Tetrahedron, 1958, Vol. 3, pp. 37–42. Pergamon Press Ltd., London

THE ADDITION OF HYDROCYANIC ACID TO Δ^{16}-PREGNEN-20-ONES

J. Romo
Instituto de Química de la Universidad Nacional Autónoma de México, México 20, D.F.

(*Received* 21 *January* 1958)

Abstract—Hydrocyanic acid adds to the 16-double bond of $\Delta^{5,16}$-pregnadien-3β-ol-20-one acetate to produce 16α-cyano-Δ^{5}-pregnen-3β-ol-20-one. Similar additions of hydrocyanic acid to Δ^{16}-20-oxo pregnenes are described. By alkaline hydrolysis of the 16α-nitrile group the corresponding acid was obtained, of which several derivatives are described.

The addition of alcohols,[1,2,3] mercaptans[4] and amines[5] to the 16-double bond of $\Delta^{5,16}$-3β-hydroxypregnadien-20-one (I) has been reported recently. The purpose of this paper is to report the addition of hydrocyanic acid to Δ^{16}-pregnen-20-ones, when a 16-nitrile group is formed. It was found that, by heating a methanolic solution of the ketone (Ia) under reflux with sodium cyanide, there was a smooth addition of hydrocyanic acid. The strongly alkaline medium catalyzes the reaction, simultaneously producing hydrolysis of the 3-acetyl group, to give a good yield of the cyano derivative (IIa). It was proved that the hydrocyanic acid did not react with the 20-oxo group to form a cyanohydrin, because the cyano derivative shows, in the infrared region, bands at 4·5 μ, corresponding to a nitrile, and at 5·9 μ, due to the 20-oxo group. An oxime can also be obtained. The more stable equatorial α-configuration was assigned to the 16-nitrile group by similarity with other additions to this double bond.[2,3]

The Oppenauer oxidation of Δ^{5}-3β-hydroxypregnen-20-one (IIa) yielded 16α-cyanoprogesterone (III).

The addition of hydrocyanic acid to $\Delta^{1,3,5(10),16}$-3-acetoxy-17β-acetylestratetraene (IV)[6] furnished the cyano derivative (Va), while the $\Delta^{5,16}$-3β,21-diacetoxypregnadien-20-one (Ib)[7] yielded the corresponding nitrile, isolated as the 3,21-diacetate (IIc).

The alkaline hydrolysis of the cyano derivative (IIa) produced the Δ^{5}-3β-hydroxy-16α-carboxypregnen-20-one (VIa). The Oppenauer oxidation of its methyl ester (VIb) gave 16α-carbomethoxyprogesterone (VIIb), which by alkaline hydrolysis furnished 16α-carboxyprogesterone (VIIa). This product is produced also by alkaline hydrolysis of 16α-cyanoprogesterone (III).

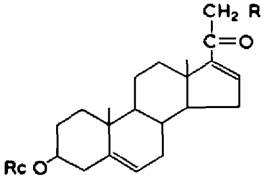
Hydroxymethylprogesterone (IXa) was prepared for biological tests. This was accomplished by blocking the two keto groups of (VIIb) to form the bisethylenedioxyderivative (VIII), followed by reduction with lithium aluminum hydride and

---

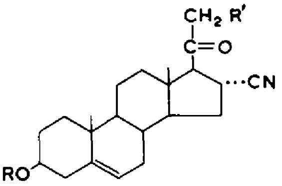
[1] D. K. Fukushima and T. F. Gallagher, *J. Amer. Chem. Soc.* **72**, 2306 (1950).
[2] D. K. Fukushima and T. F. Gallagher, *J. Amer. Chem. Soc.* **73**, 196 (1951).
[3] H. Hirschmann, E. B. Hirschmann and M. A. Daus, *J. Amer. Chem. Soc.* **74**, 539 (1952).
[4] J. Romo, M. Romero, C. Djerassi and G. Rosenkranz, *J. Amer. Chem. Soc.* **73**, 1528 (1951).
[5] D. Gould, E. L. Shapiro, L. E. Finckenor, F. Gruen and E. B. Hershberg, *J. Amer. Chem. Soc.* **78**, 3158 (1956).
[6] C. Djerassi, G. Rosenkranz, J. Iriarte, J. Berlin and J. Romo, *J. Amer. Chem. Soc.* **73**, 1523 (1951).
[7] C. Djerassi and C. T. Lenk, *J. Amer. Chem. Soc.* **76**, 1722 (1954).

acid hydrolysis of the ketal groupings. The infrared spectrum of hydroxymethylprogesterone (IXa) shows an unusually weak band at 5·9 μ, corresponding to the 20-oxo group. For this reason it is assumed that the above-mentioned product is a mixture of the tautomers (IXa) and (IXb), (IXb) predominating.* This type of hemiketal ring in (IXb) is very similar to that present in aldosterone.[8]

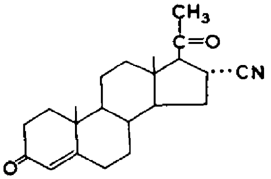
The sodium borohydride reduction of the methyl ester (VIc) yielded the hydroxy derivative (Xa), which on alkaline hydrolysis afforded the free diol (Xb). This product does not form a lactone between the 16α-carboxyl and the 20-hydroxyl groups



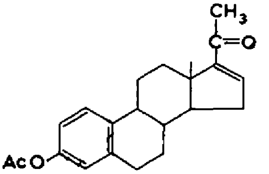
I a, $R = H$
b, $R = OCOCH_3$



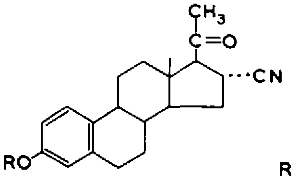
II a, $R = H$, $R' = H$
b, $R = Ac$, $R' = H$
c, $R = Ac$, $R = OCOCH_3$



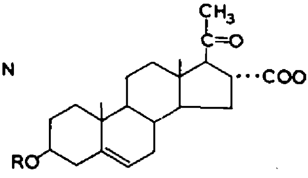
III



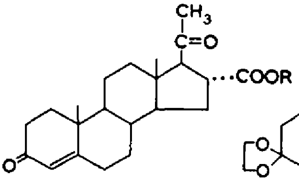
IV



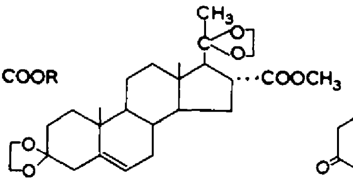
V a, $R = H$
b, $R = Ac$



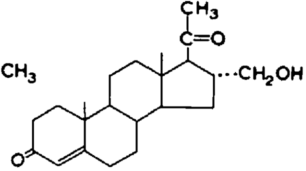
VI a, $R = H$, $R' = H$
b, $R = H$, $R' = CH_3$
c, $R = Ac, R' = CH_3$



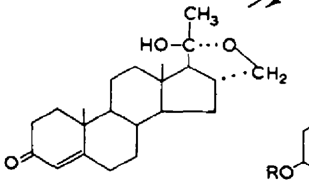
VII a, $R = H$
b, $R = CH_3$



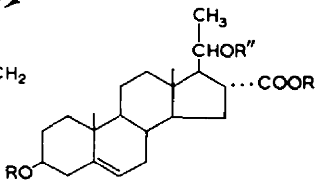
VIII



IX a



IX b



X a, $R = Ac$, $R' = CH_3$, $R'' = H$
b, $R = H$, $R' = H$, $R'' = H$
c, $R = Ac$, $R' = H$, $R'' = Ac$

---

* The optical rotatory dispersion of this mixture (to be published by Dr. Carl Djerassi) substantiates this assumption.

[8] S. A. Simpson, J. F. Tait, A. Wettstein, R. Neher, J. V. Euw, O. Schindler and T. Reichstein, *Experientia* **10**, 132 (1954).

even on treatment with dehydrating agents like acetic anhydride, which produces only the acid diacetate (Xc). This fact proves that the 16-carboxyl and the 20-hydroxyl groups are *trans* to each other and that the reduction with soldium borohydride in this case has produced the β isomer.

The pharmacological activity of the new compounds will be reported elsewhere.

EXPERIMENTAL*

Δ^{5}-3β-*Hydroxy*-16α-*cyanopregnen*-20-*one* (IIa).

To a solution of 3 g of $\Delta^{5,16}$-3β-acetoxypregnadien-20-one (I) in 80 ml of methanol, 8 g of sodium cyanide were added. The mixture was heated under reflux for 3 hr and then poured into 400 ml of cold water. The precipitate was collected and washed thorougly with water. Crystallization from methanol afforded the *cyano derivative* (IIa) (2·17 g), m.p. 228–232°. The analytical sample was obtained by recrystallizations from acetone–methanol, m.p. 232–234° (thick prisms); $[\alpha]_D$ +14°; λ_{max} 3, 4·5, 5·9 μ. *Anal.* Calcd. for $C_{22}H_{31}O_2N$: C, 77·37; H, 9·15; N, 4·10. Found: C, 77·57; H, 9·22; N, 4·31.

The *acetate* (IIb) (acetic anhydride and pyridine on the steam-bath) showed m.p. 196–198°; $[\alpha]_D$ +16°; λ_{max} 4·5, 5·8, 5·85 μ. *Anal.* Calcd. for $C_{24}H_{33}O_3N$: C, 75·16; H, 8·67; N, 3·65. Found: C, 75·01; H, 8·80; N, 3·55.

The *oxime* (hydroxylamine hydrochloride in pyridine and methanol) showed m.p. 241–243°. *Anal.* Calcd. for $C_{24}H_{34}O_3N_2$ C, 72·33; H, 8·60; N, 7·03. Found: C, 72·03; H, 8·46; N, 6·95.

16α-*Cyanoprogesterone* (III)

The cyano derivative (IIa) (8 g) was dissolved in 250 ml of toluene, 20 ml were distilled off to remove moisture, and 90 ml of *cyclo*hexanone and a solution of 4 g of aluminum tri-*iso*propoxide in 20 ml of toluene were added and the mixture was heated under reflux for 1 hr. The volatile components were then removed by steam-distillation. The semi-crystalline residue was extracted with ether, dried over anhydrous sodium sulfate and evaporated to dryness. Crystallization from acetone–hexane gave prisms, m.p. 216–218° (6·33 g). Further crystallizations from acetone-methanol raised the m.p. to 240–242°; $[\alpha]_D$ +159°; λ_{max} 240 mμ; log ε 4·23; λ_{max} 4·5, 5·9, 6·05 μ. *Anal.* Calcd. for $C_{22}H_{29}O_2N$: C, 77·84; H, 8·61; N, 4·13. Found: C, 78·46; H, 8·40; N, 4·05.

$\Delta^{1,3,5(10)}$-3-*Hydroxy*-16α-*cyano*-17β-*acetylestratriene* (Va)

The phenol (IV) (435 mg) was converted into the *cyano derivative*, as in the previous case. Crystallization from acetone–methanol gave prisms, m.p. 240–243° (230 mg); $[\alpha]_D$ +159°; λ_{max} 280–282 mμ; logε 3·36; λ_{max} 3·05, 4·5, 5·9, 6·2, 6·35 μ. *Anal.* Calcd. for $C_{21}H_{25}O_2N$: C, 77·98; H, 7·79; N, 4·33. Found: C, 77·95; H, 7·83; N, 4·26.

The *acetate* (Vb) showed m.p. 175–176°; $[\alpha]_D$ +150°; λ_{max} 268, 276 mμ; log ε

---

* The melting points are uncorrected. Rotations were determined in chloroform (unless noted otherwise). The ultraviolet absorption spectra were determined in 95 per cent ethanol solution in a Beckman DK2 spectrophotometer. The infrared spectra were measured on a Perkin-Elmer double-beam spectrophotometer in chloroform solution (unless stated otherwise). The microanalyses were performed by Dr. Franz Pascher, Bonn, Germany.

3·30, 3·22; λ_{max} 4·5, 5·75, 5·9, 6·2, 6·35 μ. *Anal,* Calcd. for $C_{23}H_{27}O_3N$: C, 75·59; H, 7·45; N, 3·83. Found: C, 75·26; H, 7·40; N, 3·71.

Δ^5-3β,21-*Diacetoxy*-16α-*cyanopregnen*-20-*one* (IIc)

A solution of 1·3 g of $\Delta^{5,16}$-3β,21-diacetoxy-16α-cyanopregnadien-20-one (Ib) in 50 ml of ethanol was heated under reflux with 2 g of sodium cyanide for 3 hr. It was then diluted with water and extracted with ether; the ethereal extract was washed thoroughly with water, dried and evaporated to dryness. The solid residue was treated with 4 ml of acetic anhydride and 4 ml of pyridine, heated for 1 hr on the steam-bath and poured into water. The precipitate was extracted with ether, and the ethereal extract was washed with diluted hydrochloric acid, sodium bicarbonate solution and water, dried over sodium sulfate and evaporated to dryness. The *nitrile* (IIc) was crystallized from methanol to yield 170 mg, m.p. 191–194°, which on recrystallization from acetone-methanol showed m.p. 195–197°; $[\alpha]_D$ +10°; λ_{max} 4·5, shoulder at 5·75, 5·8 μ. *Anal.* Calcd. for $C_{26}H_{35}O_5N$: C, 70·71; H, 7·99; N, 3·17. Found: C, 70·56; H, 8·03; N, 3·38.

Δ^5-3β-*Hydroxy*-16α-*carboxypregnen*-20-*one* (VIa).

To a solution of 770 mg of the cyano derivative (IIa) in 50 ml of ethanol a solution of potassium hydroxide (3 g) in 10 ml of water was added. The mixture was heated under reflux for 1 hr and then diluted with cold water, the opalescent solution was acidified with 20 % hydrochloric acid and the precipitate was collected and washed with water. Crystallization of the *acid* (VIa) from acetone–ether yielded 470 mg, m.p. 217–219°. Further recrystallizations from acetone–ether raised the m.p. to 233–235°; $[\alpha]_D$ −115°; λ_{max} 3, 5·9 μ. *Anal.* Calcd. for $C_{22}H_{32}O_4$: C, 73·30; H, 8·95. Found: C, 73·00; H, 9·03.

Δ^5-3β-*Hydroxy*-16α-*carbomethoxypregnen*-20-*one* (VIb)

An ethereal solution of diazomethane (120 ml) (prepared with 4 g of *N*-nitroso-methylurea) was poured dropwise into the acid (Xa) (1·3 g) dissolved in 30 ml of methanol. The solution was left at room temperature overnight. A few drops of acetic acid were added to destroy the excess of diazomethane, and the ethereal solution was washed with water, dried over sodium sulfate and concentrated. The *ester* (VIb) (890 mg) showed m.p. 198–200°. The analytical sample was obtained by repeated crystallization from acetone–ether and showed brilliant plates with m.p. 206–207°; $[\alpha]_D$ −116°; λ_{max} 3, 5·8, 5·9 μ. *Anal.* Calcd. for $C_{23}H_{34}O_4$: C, 73·76; H, 9·15. Found: C, 73·16; H, 9·25.

The *acetate* (VIc) showed m.p. 159–160° (prisms from acetone–methanol); $[\alpha]_D$−110°; λ_{max} 5·8, shoulder at 5·9. *Anal.* Calcd. for $C_{25}H_{36}O_5$; C, 72·08; H, 8·71. Found: C, 71·79; H, 8·67.

16α-*Carbomethoxyprogesterone* (VIIb)

The Oppenauer oxidation of the ester (Xb) (5 g) was carried out as described before. Crystallization of the *diketone* (VIIb) from acetone–methanol yielded 3 g, m.p. 151–153°. Recrystallization from acetone–methanol raised the m.p. to 157–158°; $[\alpha]_D$ +31°; λ_{max} 240 mμ; log ε 4·23; λ_{max} 5·8, 5·9, 6·05 μ. *Anal.* Calcd. for $C_{23}H_{32}O_4$: C, 74·16; H, 8·66. Found: C, 74·59; H, 8·49.

16α-*Carboxyprogesterone* (VIIa)

(i) *By saponification of* 16α-*carbomethoxyprogesterone* (VIIb). The diketone (VIIb) (1 g) was dissolved in methanol (30 ml) and a solution of potassium hydroxide (1 g) in water (4 ml) was added. The mixture was heated under reflux for 1 hr, diluted with water and acidified with hydrochloric acid. The precipitate was collected, washed thoroughly with water and, on crystallization from acetone–ether yielded 560 mg of (VIIa), m.p. 240–244°. The analytical sample obtained by several recrystallizations from acetone-ether showed m.p. 250–254°; $[\alpha]_D$ +17°; λ_{max} 240 mμ; log ε 4·22; λ_{max} 5·9, 6·05 μ. *Anal.* Calcd. for $C_{22}H_{30}O_4$: C, 73·71; H, 8·44. Found: C, 73·43; H, 8·53.

(ii) *By alkaline hydrolysis of* 16α-*cyanoprogesterone* (III). To a solution of the diketone (III) (500 mg) in 40 ml of methanol a solution of potassium hydroxide (1 g) in 4 ml of water was added. Then the experiment was carried out as described above.

The 16α-carboxyprogesterone (170 mg) showed m.p. 238–242°; λ_{max} 240–242 mμ; log ε 4·22; $[\alpha]_D$ +16° (the mixture with the above specimen gave no depression in the m.p. and the infrared spectra were identical).

3,20-*Bisethylenedioxy*-16α-*carbomethoxy*-Δ⁵-*pregnene* (VIII)

A solution containing 3 g of 16α-carbomethoxyprogesterone (VIIb) and toluene-*p*-sulfonic acid (400 mg) in benzene (600 ml) and ethylene glycol (40 ml) was heated under reflux for 20 hr, a Stark trap being used for the elimination of water. After completion of the reaction, a solution of sodium bicarbonate was added and the benzene layer was washed with water, dried over anhydrous sodium sulfate and evaporated to dryness. The oily residue was crystallized from methanol, to furnish the 1·7 g of *diketone* (VIII), m.p. 174–176°. Repeated crystallization raised the m.p. to 182–183° (needles from acetone-methanol); $[\alpha]_D$ −70°. *Anal.* Calcd. for $C_{27}H_{40}O_6$: C70·40; H, 8·75. Found: C, 70·92; H, 8·67.

16α-*Hydroxymethylprogesterone* (IXa, IXb).

A solution of 2 g of the diketal (VIII) in 25 ml of anhydrous tetrahydrofuran was added slowly to a slurry of 500 mg of lithium aluminum hydride in 80 ml of ether; the mixture was heated under reflux for 30 min, water was added to destroy the excess of lithium aluminum hydride, and the mixture was acidified with hydrochloric acid. The organic layer was washed with water, dried and evaporated, and the oily residue was dissolved in 20 ml of methanol with four drops of concentrated hydrochloric acid. The solution was heated under reflux for 15 min, and then diluted with water and extracted with ether; the extract was washed with water, dried over sodium sulfate and evaporated to dryness. Crystallization of the residue from acetone–hexane gave 380 mg having m.p. 159–161°. Repeated crystallizations raised the m.p. to 166–168°; $[\alpha]_D$ +77°; λ_{max} 240–242 mμ; log ε 4·23; λ_{max} 3·59 (weak), 6·05 μ. *Anal.* Calcd. for $C_{22}H_{32}O_3$: C, 76·70; H, 9·36. Found: C, 76·42; H, 9·49.

Δ⁵-3β-*Acetoxy*-20β-*hydroxy*-16α-*carbomethoxypregnene* (Xa).

To a solution of 2·6 g of Δ⁵-3β-acetoxy-16α-carbomethoxypregnen-20-one (VIc) in 80 ml of tetrahydrofuran, 1 g of sodium borohydride and 0·3 ml of water were added. The mixture was heated under reflux for 1 hr, diluted with water and extracted immediately with ether. The organic layer was washed with water, dried and evaporated. Crystallization of the residue from acetone–hexane yielded (Xa) in brilliant plates (1·05 g), m.p. 147–149°, which on recrystallization melted at 157–158°; [α] —78°; λ_{max} 3, 5·8 μ. *Anal.* Calcd. for $C_{25}H_{38}O_5$: C, 71·74; H, 9·15. Found: C, 71·81; H, 9·07.

Δ^5-3β,20β-*Dihydroxy*-16α-*carboxypregnene* (Xb)

The monoacetate (Xa) (550 mg) was dissolved in 50 ml of methanol and a solution of 800 mg of potassium hydroxide in 5 ml of water was added. The mixture was heated under reflux for 1 hr diluted with water and acidified with hydrochloric acid. The precipitate was collected and washed with water and, on crystallization from methanol, gave needles (275 mg) of the *acid* (Xb), m.p. 273–275°. The analytical sample showed m.p. 281–283°; [α] —84·5° (dioxan); λ_{max} 3, 5·95 μ (Nujol). *Anal.* Calcd. for $C_{22}H_{34}O_4$: C, 72·89; H, 9·45. Found: C, 72·74; H, 9·45.

Δ^5-3β-20β-*Diacetoxy*-16α-*carboxypregnene* (Xc).

The free diol (200 mg) was dissolved in 1·5 ml of acetic anhydride and 1·5 ml of pyridine, and the mixture was left at room temperature overnight. It was then poured into water, and the precipitate was extracted with chloroform and washed with hydrochloric acid and water. After concentration and addition of ether, the *diacetate* (Xc) crystallized as needles (210 mg), m.p. 210–212°, which on recrystallization from acetone–ether melted at 213–215°; $[\alpha]_D$ —53·5°; λ_{max} 5·8, shoulder at 5·9 μ. *Anal.* Calcd. for $C_{26}H_{38}O_6$: C, 69·93; H, 8·58. Found: C, 70·15; H, 9·19.

Acknowledgements—I am indebted to Dr. George Rosenkranz of Syntex S.A. for a generous gift of the steroids that were used in this work.