

acid A obtained by ethanolic hydrochloric acid hydrolysis of the N-benzoyl derivative. The crude ester was recrystallized from hexane giving pure methyl  $\alpha$ -amino- $\beta$ -hydroxystearate B melting at 71–73°.

*Anal.* Calcd. for C<sub>19</sub>H<sub>39</sub>O<sub>2</sub>N: C, 69.25; H, 11.93; N, 4.25. Found: (A) C, 69.03; H, 11.65; N, 4.21; (B) C, 69.53; H, 12.03; N, 4.06.

Attempts to prepare ester A from the unfractionated hydrochloride obtained by glacial acetic acid–hydrochloric acid hydrolysis of N-benzoyl acid A gave products melting at 50–55°. Such preparations appeared to be a mixture of the two esters.

**Oxazoline Interconversions.**—Methyl  $\alpha$ -benzamido- $\beta$ -hydroxystearates A and B were converted to the corresponding oxazolines with thionyl chloride as described by Elliott.<sup>11b,c</sup> The crude oxazolines were obtained as oily residues on concentration of the chloroform solutions. The crude oxazolines without further purification were hydrolyzed directly or after sodium ethoxide treatment as follows:

(a) **Direct Acid Hydrolysis of Oxazoline.**—The oxazoline from 1.0 g. of N-benzoyl A methyl ester was dissolved in 42 ml. of methanol, and 4 ml. of 3 N hydrochloric acid was added. The solution was allowed to stand for 18 hours at room temperature to convert the oxazoline to the O-benzoyl derivative. The resulting solution was neutralized with 5% sodium hydroxide; 10 ml. of 10% sodium hydroxide was added and the solution was refluxed for 35 minutes. The solution was acidified with 5 ml. of concentrated hydrochloric acid and the precipitate was filtered and dried (yield 0.86 g., 88%, m.p. 83–90°). Recrystallization of the crude product from a mixture of 3 ml. of ethyl acetate and 5 ml. of

hexane gave 0.62 g. of pure N-benzoyl acid B melting at 91–92°.

Treatment of the oxazoline from 0.40 g. of the N-benzoyl ester B under the above conditions gave 0.32 g. of N-benzoyl acid A melting at 165–173°.

(b) **Sodium Ethoxide Treatment of Oxazoline.**—To the crude dry oxazoline from 1.0 g. of methyl  $\alpha$ -benzamido- $\beta$ -hydroxystearate A was added a solution of 1.7 g. of sodium ethoxide in 25 ml. of anhydrous ethanol. The solution became turbid and a precipitate formed. The suspension was allowed to stand for 10 minutes. Then 5 ml. of water was added and the solution was refluxed for 15 minutes. The white suspension was acidified with concentrated hydrochloric acid and allowed to stand for 4 hours at room temperature. The suspension was diluted with 50 ml. of methanol and made to alkaline (pH 11) with 10% sodium hydroxide. After 5 minutes the mixture was acidified with concentrated hydrochloric acid and water was added to cause complete precipitation of the N-benzoyl derivative. The crude product weighed 0.82 g. (84% yield) and melted at 84°. One recrystallization of this material from ethyl acetate–hexane gave pure N-benzoyl- $\alpha$ -amino- $\beta$ -hydroxystearic acid B melting at 91–93°. There was no indication of the presence of the A isomer in the mother liquors.

The oxazoline from 0.40 g. of methyl N-benzoyl- $\alpha$ -amino- $\beta$ -hydroxystearate B when treated as described above gave 0.37 g. of crude N-benzoyl acid B melting at 85–87°. Recrystallization from ethyl acetate–hexane gave 0.23 g. melting at 91–93°. No N-benzoyl A could be isolated from the mother liquors.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY]

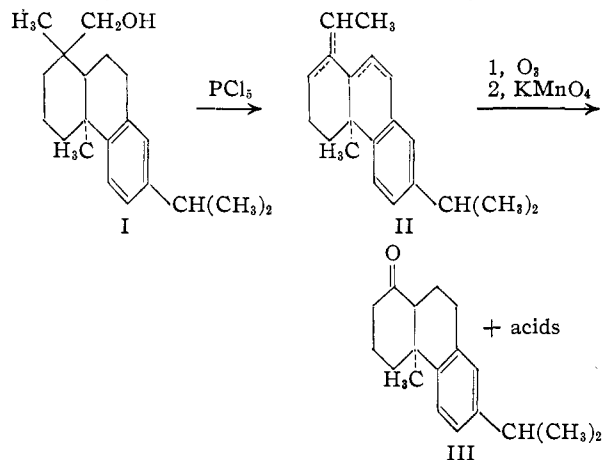
## A New C<sub>1</sub>-Ketone from Dehydroabietic Acid<sup>1</sup>

BY ROBERT P. JACOBSEN

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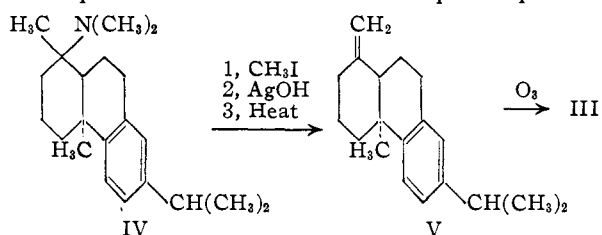
A report is made of the degradation of dehydroabietinol (I) and its 6-bromo derivative VII to the corresponding C<sub>1</sub>-ketones, IIIa and VIII. The ketone IIIa, from the unsubstituted carbinol, isolated *via* its crystalline semicarbazone, was found to be different from that previously reported.

In their report<sup>2</sup> of the degradation of dehydroabietinol (I), Brossi, Gutmann and Jeger described the isolation and properties of the C<sub>1</sub>-ketone III. In its formation the intermediate hydrocarbon mixture (II), obtained in the dehydration–rearrangement of I with phosphorus pentachloride, was subjected to ozonolysis followed by oxidation



with potassium permanganate and isolation of the neutral ketonic fraction with Girard reagent T. Esterification of the accompanying acidic fraction followed by separation of the ketonic and non-ketonic esters provided compounds arising through cleavage of the tricyclic ring system at positions 1,2 or 10,10a and 9,10.

Recently Zeiss and Martin<sup>3</sup> have described another route for the degradation of dehydroabietic acid involving in its final stages the Hofmann degradation of nordehydroabietyldimethylamine (IV) to the hydrocarbon V. Ozonolysis of the latter afforded III whose structural identity with synthetic 1-oxo-4a-methyl-7-isopropyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene<sup>4</sup> was demonstrated by a comparison of their infrared absorption spectra.



(1) The work described in this paper was supported by a grant from G. D. Searle & Company.

(2) A. Brossi, H. Gutmann and O. Jeger, *Helv. Chim. Acta*, **33**, 1730 (1950).

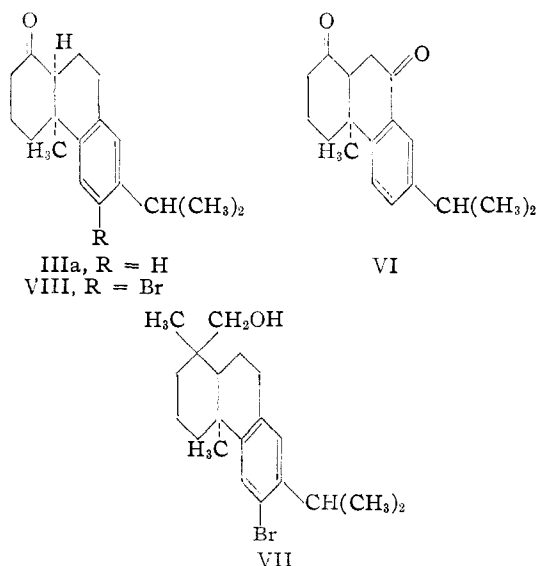
(3) Presented before the 121st Meeting of the American Chemical Society at Buffalo, N. Y., March, 1952.

(4) G. Stork and A. Burgstahler, *THIS JOURNAL*, **73**, 3544 (1951).

Inasmuch as these two preparations of  $C_{11}$ -ketone appeared to be identical, the author was very surprised when a similar preparation (IIIa) of ketone obtained *via* the dehydration-rearrangement of I was found to possess properties unlike those of the above products.

In attempting to prepare a quantity of the above ketone to be used as starting material for other synthetic work, the author employed phosphorus pentoxide in boiling hexane for the preparation from I of a hydrocarbon mixture (IIa) similar in its dextrorotatory character to that (II) of Bossi, *et al.* However, the ozonolysis of this mixture provided a neutral fraction from which was isolated a sparingly soluble semicarbazone possessing the empirical formula of III semicarbazone, but melting with decomposition about thirty degrees higher than the compound previously described.<sup>2</sup> Moreover the specific rotation of the isomeric ketone IIIa obtained by hydrolysis of the semicarbazone was found to be about thirty degrees higher than that reported<sup>2</sup> for III. The hydrolysate re-formed the high-melting semicarbazone in nearly the theoretical yield.

Oxidation of the isomeric ketone, under conditions previously used<sup>5</sup> for the preparation of 9-oxo derivatives in the dehydroabietane series, converted it to a crystalline diketone (VI) whose ultraviolet absorption maxima proved to be typical of this class of compounds. For purposes of comparison corresponding derivatives were prepared from 6-bromodehydroabietinol (VII).



The above derivatives adequately characterized the parent ketone IIIa and a study of the infrared absorption spectra of liquid films of IIIa and of synthetic ketone<sup>4</sup> kindly supplied by Dr. Gilbert Stork showed that the former is correctly represented by the structure shown.

Although the yield of IIIa from methyl dehydroabietate was very low its preparation was readily reproducible and both IIIa and VIII are believed to be pure compounds. The difference between III and IIIa may be a stereochemical one for the

(5) R. P. Jacobsen, *THIS JOURNAL*, **73**, 3463 (1951); see also V. T. Pratt, *ibid.*, **73**, 3803 (1951).

latter compound behaves like a *cis*- $\alpha$ -decalone derivative in its sensitivity to alteration under conditions conducive to enolization. This lability of the ketone was noted when its solution in methanol containing a small amount of potassium hydroxide was found to undergo a change in rotation at room temperature, the value at equilibrium being thirty-seven degrees lower than that of the freshly prepared solution. The 6-bromo ketone VIII was found to behave similarly in the presence of alkali, the rotation falling thirty-three degrees under the conditions specified.

Various derivatives of IIIa are being studied in a project for which the preparation of the  $C_{11}$ -ketone was originally undertaken.

The author wishes to thank Dr. Harris Rosenkrantz for his determination of infrared absorption data. Analyses were performed by Dr. Robert T. Dillon and Staff of the Analytical Division, G. D. Searle & Company, whose assistance in this work the author gratefully acknowledges.

### Experimental<sup>6</sup>

**The Dehydration-Rearrangement of Dehydroabietinol (I) to the Hydrocarbon Mixture IIa.**—The carbinol was prepared by reducing 100 g. of methyl dehydroabietate<sup>7</sup> (m.p. 60–62°,  $[\alpha]^{25}_D +55^\circ$  (*c* 4.00)) with 10 g. of lithium aluminum hydride in 650 ml. of ether. After the usual work-up the unpurified carbinol was dried by distillation of its benzene solution and the residue made up to 250 ml. with dry benzene. One-half of this solution was added at a rate of 7 to 8 ml./min. to a stirred boiling suspension of 50 g. of phosphorus pentoxide in 800 ml. of pretreated<sup>8</sup> hexane. When the addition was complete the heater was removed and the flask lowered before stopping the stirrer. The reaction vessel was placed in cold water during settling of the spent dehydrating agent after which the warm supernatant was decanted and the residue washed superficially with hexane. The hexane solution was allowed to stand with intermittent swirling over a water slurry of sodium bicarbonate until free of acid. The colorless solution was then shaken with anhydrous sodium bicarbonate, filtered and most of the hexane recovered for re-use while the residual solution was freed of solvent under diminished pressure. The oily product from the total 100 g. of ester was distilled in vacuum, the fraction, b.p. 119–123° (0.1 mm.),  $[\alpha]^{25}_D +202^\circ$  (*c* 5.02), weighing 65.5 g.

*Anal.* Calcd. for  $C_{20}H_{28}$ : C, 89.49; H, 10.51. Found: C, 89.65, 89.57; H, 10.75, 10.64.

**Ozonolysis of the Hydrocarbon Mixture IIa.**—A solution of 44.9 g. of the distilled hydrocarbon in 450 ml. of methyl acetate cooled to  $-75^\circ$  was treated with 4% ozone for about six hours (nearly three-quarters of the calculated amount of ozone).<sup>9</sup> A jet of steam was passed into the solution to distill the solvent and the residue was then vigorously steam distilled for 20–30 minutes to decompose the ozonide. The product was extracted with ether, the extract washed with dilute sodium bicarbonate solution, dried and distilled providing a nearly colorless oil.

**Isolation of the Semicarbazone of IIIa.**—The neutral oil obtained as described above from 100 g. of methyl dehydro-

(6) Melting points were taken in open Pyrex capillaries; rotations are reported for chloroform solutions. Samples for analysis were dried at 110° or as specified and 0.05 mm. over phosphorus pentoxide. Infrared measurements were made using a Perkin-Elmer model 12C spectrometer and ultraviolet measurements with a Beckman instrument.

(7) Generously supplied by the Hercules Powder Company, Wilmington, Del.

(8) Phillips Petroleum Company normal hexane, technical grade, was boiled with several portions of phosphorus pentoxide and distilled so that the boiling suspension at the start of the carbinol addition was colorless or only faintly pink.

(9) The optimum yield of desired product was obtained by this means, the ethylidene component of IIa apparently reacting completely in this time.

abietate was refluxed for two hours with methanolic semicarbazide<sup>10</sup> containing acetic acid. The sparingly soluble semicarbazone usually began to crystallize during this period but was not removed. Instead the cooled methanol suspension was poured into 2.5 l. of well-stirred cold water and the precipitated solid was collected, washed with water and air-dried. The dry solid was then triturated with a smaller volume of methanol, allowed to stand for some time and the insoluble portion collected and washed with methanol. The filtrate was diluted with methanol and again poured into water. In this manner 14.4 g. of nearly pure IIIa semicarbazone and about 60 g. of amorphous solid by-product were obtained. A single recrystallization of the former from methanol-chloroform mixture provided 14 g. (14%) of product melting with decomposition at or slightly above 240° (pre-heated bath),  $[\alpha]^{25D} +286^\circ$  (*c* 1.38). The sample for analysis was again crystallized forming soft nodules consisting of microscopic blades, m.p. 242° dec. (pre-heated bath),  $[\alpha]^{25D} +289^\circ$  (*c* 2.96).

*Anal.* Calcd. for C<sub>19</sub>H<sub>27</sub>ON<sub>3</sub>: C, 72.80; H, 8.68; N, 13.41. Found: C, 72.56, 72.61; H, 8.53, 8.45; N, 13.42, 13.26.

**1-Oxo-bisnordehydroabietane (IIIa).**—Regeneration of the ketone from the semicarbazone was accomplished by refluxing a suspension of 14 g. of the latter for 20 minutes in 490 ml. of methanol and 210 ml. of water containing 14 ml. of 6 *N* hydrochloric acid, complete solution being achieved during the first five minutes of boiling. After pouring the hot solution into cold water the precipitated viscous oil was extracted with pentane. Some flocculent solid was removed and the pentane solution was washed and dried. The oil remaining after distillation of the solvent was distilled in vacuum providing 8.7 g. of colorless oil, b.p. 120–123° (0.05 mm.),  $[\alpha]^{25D} +153^\circ$  (*c* 5.61).

*Anal.* Calcd. for C<sub>18</sub>H<sub>24</sub>O: C, 84.32; H, 9.41. Found: C, 84.32, 84.22; H, 9.33, 9.38.

When refluxed with methanolic semicarbazide IIIa reformed the semicarbazone in 93% yield, m.p. 240° dec.,  $[\alpha]^{25D} +281^\circ$  (*c* 1.81), after one recrystallization from methanol-chloroform.

Refluxing IIIa with methanolic hydroxylamine afforded the oxime which crystallized from methanol in rectangular plates, m.p. 193–199° with preliminary sintering,  $[\alpha]^{25D} +292^\circ$  (*c* 1.84).

*Anal.* Calcd. for C<sub>18</sub>H<sub>25</sub>ON: C, 79.66; H, 9.29; N, 5.16. Found: C, 79.44, 79.78; H, 9.22, 9.30; N, 4.95, 4.94.

**1,9-Dioxo-bisnordehydroabietane (VI).**—One gram of IIIa in 15 ml. of acetic acid was cooled and mixed with 3 ml. of chromic acid solution (0.25 g. anhydride per ml. 80% aqueous acetic acid) and allowed to stand at 35°. At the end of 2.5 hours a second portion of 2.5 ml. of the oxidant was added. After a total reaction period of 7.5 hours water was added and the resinous product was extracted with ether. The extract was washed with water and dilute sodium bicarbonate solution, dried and the solvent distilled. The residue was induced to crystallize by rubbing with pentane and the solid was recrystallized from ether-hexane and aqueous methanol forming 0.13 g. of thin blades, m.p. 117–118°,  $[\alpha]^{25D} +144^\circ$  (*c* 0.367),  $\lambda_{\text{max}}^{\text{EtOH}}$  (log  $\epsilon$ ) 254 m $\mu$  (4.02), 301 m $\mu$  (3.29).

*Anal.* Calcd. for C<sub>18</sub>H<sub>22</sub>O<sub>2</sub>: C, 79.96; H, 8.20. Found: C, 79.76; H, 8.17.

In a similar oxidation of 0.90 g. of IIIa in 12 ml. of acetic acid with only 3 ml. of chromic acid solution at 30° for six hours, the oily neutral product (0.75 g.) was treated with hydroxylamine and the solid thus obtained was chromatographed on a 1.2 × 23-cm. column of Alorco F-20 alumina. Elution with ether-ethyl acetate mixtures provided 0.15 g. of solid which crystallized from methanol in square plates, m.p. 198.5–201.5°. The melting point of a mixture with IIIa oxime above was 195–201.5°.

The dioxime of VI was obtained in a second solid fraction (0.23 g.) eluted with ethyl acetate-methanol mixtures; it crystallized from methanol in chunky prisms, m.p. 253–256° dec.,  $[\alpha]^{25D} +270^\circ$  (*c* 1.17).

(10) This reagent was prepared by grinding 65 g. of the hydrochloride with 30 g. of anhydrous sodium carbonate with succeeding portions of methanol and adding 6.5 ml. of acetic acid to the filtered solution whose final volume was about 700 ml.

*Anal.* Calcd. for C<sub>18</sub>H<sub>24</sub>O<sub>2</sub>N<sub>2</sub>: C, 71.97; H, 8.05; N, 9.33. Found: C, 71.70; H, 7.99; N, 9.35.

**6-Bromodehydroabietinol (VII).**—Methyl 6-bromodehydroabietate<sup>11</sup> (43.5 g., m.p. 141–142°) was reduced with lithium aluminum hydride as for the unsubstituted ester except that addition of the solid ester was made by modified Soxhlet extraction. A small sample of the solid product (37 g., m.p. 111–115°) crystallized from aqueous methanol in very thin needles, m.p. 116–116.5°,  $[\alpha]^{25D} +68^\circ$  (*c* 2.42), after drying at room temperature.

*Anal.* Calcd. for C<sub>20</sub>H<sub>29</sub>OBr: C, 65.75; H, 8.00. Found: C, 65.73; H, 8.11.

**Dehydration-Rearrangement of VII.**—The reaction of 20 g. of VII (m.p. 111–115°) in 100 ml. of dry benzene with 20 g. of phosphorus pentoxide in 200 ml. of boiling hexane was carried out as described for the unsubstituted carbinol except that the rate of addition of the bromocarbinol was about 4 ml./min. The product, b.p. 144–148° (0.03 mm.),  $[\alpha]^{27D} +208^\circ$  (*c* 6.01), was a viscous oil, the yield from 43.5 g. of ester being 28.3 g.

*Anal.* Calcd. for C<sub>20</sub>H<sub>27</sub>Br: C, 69.16; H, 7.84. Found: C, 69.07, 69.35; H, 7.71, 7.79.

**Ozonolysis of the 6-Bromohydrocarbon Mixture.**—This ozonolysis was conducted in methyl acetate (28.3 g. in 400 ml.) as for IIa. The neutral ozonolytic fraction on treatment with semicarbazide provided 2.56 g. of semicarbazone, virtually insoluble in methanol, melting with decomposition at 258° (preheated bath). A sample for analysis crystallized from chloroform in very small rectangular plates, m.p. 262° dec. (preheated bath),  $[\alpha]^{30D} +212^\circ$  (*c* 0.347).

*Anal.* Calcd. for C<sub>19</sub>H<sub>26</sub>ON<sub>3</sub>Br: C, 58.16; H, 6.68; N, 10.71. Found: C, 58.14; H, 6.72; N, 10.53.

**1-Oxo-6-bromobisnordehydroabietane (VIII).**—The free ketone was obtained by refluxing a suspension of 2.5 g. of the above semicarbazone in 250 ml. of methanol and 50 ml. of water containing 4 ml. of 6 *N* hydrochloric acid for 45 minutes, nearly complete solution being achieved in this time. After pouring the reaction mixture into cold water the product was extracted with pentane. The washed and dried extract provided solid ketone which crystallized from methanol in 0.95 g. of coarse blades, m.p. 130–132°,  $[\alpha]^{25D} +135^\circ$  (*c* 1.57), after drying at 80°.

*Anal.* Calcd. for C<sub>18</sub>H<sub>23</sub>OBr: C, 64.48; H, 6.91. Found: C, 64.46; H, 6.92.

**The Rotation of IIIa and VIII in Dilute Methanolic Alkali.**—A solution of 189.9 mg. of IIIa in methanol was mixed with 0.05 ml. of a solution of potassium hydroxide in 90% methanol (0.1 g./ml.) and the mixture made up to a volume of 5.03 ml. The specific rotation of a sample of the solution measured soon after mixing was found to be +155°. The volumetric flask was filled with nitrogen and allowed to stand at room temperature for two days when a second sample was withdrawn; the rotation of this sample was found to be +118° and, after standing eight days longer, a final sample was found to give this same value.

A similar solution of 139.3 mg. of VIII in methanol containing a few drops of chloroform and the same amount of potassium hydroxide was made up to a volume of 5.03 ml. with methanol. The initial rotation of the solution was found to be +138°, this value falling to +105° after two days standing at room temperature.

The rotation of a solution of IIIa in 0.25 *N* methanolic potassium hydroxide was found to be +172° about two hours after mixing indicating that the enolate is dextrorotatory with respect to IIIa.

**By-products Formed in the Preparation of IIIa and VIII.**—In a preliminary examination of the large amount of by-product accompanying IIIa and VIII semicarbazones, two types of material were encountered. One of these, which appeared to consist of ketonic material of higher oxygen content than IIIa, was obtained as follows: 41.5 g. of the amorphous solid by-product accompanying IIIa semicarbazone was refluxed for 30 minutes in 400 ml. of methanol and 100 ml. of water containing 50 ml. of 6 *N* hydrochloric acid. After pouring the warm solution into cold water the resinous product was extracted with ether and the extract washed, dried and distilled. The resin remaining after removal of

(11) W. P. Campbell and M. Morgana, *THIS JOURNAL*, **63**, 1838 (1941).

the ether was treated with Girard reagent T and the ketonic material separated. Distillation of the latter afforded 7.0 g. of oil, b.p. 148-155° (0.1 mm.),  $[\alpha]^{23D} +68^\circ$  (c 3.48), together with considerable distillation residue which formed a brittle glass on cooling. Analysis of the distillate gave the values: C, 81.27, 81.14; H, 9.22, 9.06.

Following the separation of VIII semicarbazone the methanolic mother liquor deposited on long standing a second crop of crystalline material containing some resin. This

crystallized from methanol in needles, m.p. 96-96.5°,  $[\alpha]^{20D} +245^\circ$  (c 2.36), after drying at room temperature. The analysis of this material (C, 68.98, 68.77; H, 7.79, 7.93) indicated it to be a bromo hydrocarbon,  $C_{20}H_{27-29}Br$ . Since the material gave no immediate color with tetranitromethane it was assumed to be essentially non-olefinic in character.

SHREWSBURY, MASS.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

## Steroids. XLVII.<sup>1</sup> Synthesis of Steroidal Hormone Analogs Hydroxylated at C-2<sup>2</sup>

BY FRANZ SONDHEIMER, ST. KAUFMANN, J. ROMO, H. MARTINEZ AND G. ROSENKRANZ

RECEIVED APRIL 13, 1953

Testosterone acetate (I) on reaction with lead tetraacetate yields two isomeric substances, shown to be 2 $\beta$ -hydroxytestosterone diacetate (II) and 2 $\alpha$ -hydroxytestosterone diacetate (III). On mild alkaline saponification both of these isomers give 2 $\alpha$ -hydroxytestosterone (IV), a substance which may be reacylated to the diacetate III. Both II and III on reduction with zinc regenerate testosterone acetate, although III does so only very slowly. Two of the substances obtained previously by Ehrhart, Ruschig and Aumüller from progesterone and lead tetra-acetate are shown to be 2 $\alpha$ -hydroxydesoxycorticosterone diacetate (XVI) and 2 $\alpha$ -hydroxyprogesterone (XIIIb). The interesting observation has been made that 6-bromotestosterone acetate (V) on acetolysis yields the above-mentioned 2 $\alpha$ -acetoxy isomer III. Similarly it is shown that the acetolysis product of 6-bromo- and 6-chloro- $\Delta^4$ -cholesten-3-one (VIIIa,b), formulated by Rivett and Wallis as 6 $\alpha$ -acetoxy- $\Delta^4$ -cholesten-3-one (IX), is in fact the 2 $\alpha$ -acetoxy isomer (VII). Taking advantage of this novel rearrangement, progesterone (XI) is converted *via* the 6-bromo compound (XII) to 2 $\alpha$ -acetoxyprogesterone (XIIIa) and thence 2 $\alpha$ -hydroxyprogesterone (XIIIb), and desoxycorticosterone acetate (XIV) *via* the amorphous 6-bromo compound (XV) to 2 $\alpha$ -hydroxydesoxycorticosterone diacetate (XVI).

Steroidal hormones bearing an oxygen substituent at the C-11 position have become of considerable importance within the last few years. It is of interest to prepare hormone analogs oxygenated elsewhere in the molecule in order to investigate their biological activity. In this communication we describe the synthesis of several such analogs with a hydroxyl grouping at the C-2 position.

The only method hitherto described for preparing a  $\Delta^4$ -2-ol-3-one (as the acetate) involves the reaction of a  $\Delta^4$ -3-one with lead tetraacetate.<sup>3</sup> With  $\Delta^4$ -cholesten-3-one it was rigidly established<sup>3a</sup> that reaction had taken place at the C-2 position, to yield  $\Delta^4$ -cholesten-2 $\xi$ -ol-3-one acetate, through conversion of the product by hydrogenation, saponification and oxidation to 2,3-secocholestane-2,3-dioic acid. The configuration of the 2-acetoxy grouping was not established. The reaction of progesterone with lead tetra-acetate was shown to lead to a complex mixture of substances,<sup>3b,c</sup> and will be discussed further below.

We have carried out the lead tetra-acetate reaction with testosterone acetate (I), and have observed that two isomeric products, each containing one more acetoxy grouping than the starting material, could be isolated. The one with m.p. 202-203°,  $[\alpha]^{20D} -68^\circ$ ,<sup>4</sup> was obtained in 25% yield and that with m.p. 212-213°,  $[\alpha]^{20D} +68^\circ$  in 17% yield. When either of these substances was hydro-

lyzed under mild conditions (potassium bicarbonate) the identical saponification product was formed, which on re-acylation yielded the latter (dextrorotatory) of the initial products. These facts indicate that the two substances formed in the lead tetra-acetate reaction bear the extra acetoxy groupings at the same position, but in different configurations.<sup>5</sup> *Ab initio*, attack of the reagent might have occurred at C-2 or C-6, but the isomer pair cannot possess the epimeric 6-acetoxy structures, since 6 $\beta$ -hydroxytestosterone diacetate with completely different properties (m.p. 132-133°,  $[\alpha]^{20D} +26^\circ$ ; free glycol, m.p. 216-218°,  $[\alpha]^{20D} +34^\circ$ ) recently has been prepared in these laboratories.<sup>10b</sup> It follows that the pair must be represented by the epimeric 2-acetoxy formulations II and III, and this is in agreement with the 2-acetoxy structure demonstrated by Seebeck and Reichstein<sup>3a</sup> for the product from  $\Delta^4$ -cholesten-3-one and lead tetraacetate. It can clearly be seen by inspection of Stewart-Hirschfelder models that the 2 $\alpha$ -structure III is the less hindered of these, and since the 2 $\beta$ -acetoxy grouping in II is adjacent to a carbonyl function, it is capable of being inverted under the basic conditions of the saponification step to the more stable 2 $\alpha$ -ol-3-one structure IV. It therefore follows that the "labile" levorotatory tetraacetate product is  $\Delta^4$ -androstene-2 $\beta$ ,17 $\beta$ -diol-3-one (2 $\beta$ -hydroxytestosterone) diacetate (II), the "stable" dextrorotatory product is  $\Delta^4$ -androstene-2 $\alpha$ ,17 $\beta$ -diol-3-one (2 $\alpha$ -hydroxytestosterone) diacetate (III), and that either on saponification yields  $\Delta^4$ -androstene-2 $\alpha$ ,17 $\beta$ -diol-3-one (2 $\alpha$ -hydroxytestosterone) (IV). The correctness of the

(5) The alternative formulation of the two substances as *positional* isomers (at C-2 and C-6) is ruled out, since the shift of a hydroxyl group during the saponification step which would have to be postulated for one of the isomers is not likely to occur under the *alkaline* conditions employed.

(1) Part XLVI, O. Mancera, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.*, 2189 (1953).

(2) Part of the work described in this paper forms the basis of U. S. Patent 2,602,803.

(3) Reaction with  $\Delta^4$ -cholesten-3-one: (a) E. Seebeck and T. Reichstein, *Helv. Chim. Acta*, **27**, 948 (1944). Reaction with progesterone; (b) G. Ehrhart, H. Ruschig, and W. Aumüller, *Angew. Chem.*, **52**, 363 (1939); *Ber.*, **72**, 2035 (1939); (c) T. Reichstein and C. Montigel, *Helv. Chim. Acta*, **22**, 1212 (1939).

(4) All rotations were determined in chloroform solution, unless indicated otherwise.