrochlorides which were isolated as colorless, crystalline substances showing no tendency to become dehydrated to the styryl derivatives during five months at room temperature, as evidenced by the recovery of pure carbinol on reconversion to the base. The acetyl derivatives of the three carbinol compounds were also prepared. Attempts to reduce each nitro carbinol to the corresponding amino derivative gave inconclusive results suggestive of formation of some β-hydroxylamino derivative[4]; we were unable to purify the products satisfactorily by fractional recrystallization.

It has been shown previously[5] that the reaction of *p*-dimethylaminobenzaldehyde with quinaldine gives rise to the corresponding styryl derivative *plus* *p*-dimethylaminobenzylidene diquinaldine (β-*p*-dimethylaminophenyl-α,γ-di-2-quinolylpropane) and that a preponderance of either product is obtainable by appropriate choice of the conditions. Similarly, on attempting to prepare the pure *styryl* derivatives by condensation of the appropriate nitrobenzaldehyde with lepidine in

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[1] Walton, Tipson and Cretcher, THIS JOURNAL, **67**, 1501 (1945).

[2] Bulach, *Ber.*, **20**, 2046 (1887).

[3] Eibner, *Ber.*, **37**, 3605 (1904); Fischer, *et al.*, *J. prakt. Chem.*, **100**, 91 (1920).

[4] Fieser and Hershberg, THIS JOURNAL, **62**, 1640 (1940).

[5] Tipson, *ibid.*, **67**, 507 (1945).