

**7-Methyl- $\Delta^6$ -dehydrotestosterone (Xa).**—Approximately 1.6 g. of the crude product obtained by the addition of methyl Grignard reagent to IXa was heated for 80 minutes on the steam-bath in 65 ml. of 80% aqueous acetic acid. The solution was then poured into excess water and the resultant crystals (1.05 g., m.p. 188–191°) collected. After two recrystallizations from ether-hexane, pure Xa was obtained, m.p. 196–197°,  $[\alpha]_D^{25} +249^\circ$ ,  $\lambda_{\max}$  296–298 m $\mu$ , log  $\epsilon$  4.43.

*Anal.* Calcd. for C<sub>20</sub>H<sub>28</sub>O<sub>2</sub>: C, 79.95; H, 9.39; O, 10.66. Found: C, 79.64; H, 9.80; O, 10.28.

**7 $\beta$ -Methyltestosterone (XI).**—A suspension of 112 mg. of 5% palladium-carbon catalyst in 50 ml. of methanol containing 78 mg. of potassium hydroxide was prehydrogenated.

To this mixture 1.4 g. of Xa in 200 ml. of methanol was added and the compound hydrogenated at 25° and 570 mm. After 60 minutes, 164 ml. of hydrogen (1.2 moles) had been consumed. The mixture was filtered, acetic acid (0.5 ml.) added and the solution evaporated to dryness and water added. The residual crystalline product, 1.1 g.,  $\lambda_{\max}$  242–244 m $\mu$ , log  $\epsilon$  3.99, was chromatographed on 40 g. of unwashed alumina. Elution with benzene-ether (9:1) provided 500 mg. of crystals which after six recrystallizations from acetone provided the analytical sample, m.p. 183–185°,  $\lambda_{\max}$  244 m $\mu$ , log  $\epsilon$  4.21,  $[\alpha]_D^{25} +112^\circ$  (ethanol).

*Anal.* Calcd. for C<sub>20</sub>H<sub>30</sub>O<sub>2</sub>·C<sub>3</sub>H<sub>6</sub>O: C, 76.62; H, 10.07; O, 13.31. Found: C, 76.92; H, 9.95; O, 13.12. APARTADO POSTAL 2679, MÉXICO, D. F.

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

## Steroids. CVII.<sup>1</sup> $\Delta^{5(6)}$ -19-Nor Steroids, a New Class of Potent Anabolic Agents<sup>2</sup>

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Several  $\Delta^5$ -3 $\beta$ -alcohols and  $\Delta^5$ -3-ketones of the 19-norandrostene series have been synthesized and several of these substances have shown high biological activity.

The synthesis of 19-nortestosterone by Birch<sup>3</sup> opened a new field of biologically interesting compounds and paved the way for the preparation of the 19-nor analogs of most of the common steroid hormones,<sup>4–7</sup> compounds containing the  $\Delta^4$ -3-keto system. Later work in this series led to various 3-keto- $\Delta^{5(10)}$ -derivatives<sup>8,9</sup> and several recent publications have been devoted to ring A saturated 19-nor steroids.<sup>10–12</sup> With the exception of 19-nor- $\Delta^{5(6)}$ -androstene-3 $\beta$ ,17 $\beta$ -diol,<sup>13</sup>  $\Delta^{5(6)}$ -unsaturated analogs are unknown in this group and we should now like to report the synthesis of the 17 $\alpha$ -methyl, ethyl, vinyl and ethynyl 19-nor- $\Delta^{5(6)}$ -androstene-3 $\beta$ ,17 $\beta$ -diols as well as the corresponding 3-ketones.

Since removal of the C-10 angular methyl group in 17 $\alpha$ -methyl- and -ethyltestosterone<sup>8</sup> has led to more favorable anabolic properties,<sup>14</sup> and since 17 $\alpha$ -methyl- $\Delta^5$ -androstene-3 $\beta$ ,17 $\beta$ -diol has enjoyed some use as a relatively non-virilizing anabolic

agent,<sup>15</sup> it was of particular interest to prepare 17 $\alpha$ -methyl- and 17 $\alpha$ -ethyl-19-nor- $\Delta^{5(6)}$ -androstene-3 $\beta$ ,17 $\beta$ -diol.

The starting material for the ethynyl, vinyl and ethyl compounds was 17 $\alpha$ -ethynyl-19-nortestosterone (Ia).<sup>6</sup> Treatment of Ia with acetic anhydride and *p*-toluenesulfonic acid led to the  $\Delta^{3,5}$ -enol acetate 17-acetate IIa, a compound reported so far only in the patent literature<sup>16</sup>; the position of the double bonds was established by the ultraviolet maximum at 235 m $\mu$ . Mild alkaline hydrolysis of IIa led to 17 $\alpha$ -ethynyl-19-nortestosterone 17-acetate (Ib), a potent oral progestational agent.<sup>16</sup> Dauben and Eastham<sup>17</sup> had first shown that treatment of a steroidal  $\Delta^{3,5}$ -enol acetate with lithium aluminum hydride led to the  $\Delta^5$ -3 $\beta$ -alcohol in low yield. Subsequently, however, three groups<sup>18–20</sup> reported that high yields were obtained when lithium aluminum hydride was replaced by sodium borohydride. Application of this reaction to IIa, reduction being carried out in a mixture of methanol-tetrahydrofuran, furnished 17 $\alpha$ -ethynyl-19-nor- $\Delta^{5(6)}$ -androstene-3 $\beta$ ,17 $\beta$ -diol 17-acetate (IIIa). Removal of the 17-acetate was smoothly effected by reduction with lithium aluminum hydride, thus yielding the free diol IIIb. Hydrogenation of IIIb in pyridine solution over a palladium-calcium carbonate catalyst stopped with the uptake of one equivalent of hydrogen and gave the 19-nor-17 $\alpha$ -vinyl 3,17-diol IIIc in good yield. When the reduction was conducted in dioxane solution over a palladium-carbon catalyst and interrupted after the uptake of two equivalents of hydrogen, the 17 $\alpha$ -ethyl-19-nor- $\Delta^{5(6)}$ -diol IIIId could be obtained without difficulty.

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To prepare the 17 $\alpha$ -methyl-19-nor- $\Delta^5(6)$ -diol (IIIe) best results were encountered by stepwise conversion of 17 $\alpha$ -methyl-19-nortestosterone (Ic)<sup>6</sup> into the oily 3-enol acetate 17-acetate IIb via 17 $\alpha$ -methyl-19-nortestosterone 17-acetate (Id) followed by treatment with isopropenyl acetate in the presence of a trace of sulfuric acid. Successive reduction with sodium borohydride and then lithium aluminum hydride (for hydrolysis of the 17-acetate) and chromatography on silica gel gave crystalline 17 $\alpha$ -methyl-19-nor- $\Delta^5(6)$ -androstene-3 $\beta$ ,17 $\beta$ -diol (IIIe).

It was of further interest to convert the  $\Delta^5$ -3-alcohols III into the 19-nor-3-keto- $\Delta^5(6)$ -steroids IV. It previously has been shown<sup>21</sup> that  $\Delta^5$ -3 $\beta$ -alcohols, in acetone solution, may be smoothly oxidized with 8 *N* chromic acid in sulfuric acid<sup>22</sup> to the  $\Delta^5$ -3-ketones and this method was utilized for the synthesis of the  $\Delta^5$ -analog of progesterone, desoxycorticosterone acetate and testosterone benzoate. Application of this oxidation to the diols (IIIb, IIIc, IIIe) described above yielded the  $\Delta^5$ -analogs of 19-nor-ethynyl- (IVa), ethyl- (IVb) and methyl- (IVc) testosterone. Confirmation of the structure was obtained in each case by the absence of an ultraviolet absorption maximum in the 240  $m\mu$  region while addition of a trace of alkali developed the typical  $\Delta^4$ -3-ketone maximum. 17 $\alpha$ -Methyl- $\Delta^5$ -androstene-3 $\beta$ ,17 $\beta$ -diol was also converted by 8 *N* chromic acid oxidation to the hitherto unknown 17 $\alpha$ -methyl- $\Delta^5$ -androstene-17 $\beta$ -ol-3-one (IVd), a double bond isomer of the potent androgen 17 $\alpha$ -methyltestosterone.

The 17 $\alpha$ -ethyl- (IIIId) and 17 $\alpha$ -methyl- (IIIe) 19-nor- $\Delta^5(6)$ -diols exhibited highly favorable anabolic-androgenic ratios in the experimental animal. The levator ani, prostate and seminal vesicle responses<sup>23</sup> of IIIId and IIIe in a seven day assay (oral route)<sup>24</sup> with twenty-one day old castrate male rats, are summarized in Table I.

TABLE I

	Androgenic activity	Anabolic activity
17 $\alpha$ -Methyltestosterone	1	1
17 $\alpha$ -Methyl-19-nor- $\Delta^5(6)$ -androstene-3 $\beta$ ,17 $\beta$ -diol (IIIe)	0.5	7
17 $\alpha$ -Ethyl-19-nor- $\Delta^5(6)$ -androstene-3 $\beta$ ,17 $\beta$ -diol (IIIId)	0.2	4

The anabolic, androgenic and progestational properties of the 19-nor- $\Delta^5$ -3-keto compounds IVa, b and c by the oral route were found to be very similar to those of the  $\Delta^4$ -3-keto compounds. The same held true for the anabolic-androgenic activity of the  $\Delta^5$ -analog XI corresponding to 17 $\alpha$ -methyltestosterone. Thus, it is most likely that the  $\Delta^5$ -3-keto compounds, under the influence of the acid pH of the stomach, are rearranged to the  $\Delta^4$ -3-ketones as already has been observed<sup>25</sup> with the corresponding  $\Delta^5(10)$ -3-ketones.

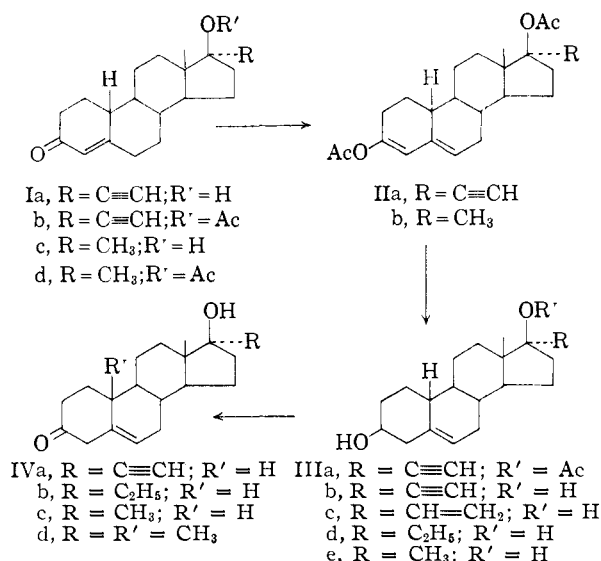
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### Experimental<sup>26</sup>

**17 $\alpha$ -Ethynyl-19-nor- $\Delta^5(6)$ -androstadiene-3,17 $\beta$ -diol Diacetate (IIa).**—A mixture of 17 $\alpha$ -ethynyl-19-nortestosterone (Ia)<sup>6</sup> (5 g.), acetic anhydride (50 ml.) and *p*-toluenesulfonic acid monohydrate (0.5 g.) was heated for one hour at 90°. The cooled solution was poured into water, sodium bicarbonate added to neutrality and the product extracted with ether. Evaporation of the extract and methanol crystallization of the residue gave 2.6 g. of enol acetate 17-acetate (IIa),<sup>16</sup> m.p. 165–167°,  $[\alpha]_D -203^\circ$ ,  $\lambda_{max}$  235  $m\mu$ ,  $\log \epsilon$  4.27. Recrystallization from methanol raised the melting point to 167–169°;  $\nu_{max}^{KBr}$  3320, 1760, 1740, 1670 and 1640  $cm^{-1}$ .

*Anal.* Calcd. for C<sub>24</sub>H<sub>30</sub>O<sub>4</sub>: C, 75.36; H, 7.91; O, 16.73. Found: C, 74.96; H, 7.91; O, 17.31.

**17 $\alpha$ -Ethynyl-19-nor- $\Delta^5(6)$ -androstene-3 $\beta$ ,17 $\beta$ -diol 17-Acetate (IIIa).**—The enol acetate IIa (21 g.), dissolved in a mixture of methanol (125 ml.) and tetrahydrofuran (60 ml.), was treated with a solution of 2.5 g. of sodium borohydride in 5 ml. of water and the solution was allowed to stand for 20 hours at 25°. Water precipitation, filtration and crystallization from ether yielded 0.8 g. of IIIa, m.p. 98–102°. The analytical specimen, from the same solvent, exhibited m.p. 105°, but drying in high vacuum raised the melting point to 145–150°,  $[\alpha]_D -62^\circ$ , no selective absorption in the ultraviolet.

*Anal.* Calcd. for C<sub>22</sub>H<sub>30</sub>O<sub>3</sub>: C, 77.15; H, 8.83. Found: C, 77.59; H, 9.04.

Hydrolysis of the mother liquors with lithium aluminum hydride as described below gave 0.36 g. of the diol IIIb, m.p. 210–217°, thus raising the yield to 64%.

**17 $\alpha$ -Ethynyl-19-nor- $\Delta^5(6)$ -androstene-3 $\beta$ ,17 $\beta$ -diol (IIIb).**—A solution of 0.8 g. of IIIa in 50 ml. of tetrahydrofuran was added to 2 g. of lithium aluminum hydride in 150 ml. of the same solvent. The mixture was boiled for one hour, cooled and treated dropwise with ethyl acetate to decompose the excess hydride. A saturated solution of sodium sulfate and then anhydrous sodium sulfate was added, the mixture was filtered and the inorganic residue was washed thoroughly with ethyl acetate. The combined filtrate and washings were evaporated to dryness yielding 0.62 g. (90%) of free diol IIIb, m.p. 210–217°. Recrystallization from methanol yielded the analytical sample, m.p. 216–217.5°,  $[\alpha]_D -52^\circ$ .

*Anal.* Calcd. for C<sub>20</sub>H<sub>28</sub>O<sub>2</sub>: C, 79.95; H, 9.39, O, 10.66. Found: C, 79.44; H, 9.41; O, 11.29.

**17 $\alpha$ -Vinyl-19-nor- $\Delta^5(6)$ -androstene-3 $\beta$ ,17 $\beta$ -diol (IIIc).**—The ethynyl diol IIIb (0.5 g.) in 40 ml. of pyridine was hydrogenated at 25° and 570 mm. in the presence of 100 mg. of pre-hydrogenated 2% palladium–calcium carbonate catalyst.

(26) Melting points were determined in capillary tubes in sulfuric acid and are uncorrected. Rotations were measured in chloroform and ultraviolet absorption spectra in 95% ethanol. We are grateful to Dr. L. Throop and his staff for these determinations as well as for the infrared and ultraviolet spectra. The elemental analyses were carried out by Dr. A. Bernhardt, Mülheim, Ruhr, Germany.

Hydrogen uptake ceased with the absorption of one equivalent (53 ml.), the catalyst was filtered, washed with ethyl acetate and the combined solutions evaporated to dryness *in vacuo* yielding 0.5 g. of the vinyl diol IIIc, m.p. 158–163°. Recrystallization from acetone gave 0.3 g. of the analytical specimen, m.p. 167–168.5°,  $[\alpha]_D -11^\circ$  (dioxane).

*Anal.* Calcd. for  $C_{20}H_{30}O_2$ : C, 79.42; H, 10.00. Found: C, 79.34, H, 10.26.

**17 $\alpha$ -Ethyl-19-nor- $\Delta^{5(6)}$ -androstene-3 $\beta$ ,17 $\beta$ -diol (IIIId).**—The ethynyl-diol IIIb (1.0 g.) in 125 ml. of dioxane was hydrogenated at 25° and 570 mm. using 200 mg. of pre-hydrogenated 10% palladium-charcoal catalyst. Hydrogenation was discontinued after the absorption of two equivalents (200 ml.), the solution was filtered and evaporated to dryness *in vacuo*. The residue was recrystallized from acetone to yield 0.95 g. of the 19-nor-ethyl diol IIIId, m.p. 183–185°. Further crystallization from acetone gave material of m.p. 188–189°,  $[\alpha]_D +3^\circ$  (dioxane).

*Anal.* Calcd. for  $C_{20}H_{32}O_2$ : C, 78.89, H, 10.60, O, 10.51. Found: C, 79.19, H, 10.59; O, 10.38.

**17 $\alpha$ -Methyl-19-nor- $\Delta^{5(6)}$ -androstene-3 $\beta$ ,17 $\beta$ -diol (IIIe).**—17 $\alpha$ -Methyl-19-nortestosterone (Ic)<sup>6</sup> (10 g.) was heated for 16 hours in 200 ml. of boiling acetic anhydride. The cooled solution was poured into ice-water and after the mixture was stirred for two hours at 0°, to decompose excess anhydride, the product was extracted with ether. The ether extract, after washing with water, sodium bicarbonate, water and drying over sodium sulfate, was evaporated to dryness leaving a mixture of 17-acetate Id and enol acetate 17-acetate IIb. The crude product was taken up in 30 ml. of isopropenyl acetate, sulfuric acid (0.2 ml.) was added, and the solution was distilled slowly for 2 hours to approximately 25% of the original volume. An additional 110 ml. of isopropenyl acetate and 0.2 ml. of sulfuric acid were added and distillation continued again for 2 hours. The cooled solution was then poured into water and the crude enol acetate 17-acetate IIb extracted with ether and the extract evaporated to dryness. The residue, dissolved in 300 ml. of 96% ethanol, was added dropwise, with stirring, over a 30 min. period, to an ice-cold solution of sodium borohydride (15 g.) in water (25 ml.) and ethanol (250 ml.). The solution after storage for 24 hours at 0° was evaporated to 75 ml., acidified with 2 N hydrochloric acid, diluted with 300 ml. of water and the product isolated by extraction with ether. An ether solution of it was added dropwise to a stirred suspension of lithium aluminum hydride (5 g.) in ether (200 ml.), the mixture was allowed to stand overnight and the excess hydride was decomposed by cautious addition of ethyl acetate. A saturated solution of sodium sulfate was added until the precipitate began to adhere to the sides of the flask. Solid sodium sulfate was then added, the inorganic precipitate filtered, washed well with ether and the solvent evaporated to give crude IIIe which was purified by chromatography on 200 g. of neutral alumina. The benzene-ether extracts (9:1, 2:1) afforded 17 $\alpha$ -methyl-19-nor- $\Delta^{5(6)}$ -androstene-3 $\beta$ ,17 $\beta$ -diol (IIIe) (1.82 g.), m.p. 183–185°, raised by several crystallizations from acetone-hexane to 188–190°,  $[\alpha]_D -18^\circ$ , no selective absorption in the ultraviolet.

*Anal.* Calcd. for  $C_{19}H_{30}O_2 \cdot \frac{1}{2}C_3H_6O$ : C, 77.05; H, 10.40. Found: C, 76.97; H, 10.12.

**17 $\alpha$ -Ethynyl-19-nortestosterone 17-Acetate (Ib).**—To a cold solution of 3.4 g. of the enol acetate 17-acetate (IIa) in methanol (600 ml.) and tetrahydrofuran (100 ml.) was added 200 ml. of cold 2% methanolic potassium hydroxide. The

solution was kept at 0–5° for one hour and then poured into water and neutralized with dilute hydrochloric acid. Ether extraction furnished an amorphous product which was chromatographed on 600 g. of ethyl acetate-washed alumina. The hexane-benzene (1:3) and benzene eluates gave, after crystallization from acetone-hexane, 2.8 g. (90%) of the desired acetate Ib,<sup>16</sup> m.p. 161–162°,  $[\alpha]_D -33^\circ$ ,  $\lambda_{max}$  240  $\mu$ ,  $\log \epsilon$  4.20.

*Anal.* Calcd. for  $C_{29}H_{38}O_3$ : C, 77.61; H, 8.29. Found: C, 77.32; H, 8.22.

**17 $\alpha$ -Methyl-19-nor- $\Delta^{5(6)}$ -androstene-17 $\beta$ -ol-3-one (IVc).**—A solution of 600 mg. of 17 $\alpha$ -methyl-19-nor- $\Delta^{5(6)}$ -androstene-3 $\beta$ ,17 $\beta$ -diol (IIIe) in 200 ml. of acetone (distilled from potassium permanganate) was cooled to 5°, and, while nitrogen was bubbled through the solution, an 8 N solution of chromic acid in sulfuric acid<sup>22</sup> was added dropwise over a 5-min. period. When a yellow color persisted in the acetone solution the mixture was poured into water and the product extracted with ether. Evaporation of the extract gave 0.485 g. of IVc, m.p. 138–139°. The analytical specimen (from ether) exhibited m.p. 139–140°,  $[\alpha]_D \pm 0^\circ$ , no ultraviolet maximum (ethanol solution) at 240  $\mu$ ,  $\lambda_{max}^{KOH}$  241  $\mu$ ,  $\log \epsilon$  4.19;  $\nu_{max}^{KBr}$  3470, 1710  $cm^{-1}$ .

*Anal.* Calcd. for  $C_{19}H_{28}O_2$ : C, 79.12; H, 9.78. Found: C, 78.70; H, 9.73.

**17 $\alpha$ -Ethynyl-19-nor- $\Delta^{5(6)}$ -androstene-17 $\beta$ -ol-3-one (IVa).**—17 $\alpha$ -Ethynyl-19-nor- $\Delta^{5(6)}$ -androstene-3 $\beta$ ,17 $\beta$ -diol (IIIb) (1 g.) in 250 ml. of acetone was oxidized as described above. Evaporation of the ether extract gave a residue ( $\lambda_{max}^{EtOH}$  240  $\mu$ ,  $\log \epsilon$  3.10;  $\lambda_{max}^{KOH-EtOH}$  240  $\mu$ ,  $\log \epsilon$  3.86) which was a mixture of starting material IIIb,  $\Delta^4$ -3-ketone Ia and  $\Delta^5$ -3-ketone IVa. Separation was effected by chromatography on silica gel, the benzene-ether (9:1 and 4:1) extracts yielding 0.24 g. of IVa, m.p. 145–153°. Crystallization from ether raised the melting point to 151–154°,  $[\alpha]_D -21^\circ$ , no ultraviolet maximum at 240  $\mu$ ,  $\lambda_{max}^{KOH-EtOH}$  240  $\mu$ ,  $\log \epsilon$  4.19,  $\nu_{max}^{KBr}$  1710  $cm^{-1}$ , hydroxyl and ethynyl bands.

*Anal.* Calcd. for  $C_{20}H_{26}O_2$ : C, 80.49; H, 8.78; O, 10.73. Found: C, 80.11; H, 8.70; O, 11.18.

Elution of the column with benzene-ether (3:1 and 3:2) gave 420 mg. of recovered diol IIIb.

**17 $\alpha$ -Ethyl-19-nor- $\Delta^{5(6)}$ -androstene-17 $\beta$ -ol-3-one (IVb).**—The oxidation of 0.6 g. of IIIId in 150 cc. of acetone was carried out as described above. Ether extraction gave 0.45 g. of crude IVb, m.p. 144–146°,  $\lambda_{max}^{EtOH}$  240  $\mu$ ,  $\log \epsilon$  3.17,  $\lambda_{max}^{KOH-EtOH}$  241  $\mu$ ,  $\log \epsilon$  4.12. Three recrystallizations from ether furnished 160 mg. of the analytical specimen of IVb with m.p. 154–157°,  $[\alpha]_D +9^\circ$ , no ultraviolet maximum at 240  $\mu$ ,  $\lambda_{max}^{KOH-EtOH}$  241  $\mu$ ,  $\log \epsilon$  4.14;  $\nu_{max}^{KBr}$  3460, 1713  $cm^{-1}$ .

*Anal.* Calcd. for  $C_{20}H_{32}O_2$ : C, 78.89; H, 10.60; O, 10.51. Found: C, 79.19; H, 10.59; O, 10.38.

**17 $\alpha$ -Methyl- $\Delta^5$ -androstene-17 $\beta$ -ol-3-one (IVd).**—17 $\alpha$ -Methyl- $\Delta^5$ -androstene-3 $\beta$ ,17 $\beta$ -diol (1 g.) in 400 ml. of acetone was oxidized with 8 N chromic acid in the usual manner. The residue, after ether extraction, was chromatographed on silica gel. The benzene-ether (4:1) eluted material was crystallized from acetone-ether to yield 300 mg. of  $\Delta^5$ -3-ketone IVd, m.p. 156–157°,  $[\alpha]_D -43^\circ$ , no ultraviolet maximum at 240  $\mu$ ,  $\lambda_{max}^{KOH-EtOH}$  242  $\mu$ ,  $\log \epsilon$  4.18,  $\nu_{max}^{KBr}$  1715  $cm^{-1}$  and hydroxyl band.

*Anal.* Calcd. for  $C_{20}H_{30}O_2$ : C, 79.42; H, 10.00; O, 10.58. Found: C, 79.13; H, 9.99; O, 10.93.

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