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Studies in Steroid Total Synthesis. II. Correlation of Optically Active Bicyclic Intermediates with Natural Steroids[1]

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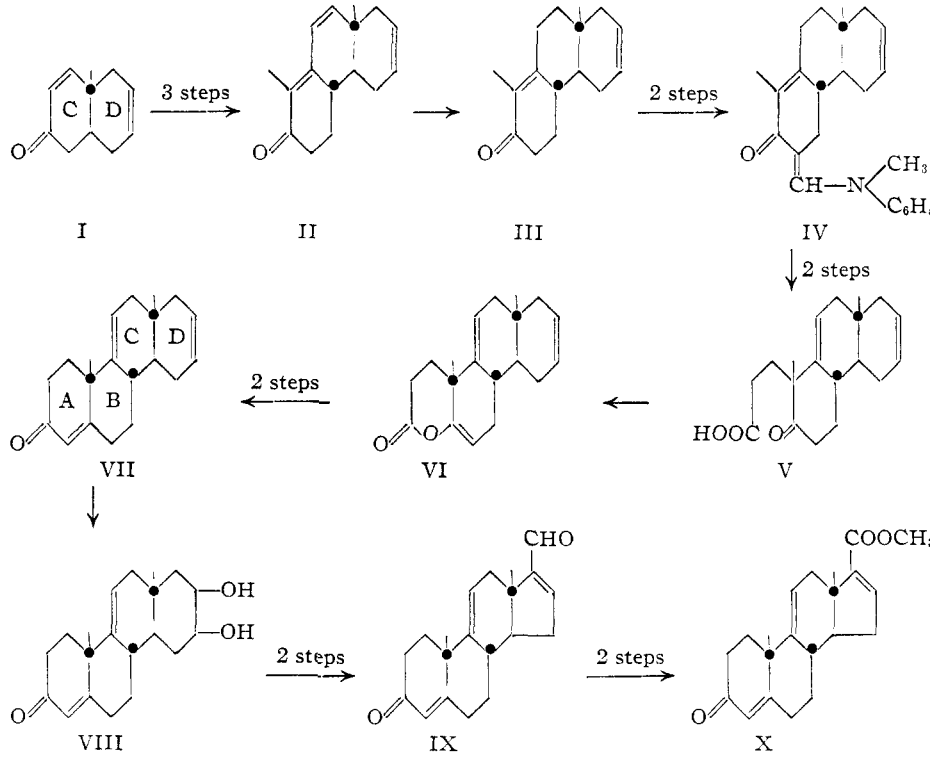
We have converted the Woodward bicyclic ketone (I) and its levorotatory enantiomorph to $\Delta^{9(11),16}$-bisdehydro-21-norprogesterone (IX) by a modified route. Conversion of optically active IX to methyl 3-keto-$\Delta^{4,9(11),16}$-etiocholatrienate (X) established the fact that (−)I has the same configuration as rings C and D of the natural steroids.

A previous paper from this Laboratory[2] described the synthesis of the Woodward bicyclic ketone (I)[3] and both of its optically active forms by an alternate route involving a resolution. We have now converted racemic I and its levorotatory enantiomorph to $\Delta^{9(11),16}$-bisdehydro-21-norprogesterone (IX), using a modification of the Woodward route. Conversion of the active norprogesterone to methyl 3-keto-$\Delta^{4,9(11),16}$-etiocholatrienate (X) established the fact that levorotatory bicyclic ketone (I), $[\alpha]^{25}D$ −239°, has the same absolute configuration as rings C and D of the natural steroids.[2,4]

The preparation of the tricyclic ketone II from levorotatory I paralleled Woodward's procedures.[3] At this point our synthesis was continued both in the active and the *dl* series *via* different intermediates. Selective hydrogenation of II with a palladium-on-strontium carbonate catalyst in the presence of alkali gave the dihydro derivative in quantitative yields. This technique enabled us to avoid the use of the acid sensitive acetonide group during the ring A synthesis. Compound III was blocked in the 3-position with the methylanilinomethylene group and using either acrylonitrile[3,5] or β-propiolactone,[6] a 20% yield of the desired keto acid V was obtained. When working in the *dl* series this acid crystallized from the epimeric mixture. In the optically active series the mixture remained an oil and as a convenient expedient the acids were separated as their crystalline quinine salts.

Treatment of V with acetic anhydride and sodium acetate formed the enol lactone VI which was stirred with excess methylmagnesium bromide at −50°.[3,7] Under these conditions the natural isomer will not over-react appreciably, whereas the isomeric enol lactone will give entirely hydroxylated compounds. Thus impure VI can be used and the hydroxylic impurities readily separated at the tetracyclic stage by means of activated alumina. The crude Grignard reaction product was cyclized with base to the crystalline tetracyclic ketone VII.

The structure of VII was proved by first oxidizing to the 16β,17β-*cis*-glycol (VIII) with iodine and silver acetate in wet acetic acid.[8] The crude



(1) A portion of this subject matter has been reported in a preliminary communication [L. B. Barkley, M. W. Farrar, W. S. Knowles and H. Raffelson, THIS JOURNAL, **75**, 4110 (1953)].

(2) A. J. Speziale, J. A. Stephens and Q. E. Thompson, *ibid.*, **76**, 5011 (1954).

(3) *Cf.* R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, *ibid.*, **74**, 4223 (1952).

(4) The results of our work have been mentioned in a preliminary communication [B. Riniker, J. Kalvoda, D. Arigoni, A. Fürst, O. Jeger, A. M. Gold and R. B. Woodward, *ibid.*, **76**, 313 (1954)].

(5) *Cf.* P. Wieland, H. Ueberwasser, G. Anner and K. Miescher, *Helv. Chim. Acta*, **36**, 1231 (1953).

(6) *Cf.* T. L. Gresham, J. E. Jansen, F. W. Shaver, M. R. Frederick and W. L. Beears, THIS JOURNAL, **73**, 2345 (1951), and earlier papers.

(7) The use of low temperatures was described in a private communication from R. B. Woodward and Emil White.

(8) This reagent which gives a *cis*-glycol directly without isolating any intermediates was described in a private communication from R. B. Woodward and F. V. Brutcher, Jr., *cf.* S. Winstein and R. E. Buckles, THIS JOURNAL, **64**, 2787 (1942); C. Prévost, *Compt. rend.*, **196**, 1129 (1933); **197**, 1661 (1933).

glycol VIII, characterized as the acetonide XI,[9] was converted to $\Delta^{9(11),16}$-bisdehydro-21-norprogesterone (IX) by means of periodic acid followed by cyclization with piperidine acetate.[3]

It still remained to be proved that optically active IX had the same absolute configuration as the natural steroids. This correlation was accomplished by converting IX to methyl 3-keto-$\Delta^{4,9(11),16}$-etiocholatrienate (X)[3] identical in all respects to material obtained by Woodward from natural sources. Thus the arbitrary choice of the levorotatory bicyclic ketone I proved to be fortunate.

Experimental

All rotations were measured in chloroform at 2% concentration unless otherwise stated. Analyses were done by Mr. A. Bybell of this Laboratory.

The (−)1,14-Dimethyl-2-keto-$\Delta^{1(11),6,9}$-octahydrophenanthrene (II).—The method for converting I to II was the same as in the *dl* series.[3] The physical properties of the various intermediates were not sufficiently different to require an appreciable change in procedure. They are recorded as follows: (−)*trans*-2-keto-10-methyl-$\Delta^{3,6}$-hexahydronaphthalene (I),[2] m.p. −4 to −2°, $n^{25}D$ 1.5197, $[\alpha]^{25}D$ −239°. *Anal.* Calcd. for $C_{11}H_{14}O$: C, 81.4; H, 8.7. Found: C, 81.4; H, 9.0. (−)*trans*-1-Hydroxymethylene-2-keto-10-methyl-$\Delta^{3,6}$-hexahydronaphthalene, b.p. 88–90° (1.0 mm.), $n^{25}D$ 1.5581, $[\alpha]^{25}D$ −154°. *Anal.* Calcd. for $C_{12}H_{14}O_2$: C, 75.8; H, 7.4. Found: C, 75.9; H, 7.6. (−)*trans*-1-Formyl-1-γ-ketopentyl-2-keto-10-methyl-$\Delta^{3,6}$-hexahydronaphthalene, m.p. 97–97.5°, $[\alpha]^{25}D$ −258°. *Anal.* Calcd. for $C_{17}H_{22}O_3$: C, 74.4; H, 8.1. Found: C, 74.2; H, 8.2. (−)1,14-Dimethyl-2-keto-$\Delta^{1(11),6,9}$-octahydrophenanthrene (II), m.p. 38–40°, $[\alpha]^{25}D$ −492°. *Anal.* Calcd. for $C_{16}H_{20}O$: C, 84.2; H, 8.8. Found: C, 83.9; H, 8.9.

***dl*-1,14-Dimethyl-2-keto-$\Delta^{1(11),6}$-decahydrophenanthrene (III).**—To two liters of isopropyl alcohol in a five-liter round-bottom flask was added 45.6 g. of palladium-on-strontium carbonate containing 2% palladium.[3] The flask was evacuated and flushed with hydrogen several times and the slurry agitated for one hour at 25° under a hydrogen atmosphere to reduce the catalyst. A 10% sodium hydroxide solution (45.6 ml.) was then added and the mixture was agitated for 15 minutes. At the end of this period, the stirrer was stopped and 456.4 g. (2 moles) of 1,14-dimethyl-$\Delta^{1(11),6,9}$-octahydrophenanthrene (II) was added and washed in with 280 ml. of isopropyl alcohol. The slurry was vigorously agitated and exactly two moles of hydrogen was carefully metered into the flask through a Precision Wet Test Meter over a period of 38 minutes, keeping the reaction temperature at 25°. The mixture was filtered, neutralized with dilute hydrochloric acid, and isopropyl alcohol was removed under reduced pressure. The residual oil was dissolved in ether, washed with water, dried, filtered, and the solvent was removed. The residue remained a liquid, $n^{25}D$ 1.5515, λ_{max}^{alc} 250 mμ, ε 15,300.

Anal. Calcd. for $C_{16}H_{22}O$: C, 83.4; H, 9.6. Found: C, 83.5; H, 9.5.

The fact that a high ε value at 250 mμ was obtained coupled with an extremely low value of ε 131 at 288 mμ and the use of exactly one equivalent of hydrogen showed that the double bond at position 6 had not been reduced appreciably and that the starting material was entirely consumed.

(−)1,14-Dimethyl-2-keto-$\Delta^{1(11),6}$-decahydrophenanthrene (III).—Reduction of (−)II by an identical procedure gave the optically active dihydro derivative, m.p. 29–33°, $n^{25}D$ 1.5519, λ_{max}^{alc} 250 mμ, ε 15,300, $[\alpha]^{25}D$ −152°.

Anal. Calcd. for $C_{16}H_{22}O$: C, 83.4; H, 9.6. Found: C, 83.5; H, 9.5.

***dl*-1,14-Dimethyl-2-keto-3-hydroxymethylene-$\Delta^{1(11),6}$-decahydrophenanthrene.**[3]—To a stirred solution of 828 ml. of dry ethyl formate in 3450 ml. of benzene was added 324 g. of commercial sodium methoxide. After agitation for one hour at 25° 460 g. of *dl*-III was added and the mixture, which soon became very thick, was stirred for 16 hours. The slurry was then cooled to 5° and acidified with 10% sulfuric acid. The benzene solution was washed with water, dried and evaporated to leave a brown crystalline residue. Recrystallization from 1000 ml. of Skellysolve B gave 405 g. of hydroxymethylene compound, m.p. 83–84°. A second crop of nearly equal quality made the total yield 86%. Without further treatment both crops were combined and converted to the methylanilinomethylene compound.

(+)1,14-Dimethyl-2-keto-3-hydroxymethylene-$\Delta^{1(11),6}$-decahydrophenanthrene.—Using (−)III the optically active hydroxymethylene compound was made by the same procedure, m.p. 97–98°, $[\alpha]^{25}D$ +58°.

Anal. Calcd. for $C_{17}H_{22}O_2$: C, 79.0; H, 8.6. Found: C, 78.9; H, 8.9.

***dl*-1,14-Dimethyl-2-keto-3-methylanilinomethylene-$\Delta^{1(11),6}$-decahydrophenanthrene (IV).**—A solution of 388.7 g. of *dl*-1,14-dimethyl-2-keto-3-hydroxymethylene-$\Delta^{1(11),6}$-decahydrophenanthrene in 2220 ml. of methanol was prepared by warming to 50°. To this was added 409 ml. of methylaniline and the mixture was stirred for 16 hours. After cooling to 3° the crystals were filtered and washed with methanol. The first crop weighed 448 g. (85.9%), m.p. 124.5–126°. Combined with the second crop the yield was 96% or about 83% over-all from II. The analytical sample was crystallized from methanol, m.p. 124.5–126°.

Anal. Calcd. for $C_{24}H_{29}ON$: C, 83.0; H, 8.4. Found: C, 82.8; H, 8.3.

(+)1,14-Dimethyl-2-keto-3-methylanilinomethylene-$\Delta^{1(11),6}$-decahydrophenanthrene (IV).—Using optically active (+)1,14-dimethyl-2-keto-3-hydroxymethylene-$\Delta^{1(11),6}$-decahydrophenanthrene by the above procedure an oily methylanilinomethylene compound (IV) was obtained after evaporation of the methanol and removal of the unreacted methylaniline at 100° and 2 mm. This crude product ($[\alpha]^{25}D$ + 234°) was used as such for the preparation of V.

***dl*-1-(β-Carboxyethyl)-1,14-dimethyl-2-keto-$\Delta^{6,10}$ decahydrophenanthrene (V). Method A.**[3]—One hundred grams of *dl*-IV was dissolved in 1750 ml. of *t*-butyl alcohol at 50°. To the yellow solution was added 60 g. of freshly distilled acrylonitrile and a solution of 18 g. of 40% aqueous Triton B in 39 g. of *t*-butyl alcohol and 5 g. of water. The red mixture was stirred under nitrogen at 50–55° for 44 hours. At the end of this period the catalyst was neutralized with 2.5 ml. of acetic acid and the solvent stripped off under vacuum up to a maximum temperature of 50°. The oily residue was treated with 325 ml. of water and 450 ml. of ether. The ether layer was separated and the aqueous phase was given several more ether extractions. The combined extracts were washed twice with 10% hydrochloric acid and twice with water to remove methylaniline. The residue from the evaporation of the ether was dissolved in a solution of 120 g. of potassium hydroxide in one liter of water. The cold solution was extracted with ether to remove alkali insolubles and then heated at reflux (100–102°) for ten hours under nitrogen.

The resulting alkali solution of keto acids was cooled and extracted with ether. The aqueous phase was acidified with concentrated hydrochloric acid and the keto acid mixture extracted with ether. Evaporation of the dried extract gave 74.3 g. of crude keto acids which on trituration with ether yielded 16.8 g. (22.2%) of keto acid V melting at 170–172°. The analytical sample on crystallization from benzene melted at 171–173°.

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.5; H, 8.7. Found: C, 75.2; H, 8.7.

Since the crystals turned out to be the desired isomer, little work was done on the oil which undoubtedly contained mostly epimeric material.

Method B.—A mixture of 0.5 g. of potassium and 0.025 g. of ferric oxide in 80 ml. of liquid ammonia was stirred for 30 minutes after the blue color had disappeared. The ammonia was boiled off and replaced with 150 ml. of ether.

(9) The acetonide XI differs from Woodward's[3] in that it was derived from a β-*cis*-glycol whereas his was from an α-*cis*-glycol, where α and β designate configuration corresponding to standard steroid convention. The configuration of the Woodward acetonide, m.p. 200–202°, was assigned on the basis of the assumption that major attack of osmium tetroxide occurred on the less hindered backside of his tricyclic ketone (II) to give an α-*cis*-glycol. Since our acetonide, m.p. 172–175°, has been correlated with the minor osmium reaction product it is presumed to be derived from a β-*cis*-glycol, *cf.* Woodward's[3] footnote (28).

After adding 3.47 g. of *dl*-IV at 25°, the rust colored mixture was stirred for one hour. At the end of this period the mass was cooled to 0° and 4.0 g. of β-propiolactone[6] in 50 ml. of ether was introduced over one hour. After stirring another hour, 5 ml. of methanol was added followed by 75 ml. of 15% potassium hydroxide. The aqueous layer was separated, refluxed for 5 hr., cooled and extracted with ether. The alkaline solution was acidified and the oil which separated was taken up in several portions of ether. These extracts were combined, washed, dried, and stripped leaving 1.57 g. of oily residue. Trituration with ether yielded 0.455 g. (17%) of crystalline keto acid V, m.p. 169–171°. Mixed melting point showed no depression with material made by method A.

(−)1-(β-Carboxyethyl)-1,14-dimethyl-2-keto-$\Delta^{6,10}$-decahydrophenanthrene (V).—In the optically active series method A, starting with oily methylanilinomethylene compound IV, gave a keto acid mixture which remained as an oil. In order to separate the epimers 100 g. of this mixture was dissolved in 900 ml. of methanol and a solution of 14.2 g. of sodium hydroxide in 100 ml. of water was added. Quinine hydrochloride (119.0 g.) was introduced and the mass was refluxed at 68–70° for three hours. Subsequently the solution was cooled and the resulting crystals were collected and washed twice with 100-ml. portions of cold methanol. The quinine salt (m.p. 115–116°) was then decomposed by slurrying in 420 ml. of water, 90 ml. of methanol and 20 g. of sodium hydroxide at 70–75° for 30 minutes. After cooling, the free base was filtered and washed with 125 ml. of water. Acidification of the filtrate followed by extraction with ether and removal of the solvent gave 23.1 g. of keto acid V, m.p. 125–127°. Crystallization from benzene and Skellysolve C gave a product melting at 131.5°, $[\alpha]^{25}D$ −58.8°.

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.5; H, 8.7. Found: C, 75.4; H, 8.7.

***dl*-3-Keto-$\Delta^{5,9(11),16}$-4-oxa-D-homoandrostatriene (VI).**—A solution of 30.8 g. of *dl*-V in 230 ml. of acetic anhydride containing 0.15 g. of anhydrous sodium acetate was refluxed at 135–140° for four hours under nitrogen. The acetic anhydride was removed under vacuum at 100° and the cooled residue taken up in ether, washed with dilute sodium carbonate then with water and dried over magnesium sulfate. Evaporation yielded 26.6 g. (91.5%) of enol lactone melting at 100–101°. This material was used in subsequent steps without further treatment.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.2; H, 8.5. Found: C, 80.0; H, 8.4.

(−)3-Keto-$\Delta^{5,9(11),16}$-4-oxa-D-homoandrostatriene (VI).—The procedure described above starting with (−)V gave optically active enol lactone VI, m.p. 124–126°, $[\alpha]^{25}D$ −219°.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.2; H, 8.5. Found: C, 79.9; H, 8.4.

***dl*-3-Keto-$\Delta^{4,9(11),16}$-D-homoandrostatriene (VII).**[7]—To a solution of 21.5 g. of *dl*-enol lactone VI in 200 ml. of benzene and one liter of ether at −50 to −55° was added over a period of ten minutes a solution of 13.7 g. (1.5 equiv.) of methylmagnesium bromide in 350 ml. of ether. The mixture was stirred at −50° for one hour and then acetone was added to consume the excess Grignard reagent. The complex was decomposed with dilute hydrochloric acid and the product was extracted with ether. After evaporation of the solvent, the solid residue was taken up in 1500 ml. of methanol and a solution of 18 g. of sodium hydroxide in 180 ml. of water was added. The mass was refluxed for 2 hours under nitrogen and then most of the methanol was removed under vacuum. Water was added and the organic material was extracted with ether. After drying and evaporation there was obtained 19.3 g. (90%) of tetracyclic ketone VII, m.p. 144–146°. Recrystallization from methanol gave a pure product, m.p. 147–148°.

Anal. Calcd. for $C_{20}H_{26}O$: C, 85.0; H, 9.3. Found: C, 84.9; H, 9.2.

(−)3-Keto-$\Delta^{4,9(11),16}$-D-homoandrostatriene (VII).—In the optically active series starting with (−)VI identical procedures were used to give the active tetracyclic ketone VII, m.p. 174–175°, $[\alpha]^{25}D$ −22.9°.

Anal. Calcd. for $C_{20}H_{26}O$: C, 85.0; H, 9.3. Found: C, 85.1; H, 9.2.

***dl*-3-Keto-16β,17β-dihydroxy-$\Delta^{4,9(11)}$-D-homoandrostadiene (VIII).**—To a solution of 28 g. of *dl*-3-keto-$\Delta^{4,9(11),16}$-D-homoandrostatriene (VII) in 760 ml. of glacial acetic acid and 1.8 ml. of water was added 38.2 g. of silver acetate and, over a period of 30 minutes, 25.3 g. of iodine.[8] The mixture was stirred for one hour at 20–25° to consume all the iodine and then was heated at 90–95° for three hours. After cooling and filtering, the bulk of the acetic acid was stripped under vacuum. The residue was taken up in 600 ml. of methanol, filtered again, and neutralized to *p*H 10. An additional 8.2 g. of potassium hydroxide in 100 ml. of methanol was added and the mixture allowed to stand at 20–25° for 16 hours under nitrogen. After neutralizing with acetic acid, the solvent was stripped and the *cis*-glycol was extracted with chloroform. Evaporation of the dried solvent gave a crude crystalline mass which on trituration with ethyl acetate gave 21.3 g. (67%) of *dl*-glycol VIII, m.p. 215–218°, which was used without purification.

***dl*-3-Keto-16β,17β-dihydroxy-$\Delta^{4,9(11)}$-D-homoandrostadiene Acetonide (XI).**—The acetonide of the *dl*-glycol VIII was made by means of acetone and anhydrous copper sulfate.[3,9] It was crystallized from methanol and melted at 173–175°.

Anal. Calcd. for $C_{23}H_{32}O_3$: C, 77.5; H, 9.1. Found: C, 77.3; H, 9.1.

***dl*-$\Delta^{9(11),16}$-Bisdehydro-21-norprogesterone (IX).**[3]—The acetonide XI was converted to IX by the use of periodic acid followed by treatment with piperidine acetate using the procedure worked out by Woodward for his analogous acetonide[3,9]; IX, m.p. 178–178.5°, showed no melting point depression with Woodward's material and had identical infrared spectrum.

(+)$\Delta^{9(11),16}$-Bisdehydro-21-norprogesterone (IX).—Starting with (−)VII and using an identical series of procedures, optically active (+)IX was prepared by way of the crude *cis*-glycol VIII, m.p. 185–187°, without preparing the acetonide. The product was crystallized from isopropyl alcohol, m.p. 160.5–161.5°, $[\alpha]^{25}D$ + 290°.

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.0; H, 8.2. Found: C, 80.8; H, 8.2.

(+)Methyl 3-Keto-$\Delta^{4,9(11),16}$-etiocholatrienate (X).[3]—Following exactly the procedures of Woodward[3] (+)IX was oxidized to the acid with sodium dichromate and esterified with diazomethane to give (+)X. Crystallization from methanol gave a pure product, m.p. 188–189°, $[\alpha]^{25}D$ +182°. The infrared spectrum as well as the melting point and rotation agreed with material made from natural sources.

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