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SYNTHESIS AND STEREOCHEMISTRY OF 16-SUBSTITUTED PREGNENES AND ISOPREGNENES[1]

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Abstract—The synthesis, stereochemistry and configurational stability of 16α- and 16β-carboxy-Δ^5-pregnene and 16α- and 16β-carboxy-17α-(iso)-Δ^5-pregnene-stereoisomers were investigated.

Among the various compounds described in this work, the 16β, 17α-series (IIa–g) and (VIIIa–c) appeared to have the thermodynamically most stable configuration. Exceptions were observed which involved ring formation between the substituents at positions 16 and 17.

The synthesis and stereochemistry of 16α-acetyl-progesterone (XXVI) and 16β-acetyl-17α-(iso)-progesterone (XXVIII) are described.

SEVERAL studies have been devoted to the Michael addition of hydrogen cyanide to the 16-double bond of various Δ^{16}-20-keto-pregnenes and to the nature of the products arising from alkaline hydrolysis of the adducts. These reactions have been re-investigated and all four possible 16-carboxy-20-keto-pregnenes, stereoisomeric at position 16 and 17, have been obtained and identified.[3]

In 1958, Romo[4] and later Ellis *et al.*[5] recorded the preparation of 16α-cyano-3β-hydroxy-Δ^5-pregnene-20-one (I), as well as the corresponding acid obtained by vigorous alkaline hydrolysis of the cyano-derivative (I). Both groups proposed the structure 16α-carboxy-3β-hydroxy-Δ^5-pregnene-20-one. Later Mazur and Cella[6] suggested, on the basis of molecular rotation differences, the 16β-carboxy-17α-(iso)-acetyl stereochemistry (IIa).

The rotatory dispersion curve[7] of the adduct I, which showed a positive Cotton effect analogous to the unsubstituted pregnane-20-one derivatives,[8] confirmed the β-orientation assigned to the 17-acetyl side chain.[9]

[1a] Steroids CCIII; for part CCII, see: A. Bowers, R. Villotti, J. A. Edwards, E. Denot and O. Halpern, *J. Amer. Chem. Soc.* **84**, 3204 (1962); [b] Contribution No. 135 from the Instituto de Quimica (U.N.A.M.).

[2] This work constitutes a part of the undergraduate thesis submitted by L. M. G. to the Universidad Ibero-Americana.

[3] Preliminary reports of parts of this work have already appeared: P. Crabbé and J. Romo [a] *Chem. & Ind.* 408 (1962); [b] *Ciencia* **22**, 29 (1962).

[4] J. Romo, *Tetrahedron* **3**, 37 (1958).

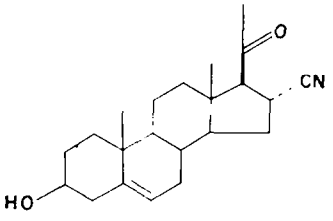
[5] B. Ellis, V. Petrow and D. Wedlake, *J. Chem. Soc.* 3748 (1958).

[6] R. H. Mazur and J. A. Cella, *Tetrahedron*, **7**, 130 (1959).

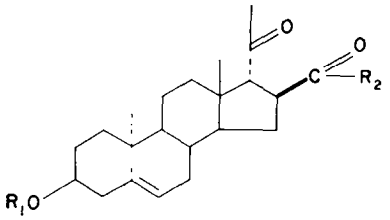
[7] For a detailed study of the rotatory dispersion curves of the compounds described in this work, see the accompanying paper: P. Crabbé, *Tetrahedron* **19**, 51 (1963).

[8] C. Djerassi, *Optical Rotatory Dispersion* pp. 51–52. McGraw-Hill, New York (1960); See also C. Djerassi, *Bull. Soc. Chim. Fr.* 741 (1957).

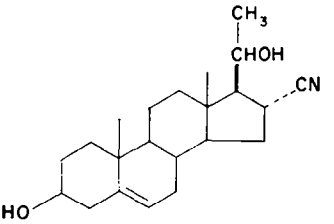
[9] During the course of this work, there appeared a paper by W. A. Struck and R. L. Houtman (*J. Org. Chem.* **26**, 3883 (1961); see also P. F. Beal and J. E. Pike *ibid.* **26**, 3887 (1961)), dealing with the rotatory dispersion of some of the compounds described here. We have reached the same conclusions as these authors on the configuration of the acetyl side chain at position 17.



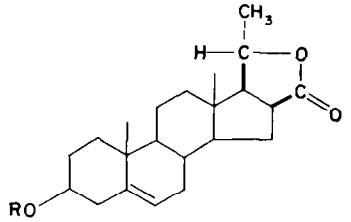
I



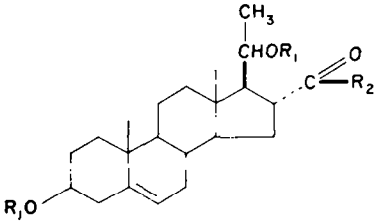
II a : $R_1 = H$; $R_2 = OH$
b : $R_1 = Ac$; $R_2 = OH$
c : $R_1 = H$; $R_2 = OCH_3$
d : $R_1 = Ac$; $R_2 = OCH_3$
e : $R_1 = Ac$; $R_2 = NH_2$
f : $R_1 = H$; $R_2 = NH_2$
g : $R_1 = Ac$; $R_2 = NEt_2$
h : $R_1 = Ac$; $R_2 = NH[CH_2]_2 NEt_2$
$CH_3^{\oplus}\ I^{\ominus}$



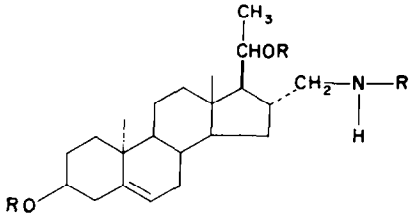
III



IV a : R = H
b : R = Ac



V a : $R_1 = H$; $R_2 = OH$
b : $R_1 = Ac$; $R_2 = OH$
c : $R_1 = Ac$; $R_2 = NH_2$
d : $R_1 = H$; $R_2 = OCH_3$
e : $R_1 = Ac$; $R_2 = OCH_3$
f : $R_1 = H$; $R_2 = NH_2$



VI a : R = H
b : R = Ac

In previous studies,[4–6] the assumption was made that the addition of the cyano anion occurred from the least hindred side of the molecule, leading to the α-configuration for the 16-cyano grouping, as in structure I. Although, by analogy with other addition reactions to this double bond,[10] this interpretation was quite reasonable, it

[10] [a] D. K. Fukushima and T. F. Gallagher, *J. Amer. Chem. Soc.* **73**, 196 (1951); [b] J. Romo, M. Romero, C. Djerassi and G. Rosenkranz, *ibid.* **73**, 1528 (1951); [c] H. Hirschmann, F. B. Hirschmann and M. A. Daus, *ibid.* **74**, 539 (1952); [d] D. Gould, F. Gruen and E. B. Hershberg, *ibid.* **75**, 2510 (1953); [e] G. P. Mueller and B. Riegel, *ibid.* **76**, 3686 (1954); [f] D. Gould, E. L. Shapiro, L. E. Finckenor, F. Gruen and E. B. Hershberg, *ibid.* **78**, 3158 (1956).

was felt necessary to prove unambiguously the configuration at C-16. In order to achieve this, the 16α-carboxy-3β,20β-diol (Va) was prepared by the known sequence:[6] (I) → (III) → (IVa) → (Va).[11] Acetylation of the diol (Va) led to the diacetate (Vb). Treatment of the latter with thionyl chloride then gave the acid chloride, which with ammonia furnished the 16α-carboxamide (Vc). This amide (Vc) was reduced with lithium aluminum hydride to afford the 16α-aminomethyl-3β,20β-diol (VIa) from which the corresponding diacetate-amide (VIb) was prepared. Reduction of 16-cyano-Δ^5-pregnene-20-one (I) with lithium aluminum hydride gave the same amine (VIa). The identity of the two compounds was established by direct comparisons (mixed m.p. and IR spectra) of both the amines (VIa) and of the corresponding diacetate-amides (VIb).[12]

Turning now to the alkaline hydrolysis of the 16-cyano compound (I), the rotatory dispersion curve of the acid (IIa) and most of its derivatives showed a negative Cotton effect.[7] The amplitude of the trough was in agreement with the postulated[6,9] 17α-acetyl side chain.[8] On the other hand, as shown previously by Romo,[4] the acid-diol (VIIa), obtained by sodium borohydride reduction of the ketone (IIa), could not form a lactone between C-16 and C-20. A *trans*-relationship between C-16 and C-17 substituents was thus deduced for compound VIIa, and consequently the 16β-carboxy-17α-acetyl configuration was suggested[6] for the alkaline hydrolysis product (IIa) of the nitrile (I). In other words this hydrolysis involved inversion of configuration at both C-16 and C-17.

A possible mechanism which would explain this fact would require first an equilibrium in alkaline conditions[13] between the 17β- and the 17α-acetyl epimers (I and A). Attack by an hydroxyl ion at the 20-carbonyl of the 17α-epimer (A) would then lead to the anion (B) which would participate readily in the hydrolysis of the cyano-grouping, through a cyclic intermediate of type (C).[14,15] Finally, attack of an hydroxyl ion on this cyclic intermediate (C) would yield the 16α,17α-amide (D). Since under the experimental conditions the *cis*-configuration is unstable (see below), the readily epimerizable 17α-acetyl grouping is inverted to 17β affording the 16α-carboxamide-17β-acetyl derivative (E), which has actually been isolated (as the Δ^5-3-alcohol) among the alkaline hydrolysis products of the adduct (I). The hydrolysis of this amide (E)

[11] A quantitative re-investigation of this sequence has shown[3a] that under mild alkaline conditions the cyano-diol (III) yields the lactone (IVa) almost exclusively, and that this compound (IVa) by further alkaline treatment is converted mainly to the *trans* acid-diol. (Va).

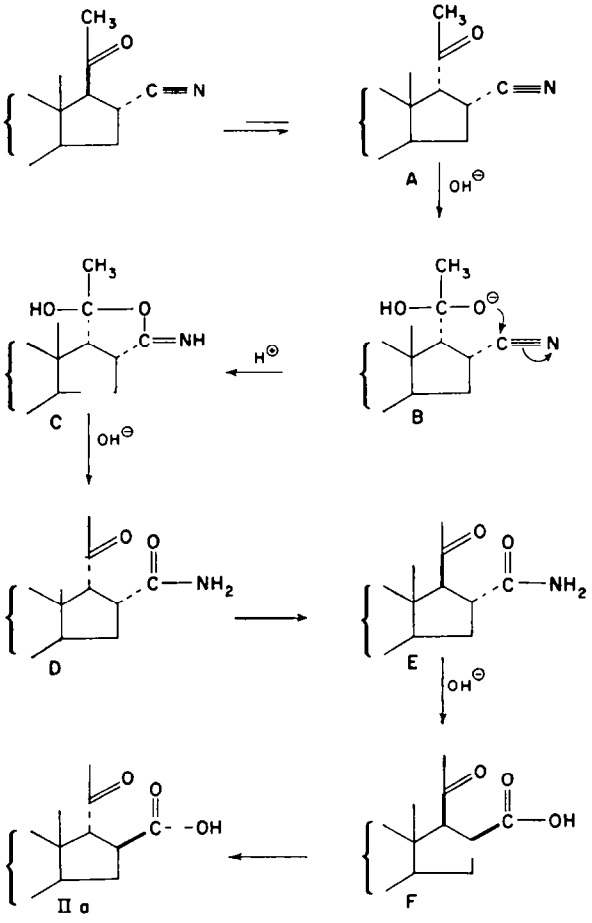
[12] The 16α-cyano-configuration of compound I could also be deduced from the N.M.R. spectrum. An extensive study of the relevant information obtained from the N.M.R. spectra of the compounds described in this work will be published at a later date by A. D. Cross and P. Crabbé.

[13] It is known that under such conditions an equilibrium exists between the 17β- and 17α-acetyl side chain in the 16-unsubstituted 20-keto-pregnane series. See L. F. Fieser and M. Fieser, *Steroids* p. 566. Reinhold, New York (1959).

[14] The participation of the 20-carbonyl function in the hydrolysis of the 16-cyano-group is apparent from the observable difference in the rates of hydrolysis of I to IIa, and III to IVa.[11] A similar rate difference has been observed between the hydrolysis of I to IIa and the hydrolysis of the 16α-cyano-17β-carboxy-Δ^5-androstene-3β-ol to the corresponding 16β,17β-dicarboxy-derivative. Furthermore, in the 3 examples mentioned above, there was observed an inversion of configuration at C-16 during the hydrolytic process of the 16-cyano to the corresponding 16-acid (P. Crabbé, M. Martínez and J. Romo, unpublished observations).

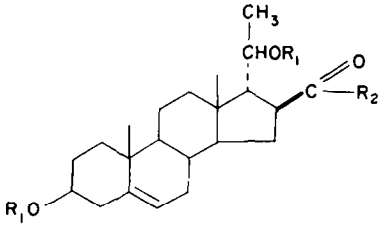
[15] This type of mechanism has some precedent in triterpene chemistry. See C. Djerassi and A. E. Lippman, *J. Amer. Chem. Soc.* **77**, 1825 (1955) and C. Djerassi and J. S. Mills, *Ibid.* **80**, 1236 (1958).

was then accompanied by an inversion of configuration at C-16,[14] yielding the 16β-carboxy-17β-acetyl compound (F), also indentified (*vide infra*) among the reaction products of this hydrolysis. The configuration at C-17 of compound (F), readily invertable, provided the thermodynamically most stable *trans*-acid (IIa).

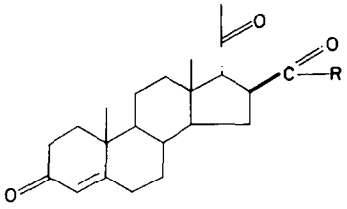


The structure of the amide (E) has been proved as follows. The 17β-acetyl configuration was readily deduced from the positive rotatory dispersion curve[7] shown by this substance (E). Reduction of the 20-keto-grouping of this amide (E) with sodium borohydride afforded the diol-amide (Vf), which, when acetylated, was shown to be identical (by mixed m.p. and superimposable IR spectra) with a sample of the diacetate-amide (Vc), obtained directly from the acid-diol (Va), as described previously.

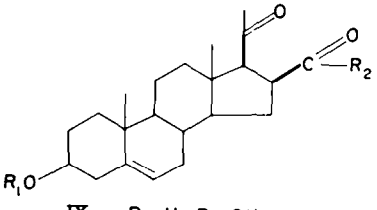
As already mentioned, the hydrolysis of the cyano-ketone (I) under mild conditions gave, besides some starting material (I) and the amide (E), a mixture of the acid (IIa) and a new acid to which the 16β-carboxy-3β-hydroxy-Δ^5-pregnene-20-one structure (IXa) was attributed. Further alkaline treatment of the acid (IXa) gave the 17α-epimer (IIa). The rotatory dispersion curves of this acid (IXa) and of its derivatives



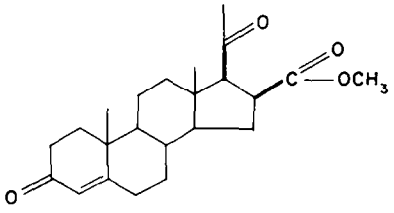
VII a : R_1 = H ; R_2 = OH
b : R_1 = Ac ; R_2 = OH
c : R_1 = Ac ; R_2 = Cl
d : R_1 = H ; R_2 = OCH_3



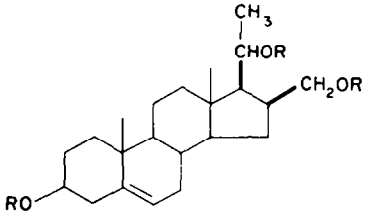
VIII a : R = OCH_3
b : R = OH
c : R = NH_2



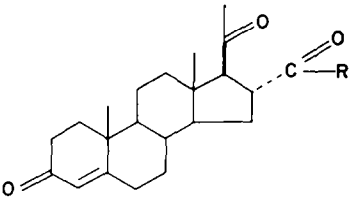
IX a : R_1 = H ; R_2 = OH
b : R_1 = H ; R_2 = OCH_3
c : R_1 = Ac ; R_2 = OCH_3
d : R_1 = Ac ; R_2 = $NH[CH_2]_2-NEt_2, CH_3^{\oplus} I^{\ominus}$



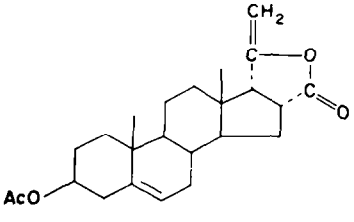
X



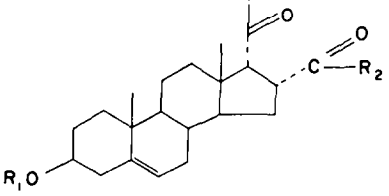
XI a : R = H
b : R = Ac



XII a : R = OCH_3
b : R = OH



XIII



XIV a : R_1 = H ; R_2 = OCH_3
b : R_1 = Ac ; R_2 = OH
c : R_1 = Ac ; R_2 = OCH_3

(IX b,c,d,) all showed a positive Cotton effect, in agreement with the assigned 17β-acetyl configuration. Furthermore, lithium aluminum hydride reduction of the ester (IXb) afforded a triol (XIa), identical with the lithium aluminum hydride reduction product of the lactone (IVa). A *cis*-relationship between the substituents at C-16 and C-17 of the keto-acid (IXa) was confirmed by sodium borohydride reduction which led to the lactone (IVa). Although the 16,17-*trans*-configuration (IIa) is more stable (*vide infra*). the epimer (IXa) could be isolated since hydrogen bonding between the hydroxyl group of the 16-carboxylic acid and the 20-ketone presumably stabilized partially the 17β-acetyl configuration.

Various derivatives of the acid (IIa) have been prepared, including the amides (IIe to IIh). These amides were made by the reaction of the acid-chloride of IIb and the corresponding amines. The amide (IIf) was obtained by mild alkaline treatment of compound (IIe), taking advantage of the greater reactivity towards potassium bicarbonate of the 3β-acetoxy function as compared to the 16β-carboxamide grouping. Similarly the corresponding 16β-carboxamido-17α-(iso)-progesterone (VIIIc) has been synthesized *via* the 16β-carboxy-17α-(iso)-progesterone (VIIIb),[4] by treatment of the sodium salt of the latter with oxalyl chloride,[16] followed by ammonia. The rotatory dispersion curves of the compounds (IIa–IIh and VIIIa–VIIIc) indicated that they had the 17α-acetyl configuration.[7]

The amide (IIh) was obtained, albeit in low yield, from the reaction of the acid chloride of the carboxy-acetate (IIb) with N,N-diethylethylenediamine. However, when the reaction was carried out for a longer time with a large excess of amine the 17β-epimer (IXd) was obtained. The configuration at C-17 in the amide (IXd) was deduced from its rotatory dispersion curve which showed a positive Cotton effect. Furthermore, a study of the stability of both epimers (IIh) and (IXd) by rotatory dispersion has shown that in alkaline medium the 17β-epimer (IXd) was the more stable.[7]

Oppenauer oxidation[17] of the methyl ester (IXb) afforded 16β-carbomethoxy-progesterone (X). This compound was different from the oxidation product (XIIa) of 16α-carbomethoxy-3β,20β-diol (Vd), arrived at by diazomethane methylation of the corresponding acid (Va). The new progesterone (X) was also shown to be different from the 16β-carbomethoxy-isoprogesterone (VIIIa).[4] Some stability studies of these progesterones in alkaline medium were undertaken, from which it appeared that the *trans*-compounds (XIIb and VIIIb) were the stable epimers. Thus by alkaline hydrolysis of the carbomethoxy-progesterone (X) the 16β-carboxy-isoprogesterone (VIIIb) was obtained. This inversion of the configuration at C-17[13,18] was clearly shown by rotatory dispersion.[7] Furthermore alkaline treatment of the esters (XIIa and VIIIa)

[16] See [a] A. L. Wilds and C. H. Shunk, *J. Amer. Chem. Soc.* **70**, 2427 (1948); [b] Hs. H. Günthard, E. Beriger, Ch. R. Engel and H. Heusser, *Helv. Chim. Acta* **35**, 2437 (1952).

[17] R. V. Oppenauer, *Rec. Trav. Chim. Pays-Bas* **56**, 137 (1937); *Org. Synth.* **21**, 18 (1941); C. Djerassi, *Org. React*, **6**, 207 (1951).

[18a] In a recent paper by J. Schmidlin and A. Wettstein (*Helv. Chim. Acta* **45**, 331 (1962)), the authors mentioned several cases of inversion occurring with the 17β-acetyl side chain when the angular substituent at C-13 is bulkier than a methyl grouping; [b] Epimerization of the 17-acetyl side chain of 3β-hydroxy-16β-methyl-5α-pregn-9(11)-en-20-one under either basic or acid conditions has recently been reported by E. J. Bailey, D. H. R. Barton, J. Elks and J. F. Templeton (*J. Chem. Soc.* 1578 (1962); see also: [c] A. Wettstein, *Helv. Chim. Acta* **27**, 1803 (1944); [d] J. Romo, J. Lepe and M. Romero, *Bol. Inst. Quim.* (Mexico), **4**, 125 (1952); [e] J. Attenburrow, J. E. Connett, W. Graham, J. F. Oughton, A. C. Ritchie and P. A. Wilkinson, *J. Chem. Soc.* 4547 (1961).

gave the acids (XIIb and VIIIb) respectively. Through methylation of these acids (VIIIb and XIIb) by diazomethane, the corresponding methyl esters (VIIIa and XIIa) respectively were regenerated.

Three of the four possible 16,17-disubstituted stereoisomers had been identified at this stage of the investigation. Access to the fourth, the 16α,17α-stereoisomer, was gained by acetylation of acid (IIa) under suitable conditions. When the acetylation of acid (IIa) was carried out overnight at room temperature with acetic anhydride and pyridine, the expected 3β-acetate (IIb) was obtained. However when the reaction conditions were more vigorous (80° for 5 hours) the 3β-acetoxy-Δ^{20}-enol-lactone (XIII) was obtained. This substance, which was neutral, did not show any absorption in the UV in the 216–320 mμ region, while the IR spectrum exhibited, besides bands at 5·78 and 8·02 μ (3β-acetate), strong absorptions at 5·59 μ (γ-lactone) and at 6·0 and 11·36 μ (*exo*-methylene). Absorption attributable to a C-20 carbonyl group (ca. 5·85 μ) was absent. The exceptionally intense absorption at 6·0 μ was in agreement with a vinyl ether double bond, present here as the *exo*-cyclic methylene of the lactone (XIII). Previous studies[19] have shown that the linkage of an oxygen atom to a double bond affected the wavelengths and intensities of the bands normally associated with the unsaturated system. The NMR spectrum of this enol lactone (XIII)[20] showed the Δ^5-olefinic-proton at 5·40 p.p.m.,[21] the two *exo*-methylene protons appeared at 4·84 and 4·20 p.p.m. and the 3β-acetoxy methyl protons at 2·02 p.p.m. In the NMR spectrum there was no absorption due to a 17-acetyl-grouping, and accordingly the product was considered to possess the enol lactone structure (XIII).[3b] While strong alkaline treatment of lactone (XIII) regenerated the acid (IIa), milder hydrolyses yielded different compounds according to the experimental conditions. Potassium bicarbonate-dioxane treatment of XIII afforded a new acetoxy-acid (XIVb). But when the hydrolysis was carried out with potassium bicarbonate in methanol instead of dioxane, either the 3-acetoxy-16-carbomethoxy derivative (XIVc) or the corresponding 3-hydroxy-ester (XIVa) was obtained according to the reaction time. The methyl esters (XIVa) and (XIVc) formed under these conditions result presumably from the opening of the enol lactone (XIII) by a nucleophilic attack of the anion CH_3O^- on the carbonyl grouping. Methylation of the acid (XIVb) with diazomethane and acetylation of the alcohol (XIVa) with acetic anhydride and pyridine at room temperature provided the *same* 3β-acetoxy-16α-carbomethoxy compound, identical with the above described product (XIVc) directly obtained from the enol lactone (XIII). All the 20-ketones of this series (XIV) were characterized by rotatory dispersion curves presenting a strong negative Cotton effect.[7]

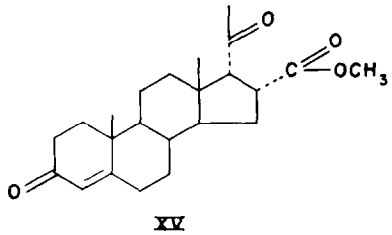
Oppenauer oxidation of the methyl ester (XIVa) afforded 16α-carbomethoxy-17α-(iso)-progesterone (XV), the configuration being assigned on the basis of the experiments described in the following sequence. This new carbomethoxy-isoprogesterone

[19] See [a] G. S. Davy, T. G. Halsall and E. R. H. Jones *J. Chem. Soc.* 2696 (1951); [b] G. D. Meakins, *Ibid.* 4170 (1953); [c] D. H. R. Barton, H. T. Cheung, A. D. Cross, L. M. Jackman and M. Martin-Smith, *Proc. Chem. Soc.* 76 (1961), and *J. Chem. Soc.* 5061 (1961); [d] L. J. Bellamy, *The Infra-red Spectra of Complex Molecules* pp. 49, 50 and references. Methuen, London (1958).

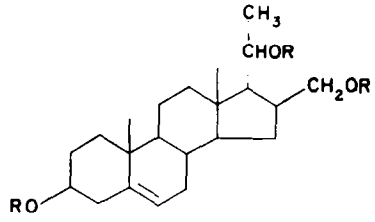
[20] Kindly provided by Prof. C. Djerassi, Stanford University.

[21] As suggested by C. Djerassi, T. Nakano, A. N. James, L. Zalkow, E. J. Eisenbraun and J. N. Shoolery (*J. Org. Chem.* **26**, 1192 (1961)), the chemical shift, δ, is given as p.p.m. from an internal tetramethylsilane reference, for a solution in deuterochloroform. A Varian A-60 spectrometer was employed.

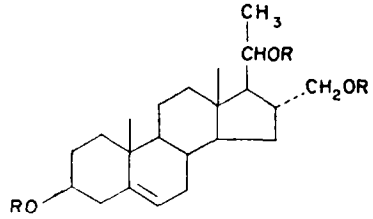
(XV) was not identical with either of the two previously obtained carbomethoxy-progesterones (X) and (XIIa), and was also different from 16β-carbomethoxy-17α) (iso)-progesterone (VIIIa). Furthermore, strong alkaline hydrolysis of the ester (XV- gave the known 16β-carboxy-17α-(iso)-progesterone (VIIIb), as identified by mixed melting point determination, comparative IR spectra and rotatory dispersion curves.



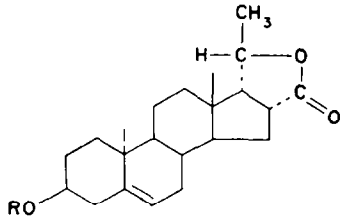
XV



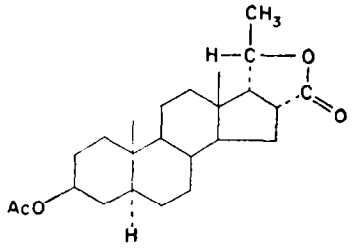
XVI a : R = H
b : R = Ac



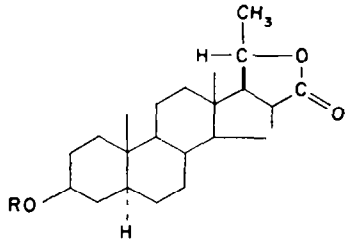
XVII a : R = H
b : R = Ac



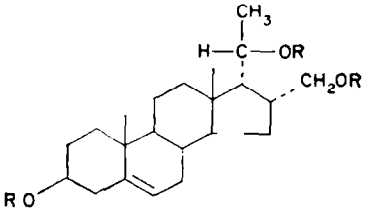
XVIII a : R = H
b : R = Ac



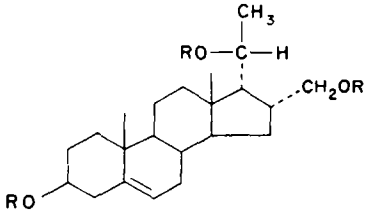
XIX



XX a : R = H
b : R = Ac



XXI a : R = H
b : R = Ac



XXII a : R = H
b : R = Ac

An examination of the geometry of the postulated enol lactone system with Dreiding molecular models[22] suggested a *cis*-relationship between the substituents at C-16 and C-17. While *trans*-γ-lactones fused to medium and large rings have been described, as for instance in the α- and β-santonins,[23] and cnicin[24] belonging to the sesquiterpene series, no γ-lactone *trans*-fused to a cyclopentane ring seemed to have been reported so far.[25,26] Although these arguments strongly suggested a *cis*-configuration for the enol lactone (XIII), it was felt necessary to investigate thoroughly the stereochemistry of this lactone and its related products.

Lithium aluminum hydride reduction of XIII afforded a triol (XXIa) which was different from the already mentioned 3β, 16β, 17β-isomer (XIa), obtained either from the lactone (IVa) or from the ester (IXb). The alcohol (XXIa) was also different from the 3β,16β,17α-isomer (XVIa), obtained by lithium aluminum hydride reduction of acid (IIa) or its derivatives. Finally the new alcohol (XXIa) was also shown to be different from the isomeric 3β,16α,17β-triol (XVIIa) derived from the acid diol (Va). In view of large differences observed between the molecular rotations of these alcohols (XIa, XVIa, XVIIa and XXIa) it was anticipated that the difference between the alcohol (XXIa) and the other triols must involve more than the stereochemistry at C-20.

When the enol lactone (XIII) was hydrogenated over palladium–charcoal, a γ-lactone (XVIIIb) was obtained. This compound had properties different from these of the lactone (IVb) described by Mazur and Cella.[6] The 16,17-*cis*-relationship of these substituents in (XVIIIb) was deduced from separate treatments of this lactone and the isomeric lactone (IVb), with a 2% potassium hydroxide methanolic solution, followed by reacetylation and chromatography, when lactones (XVIIIb) and IVb were regenerated respectively. Previous studies have shown that the 16,17-*trans*-acid-diols (Va) and (VIIa) could not form lactones between C-16 and C-20, even under rather drastic conditions.[4,6] Since lactone (XVIIIb) was recovered unchanged after alkaline treatment and reacetylation, a *cis*-relationship had to be attributed to the substituents at C-16 and C-17 in this lactone (XVIIIb).[26] This point has been confirmed by hydrogenation of both lactones (XVIIIb and IVb) in ethyl acetate over platinum catalyst to provide respectively the saturated compounds (XIX and XXb), which as expected

[22] A. Dreiding, *Helv. Chim. Acta* **42**, 1339 (1959).

[23] [a] R. B. Woodward and P. Yates, *Chem. & Ind.* 1391 (1954); [b] A. J. Haagen-Smit, *Fortschritte der Chemie Organischer Naturstoffe* (L. Zechmeister) Vol. XII; p. 1. Springer, Wien (1955). [c] W. Cocker, *Ann. Reports* **51**, 208 (1954); [d] J. D. M. Asher and G. A. Sim, *Proc. Chem. Soc.* 111 (1962); [e] D. H. R. Barton, T. Miki, J. T. Pinhey and R. J. Wells, *Ibid.* 112 (1962); [f] M. Nakazaki and H. Arakawa, *Ibid.* 151 (1962).

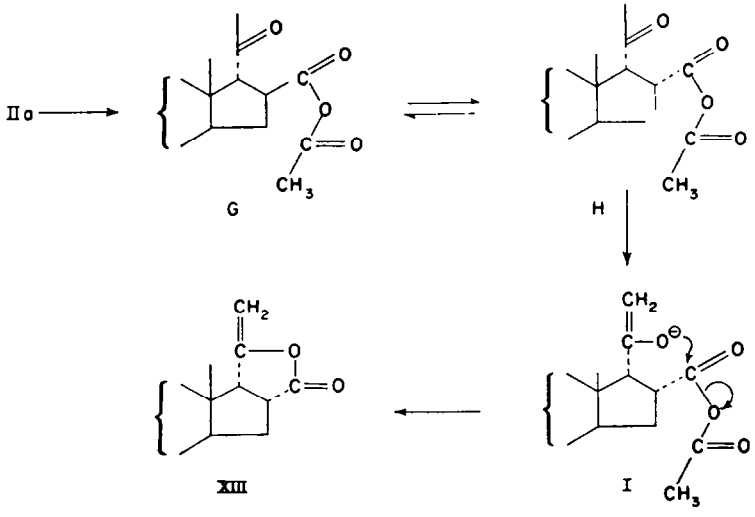
[24] M. Suchý, V. Benešová, V. Herout and F. Šorm. *Tetrahedron, Letters* No. 10, 5 (1959), and *Chem. Ber.* **93**, 2449 (1960).

[25] See Y. Mazur, N. Danieli and F. Sondheimer in *J. Amer. Chem. Soc.* **82**, 5889 (1960).

[26] [a] It is worth while mentioning here that A. Bowers, T. G. Halsall and G. C. Sayer (*J. Chem. Soc.* 3070 (1954)) have observed that the *same cis*-γ-lactone system was obtained by cyclization under rather severe conditions between either the 20α- or 20β-acid function and the 16-hydroxyl grouping on derivatives of the tetracyclic triterpene polyporenic acid C. See also, [b] G. Ourisson and P. Crabbé, *Les Triterpènes Tétracycliques* pp. 83–85. Hermann, Paris (1961). [c] J. L. Simonsen and W. C. Ross, *The Terpenes* Vol. V; pp. 46–50. University Press, Cambridge (1957). [d] Analogous observations have been made recently in the fusidic acid series: W. O. Godtfredsen and S. Vangedal, *Tetrahedron*, **18**, 1029 (1962).

were not identical.[27] Lactones (XIX and XXb) were recovered after submission to the alkaline hydrolysis and acetylation sequence described above.

Proof of the 16α,17α-configuration of these substances XIII, XIV, XVIII and XIX was provided by the reduction of the 20-keto-grouping of the acid (XIVb) with sodium borohydride in isopropanol[28] followed by mild acid treatment and reacetylation when, after chromatography, the lactone (XVIIIb) was obtained. The identity of the lactones (XVIIIb) arrived at by catalytic hydrogenation or by sodium borohydride reduction was established by mixed melting point and IR spectra comparison. Moreover, hydrogenation of the acetate (XIVb) with platinum oxide as a catalyst provided a saturated lactone which was identical with the hydrogenation product (XIX) obtained from the enol lactone (XIII). From these experiments the 16α,17α-configuration could be assigned to the compounds of these series (XIII, XIV, XV, XVIII and XIX). Consequently the triol (XXIa), from lithium aluminum hydride reduction of the enol lactone (XIII), also had the 16α,17α-stereochemistry. Lithium aluminum hydride reduction of the ester (XIVa) however gave another triol (XXIIa). These alcohols (XXIa and XXIIa) were presumably epimeric at C-20, XXIa being the α-epimer and XXIIa the β-epimer.[29] This assumption was based on the fact that the reaction mechanism[30] for the reduction of the enol lactone (XIII), presumably quite different from the reduction process involved in passing from the ester (XIVa) to the triol

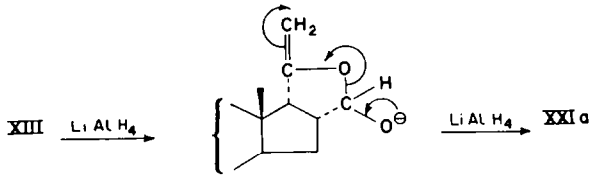


[27] Further evidence concerning the stereochemistry at C-20 of these lactones gained from NMR studies will be discussed elsewhere.[13]

[28] H. C. Brown, E. J. Mead and B. C. Subba Rao, *J. Amer. Chem. Soc.* 77, 6209 (1955).

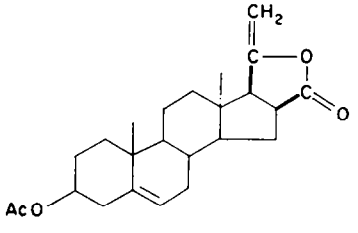
[29] P. A. Plattner, *Helv. Chim. Acta.* **34**, 1693 (1951).

[30] A possible mechanism for the reduction of XIII with lithium aluminum hydride can be written:

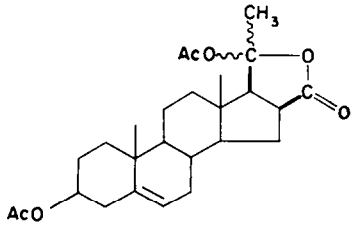


(XXIIa), being highly dependent on the stereochemistry of the enol-lactone system thus led to the α-configuration at C-20.

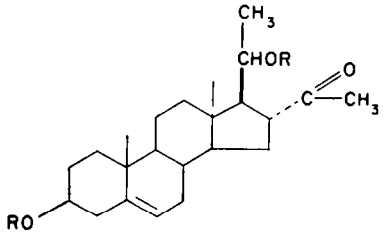
The assignment of the 16α,17α-configuration to the enol lactone (XIII) required inversion of configuration at C-16 during the acetylation of the acid (IIa) under the experimental conditions. The inversion of a secondary carboxyl grouping, for which precedent had been established in natural products chemistry,[31] could be visualized here[32] as proceeding *via* enolization of the mixed anhydride (G) to the equilibrium G ⇌ H, from one component of which (H) the enol lactone (XIII) might arise by intramolecular displacement as represented in formula (I).



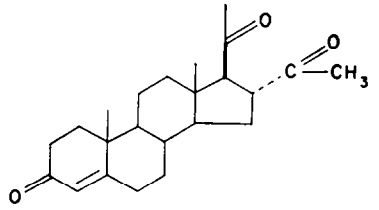
XXIII



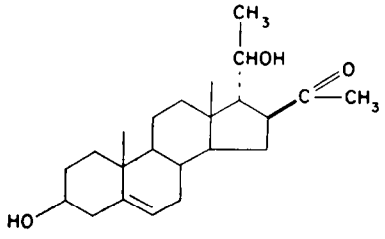
XXIV



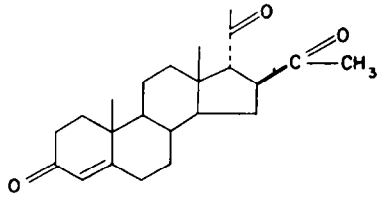
XXV a : R = H
b : R = Ac



XXVI



XXVII



XXVIII

As enol-lactonization had been carried out with the *trans*-acid (IIa), it was anticipated that identical cyclization would occur with a *cis*-acid. Hence, the 16β-carboxy-17β-acetyl compound (IXa) was submitted to similar experimental conditions as

[31] See *inter alia* [a] ref. 26*a* and *b*; [b] J. L. Simonsen and D. H. R. Barton, *The Terpenes*, The University Press, Cambridge, Vol. III, 1952, pp. 152, 295 to 327 and 401 to 404; [c] ref. 26c, pp. 46 to 50 and 538.

[32] We thank Prof. G. Stork, Columbia University, for this suggestion.

described above for the preparation of the enol lactone (XIII). There was obtained a mixture of two substances readily separated by fractional crystallization. The main product showed in the IR the typical triple absorption pattern in the carbonyl region: 5·56 μ (γ-lactone), 5·80 μ (3β-acetate) and 5·97 μ (*exo*-methylene). Thus the enol lactone structure (XXIII) was assigned to this compound. This structure was supported by examination of the NMR spectrum.[21,33] The Δ^5-olefinic-proton appeared at 5·33 p.p.m., the two *exo*-methylene protons at 4·65 and 4·21 p.p.m. respectively and the 3β-acetoxy methyl protons at 2·01 p.p.m. The chemical shift between the two methylene protons ($\Delta\delta = 0{\cdot}44$ p.p.m.) was considerably less than for the isomeric enol lactone (XIII; $\Delta\delta = 0{\cdot}64$ p.p.m.) and reflected reduced deshielding of *one* of these protons in the β-lactone (XXIII). Knowledge of the stereochemistry at C-16 and C-17 in this enol lactone (XXIII) has been gained from the full hydrogenation over platinum catalyst which afforded the previously obtained lactone (XXb). The elemental analysis of the second compound of this reaction indicated an empirical formula $C_{26}H_{36}O_6$. This substance, resulting presumably from the addition of one mole of acetic acid on the 20,21-double bond of the enol lactone (XXIII) could be represented as XXIV. The IR spectrum of this lactone (XXIV), with its two bands at 5·56 μ (γ-lactone) and 5·76 μ (3β and 20 ζ-acetate) supported this structure. Further confirmation came from the NMR spectrum[21,33] which showed the Δ^5-proton at 5·33 p.p.m. and the acetate methyl protons at 2·01 p.p.m., the area of the latter absorption being twice that of the acetate methyl proton absorption in the spectrum of the enol lactone (XXIII). The configuration of this compound (XXIV) at C-16 and C-17[27] was deduced from lithium aluminum hydride reduction, which afforded the triol (XIa), and from mild alkaline hydrolysis which led to the 16β-carboxy-17β-acetyl-compound (IXa).

Grignard reaction of methylmagnesium iodide with the lactone (IVa), as well as with the 16α-cyano-diol (III) yielded the *same* 16-acetyl-diol (XXVa).[34] Inversion of configuration at C-16 must have occurred therefore during the work up of the reaction mixture obtained from the lactone (IVa), indicating that the diol (XXVa) had the thermodynamically more stable configuration at C-16. The strong carbonyl band in the IR spectrum suggested that no hemi-ketal had formed between the 16-acetyl and the 20-alcohol grouping, which was compatible with a 16α-acetyl configuration for this diol (XXVa) and its diacetate (XXVb). Rotatory dispersion measurements[7] also supported this 16α-acetyl assignment of configuration. Oppenauer oxidation of this diol (XXVa) provided the 16α-acetyl-progesterone (XXVI). The β-configuration was assigned to the 17-acetyl side chain in XXVI on the basis of its rotatory dispersion curve which was very similar to the curve of 16β-carbomethoxy-progesterone (X).[7] Furthermore, reaction between dimethyl cadmium and the diacetate-acid-chloride (VIIc) led to the 16β-acetyl-diol (XXVII). Though the rotatory dispersion curves of diol (XXVa) and its diacetate (XXVb) showed a weak positive Cotton effect, the

[33] We are indebted to Dr. J. L. Mateos, Universidad Nacional Autónoma de México, for these measurements.

[34] The preparation of 16-acetyl steroids has already been described in other series. [a] See J. Fajkoš and F. Šorm, *Coll. Czech. Chem. Comm.* **21**, 1013 (1956) and **22**, 1873 (1957). [b] See also: J. Romo and A. Romo de Vivar, *J. Amer. Chem. Soc.* **81**, 3446 (1959) and [c] D. Taub, R. D. Hoffsommer and N. L. Wendler, *J. Org. Chem.*, **26**, 2849 (1961).

16β-acetyl-diol (XXVII) manifested a strong negative Cotton effect. Moreover compound XXVII showed a strong carbonyl absorption in the IR. This was indicative of a 16β-acetyl configuration for the new diol (XXVII). Finally, Oppenauer oxidation of the acetyl-diol (XXVII) furnished presumably the 16β-acetyl-17α-(iso)-progesterone (XXVIII), the rotatory dispersion curve of which was reminiscent of the curve of the 16α-carbomethoxy-17α-(iso)-progesterone (XV).[7]

Three major conclusions can be reached from the behaviour in alkaline media of the four possible epimers at C-16 and C-17. First, under equilibrating conditions the compounds having the C-16, C-17-*cis*-configuration are the less stable ones, except where strong secondary stereochemical factors are operative. Thus, upon alkaline treatment, the compounds belonging to the 16β,17β-series (IXa–d and IVa,b), and the compounds of the 16α,17α-series (XIVa–c and XIII) give the acid diol (Va) and the acid (IIa), both with the *trans*-16,17-stereochemistry. Secondly, of the two *trans*-stereoisomers, as in the II- and VIII-series on the one hand and the amide (E) and the XII-series on the other hand, the most stable appears to be the 16β-17α (II and VIII) where the energies of non-bonded interactions between substituents of ring D are minimized since all the substituents in this ring are now in *trans*-relationship one to the other. Thirdly, *cis*-configuration can be obtained under suitable conditions by ring formation, through hydrogen bonding as exemplified by the acid (IXa) and the amide (IXd), involving epimerization at C-17; or by formation of an enol lactone as in XIII involving inversion at C-16.

EXPERIMENTAL

Microanalyses were due to Dr. A. Bernhardt, Max Planck Institut, Mülheim (Ruhr), Germany. M.p. were determined in capillary tubes with a "Mel-temp" apparatus. They are not corrected. Rotations were taken between 16° and 22° with a 1 dm. tube at sodium D-light (5890 Å). IR spectra were taken with a Perkin-Elmer, Model 21, NaCl prism. UV absorption spectra were taken with Beckman spectrophotometers, Model D.U. and Model D.K.2 (EtOH: 95% ethyl alcohol). We are indebted to Dr. J. Matthews and his staff for these measurements.

16α-Carboxamido-Δ⁵-pregnene-3β-ol-20-one (E)

The adduct (I; 1 g) was refluxed for 10 min in 45 ml ethyl alcohol and 5 ml water containing 2·5 g potassium hydroxide, then poured into water and the precipitate filtered off and dried. The alkaline solution was extracted several times with ethyl acetate. The organic layer was washed with water until neutral, dried ($MgSO_4$) and evaporated *in vacuo*. The residue was combined with the above obtained precipitate to afford the neutral fraction (815 mg). The aqueous alkaline extracts were made acidic with a dil. hydrochloric acid solution (10%) and usual extraction procedure provided 160 mg of a mixture of acids (IIa and IXa). The neutral fraction was then chromatographed on 30 g silica gel (B.D.H. Laboratory, England). Elution with benzene–chloroform (3–1) gave 650 mg of the adduct (I). Further elution of the column with chloroform–methanol (95–5) gave first a small amount (ca. 25 mg) of a compound: m.p. 180–183°. Repeated recrystallizations from methanol gave a sample: m.p. 210–220°; $[\alpha]_D$ −59° (*c*, 0·53; methanol). IR λ_{max}^{KBr} 2·95, 3·00 and 3·1 μ (broad, OH, NH_2), 5·86 μ (20-ketone), 6·00 and 6·13 μ (amide). The rotatory dispersion curve of this material showed a peak at $[\alpha]_{307\cdot5}$ +269·5°, thus indicating a probable mixture of the amides (D) and (E). (Found: C, 73·34; H, 9·42; N, 3·92. $C_{22}H_{33}O_3N$ requires: C, 73·50; H, 9·25; N, 3·90%).

Further elution of the column with the same mixture (chloroform–methanol) provided a second compound (55 mg): m.p. 265–269°. Several recrystallizations from methanol provided *16α-carboxamido-Δ⁵-pregnene-3β-ol-20-one* (E): m.p. 272–273° (dec); $[\alpha]_D$ +5° (*c*, 0·55; methanol). IR λ_{max}^{KBr} 2·96, 3·07 and 3·19 μ (OH, NH_2, free and bonded), 5·88 μ (20-ketone), 6·04 and 6·17 μ (amide). (Found: C, 73·49; H, 9·12; N, 3·75. $C_{22}H_{33}O_3N$ requires: C, 73·50; H, 9·25; N, 3·90%).

16α-Carboxamido-Δ⁵-pregnene-3β,20β-diol (Vf).

A solution of 200 mg of the 16α-carboxamide (E) in 50 ml ethyl alcohol containing 300 mg sodium borohydride was refluxed for 3 hr. Water was then added and the organic product extracted with ethyl acetate yielding 160 mg crude amide-diol (Vf): m.p. 278–281°. Recrystallization from methanol–water provided *16α-carboxamido-Δ⁵-pregnene-3β,20β-diol* (Vf), as silky plates: m.p. 283–285°; $[\alpha]_D$ −77° (*c*, 0·15; chloroform). λ_{max}^{KBr} 2·89 and 3·04 μ (OH, NH_2, free and bonded), 6·02 and 6·21 μ (amide). (Found: C, 72·53; H, 9·83; N, 4·02. $C_{22}H_{35}O_3N$ requires: C, 73·09; H, 9·76; N, 3·87%).

Acetylation of 100 mg amide-diol (Vf) by usual acetic anhydride–pyridine technique (overnight at room temp) was followed by extraction and chromatography over 3 g neutral alumina. Elution with benzene–chloroform (1–1) yielded the diacetate-amide (Vc), which after recrystallization from methanol showed: m.p. 201–204°. This compound was found identical, by mixed m.p. and direct comparison of the IR spectra, with the diacetate-amide (Vc) prepared directly from the acid (Va) (see below).

16β-Carboxy-Δ⁵-pregnene-3β-ol-20-one (IXa)

To 15 g 16α-cyano-Δ⁵-pregnene-3β-ol-20-one (I)[4] in 2 l. methanol was added a solution of 10 g potassium hydroxide in 20 ml water, and the mixture refluxed for 1 hr. About half of the solvent was then distilled, and water added. The unreacted starting material (I), which precipitated, was filtered off (3·45 g, m.p. 226–229°). The clear filtrate was then neutralized with 20% hydrochloric acid solution. The precipitate which formed was filtered off, washed with water to neutrality and recrystallization from a large volume of methanol gave first the less soluble, high melting acid (IXa): m.p. 247–249° (dec., 1·25 g). By further recrystallization in methanol, the *16β-carboxy-Δ⁵-pregnene-3β-ol-20-one* (IXa) was obtained: m.p. 249–251° (dec.); $[\alpha]_D$ −6° (*c*, 1; pyridine). IR λ_{max}^{KBr} 3·17 μ (OH), 3·8 μ (OH, bonded), 5·88 μ (20-ketone, 16-carboxyl). (Found: C, 72·92; H, 8·96. $C_{22}H_{32}O_4$ requires: C, 73·30; H, 8·95%). From the mother liquors there was obtained 6·30 g acid (IIa), m.p. 218–221°, which by further recrystallization gave a pure sample m.p. 231–234°; $[\alpha]_D$ −107° (methanol). This did not give any depression in mixed m.p. with an authentic sample of the acid (IIa);[4] the IR spectra were also superimposable.

Alkaline treatment of acid (IXa)

The above acid (IXa; 80 mg) was dissolved in 8 ml ethanol and the solution refluxed for 1 hr with 150 mg potassium hydroxide in 1 ml water. Water was then added followed by excess of 20% hydrochloric acid. The precipitate which formed was washed with water. Further recrystallization from acetone–ether gave 40 mg acid (IIa), m.p. 234–235°, which was identical with an authentic sample[4] by mixed m.p., IR comparison and rotatory dispersion showing a negative Cotton effect.[7]

16β-Carbomethoxy-Δ⁵-pregnene-3β-ol-20-one (IXb)

To a suspension of 200 mg acid (IXa) in 30 ml methanol, 60 ml ethereal diazomethane solution (prepared from 2 g N-nitrosomethylurea) were added. The acid (XIa) slowly went into solution and the reaction mixture was allowed to stand overnight at room temp. One drop of acetic acid was then added to destroy the excess of diazomethane and the solution was evaporated to dryness. Crystallization of the residue in acetone–hexane afforded 185 mg prismatic crystals: m.p. 175–177°. Further crystallization from acetone–ether provided *16β-carbomethoxy-Δ⁵-pregnene-3β-ol-20-one* (IXb): m.p. 180°; $[\alpha]_D$ +53° (*c*, 0·45; methanol). IR λ_{max}^{KBr} 2·97 μ (OH), 5·75 μ (ester), 5·88 μ (20-ketone). (Found: C, 73·71; H, 9·01. $C_{23}H_{34}O_4$ requires: C, 73·76; H, 9·15%).

16β-Carbomethoxy-Δ⁵-pregnene-3β-ol-20-one-3-acetate (IXc)

To a solution of 80 mg ester (IXb) in 0·5 ml anhydrous pyridine, 0·5 ml freshly distilled acetic anhydride was added. The reaction mixture was heated on the steam-bath for 1 hr. Water was then added and the precipitate was washed with water. Recrystallization from acetone–hexane yielded 75 mg m.p. 186–188°. Further crystallization from acetone–hexane afforded *16β-carbomethoxy-Δ⁵-pregnene-3β-ol-20-one-3-acetate* (IXc): m.p. 188–190°; $[\alpha]_D$ +34° (*c*, 0·4; methanol). IR λ_{max}^{KBr} 5·75 μ (s)[35] and 8·06 μ (acetate and ester). (Found: C, 72·06; H, 8·66; O, 19·33. $C_{25}H_{36}O_5$ requires: C, 72·08; H, 8·71; O, 19·21%).

[35] The symbols (s), (m) and (w) refer to absorption intensity, respectively: strong, medium and weak. *Cf.* ref. 19*d*, p. 3.

Reduction of the acid (IXa) *to the lactone* (IVa)

A solution of 135 mg acid (IXa) in 30 ml tetrahydrofuran was added to a mixture of 135 mg sodium borohydride in 1 ml water and refluxed for 2 hr. Water was added (40 ml) and excess 20% hydrochloric acid. The precipitate was extracted with chloroform, washed with water and dried ($NaSO_4$). The solvent was evaporated under red. press. The product was crystallized from methanol, affording 85 mg 16β-*carboxy*-Δ^5-*pregnene*-3β,20β-*diol*-16,20-*lactone* (IVa): m.p. 241–243°; $[\alpha]_D$ −35° (*c*, 1; methanol). IR λ_{max}^{KBr} 2·98 μ (OH), 5·64 μ (γ-lactone). This compound did not give any depression in mixed m.p. with an authentic sample of the lactone (IVa).[6] The IR spectra were also identical.

Acetylation of the above lactone furnished the corresponding 3β-acetate (IVb), m.p. 236–238° identical, in mixed m.p. and IR comparison, with an authentic sample of the acetoxy-lactone (IVb).[6]

Reduction of the ester (IXb) *to the triol* (XIa)

Powdered lithium aluminum hydride (200 mg) was added to a solution of 170 mg IXb in 30 ml anhydrous tetrahydrofuran and the mixture refluxed for 3 hr. The excess lithium aluminum hydride was carefully destroyed by dropwise addition of ethyl acetate at 0°. Water was then added and finally 20% hydrochloric acid solution. The crystalline material which precipitated was washed with water. Further crystallization from methanol gave 80 mg triol (XIa): m.p. 255–265° (dec.). IR λ_{max}^{KBr} 3·08 μ (s) (OH). A mixed m.p. determination with the triol (XIa) obtained directly from the lactone (IVa) (*vide infra*), did not give any depression; the IR spectra were identical.

Acetylation of the above obtained triol (XIa; 40 mg) by usual procedure (0·5 ml acetic anhydride, 0·5 ml pyridine, 1 hr at 80°) yielded the corresponding triacetate (XIb; 35 mg) m.p. 163–165°, identical, in mixed m.p. and IR spectra comparison, with an authentic sample of this triacetate (XIb).

16β-*Carbomethoxy-progesterone* (X)

The ester (IXb; 170 mg) was dissolved in 30 ml anhydrous toluene and 10 ml of this solvent were then removed by distillation to eliminate moisture. To this solution, 4 ml cyclohexanone and then 100 mg aluminum isopropoxide in 5 ml toluene were added and the mixture refluxed for 45 min. After cooling, ether was added and then 5% hydrochloric acid solution, and finally water. Steam distillation was then performed in order to eliminate the solvents. The residue was dissolved in chloroform and dried (Na_2SO_4). The solvent was distilled under red. press. and the compound obtained crystallized from acetone–ether: m.p. 160–162° (110 mg). Two further recrystallizations from acetone–ether gave 16β-*carbomethoxy-progesterone* (X): m.p. 169–171°; $[\alpha]_D$ +136° (*c*, 0·55; methanol).[36] UV λ_{max}^{EtOH} 240 mμ (log ε 4·24). IR λ_{max}^{KBr} 5·80 μ (ester), 5·88 μ (20-ketone), 6·03 and 6·20 μ (Δ^4-3-ketone). (Found: C, 74·34; H, 8·57; O, 17·28. $C_{23}H_{32}O_4$ requires: C, 74·16; H, 8·66; O, 17·18%).

Alkaline hydrolysis of 16β-*carbomethoxy-progesterone* (X) *to* 16β-*carboxy-isoprogesterone* (VIIIb)

The progesterone (X; 80 mg) was refluxed for 30 min in 10 ml methanol containing 100 mg potassium hydroxide. Addition of water and 10% hydrochloric acid solution to the cooled reaction mixture provided, after extraction followed by one crystallization from acetone–ether, 45 mg 16β-*carboxy*-17α-(*iso*)-*progesterone* (VIIIb), m.p. 243–246°, which did not give any depression in mixed m.p. with an authentic sample of VIIIb.[4] Furthermore, the IR spectra and rotatory dispersion curves[7] were identical.

16β-*Carbox*-(N,N-*diethylethylenediamine*)-*amido*-Δ^5-*pregnene*-3β-*ol*-20-*one* 3-*acetate methyl iodide* (IXd)

Freshly distilled N,N-diethylethylenediamine (5 g) was added dropwise, at 0°, to a solution of 2·5 g acid chloride of acid (IIb; prepared by reaction of IIb with thionyl chloride, see later) in 35 ml anhydrous benzene. The reaction mixture was left for 192 hr at room temp, and was then extracted with ether. The ethereal layer was washed with water, dried (Na_2SO_4) and evaporated *in vacuo* to afford a crude product which was filtered through alumina. Elution with benzene–ether (95–5) gave 1·29 g amorphous material. This was dissolved in 12 ml anhydrous benzene and treated dropwise with 12 ml methyl iodide. The precipitate which formed slowly, was collected after 30 days, washed

[36] The earlier reported[36a] rotation $[\alpha]_D$ −20° was a printing error.

and dried: m.p. 256–257°. After four recrystallizations from acetone, (570 mg) of *16β-carbox-(N,N-diethylethylenediamine)-amido-Δ⁵-pregnene-3β-ol-20-one 3-acetate methyl iodide* (IXd) was obtained: m.p. 263–266°; $[\alpha]_D$ −5° (*c*, 1; chloroform). IR λ_{max}^{KBr} 3·1 μ (NH), 5·78 μ and 8·01 μ (acetate), 5·89 μ (20-ketone), 5·99 μ (amide). (Found: C, 57·33; H, 7·95; O, 9·88; N, 4·60; I, 20·39. $C_{31}H_{51}O_4N_2I$ requires: C, 57·93; H, 8·00; O, 9·98; N, 4·36; I, 19·74%).

Alkaline treatment of acid (IIa)

The acid (IIa[4]; 850 mg was refluxed for 6 hr in 20 ml ethylene glycol containing 1 g potassium hydroxide in 2 ml water. After extraction procedure there were obtained 550 mg acid, m.p. 225–227°. Recrystallization from methanol–ether gave 450 mg m.p. 230–233°; $[\alpha]_D$ −115° (*c*, 1; methanol), which was identical with the acid (IIa), as shown by mixed m.p. and IR spectra comparison.

Methylation of 450 mg acid (IIa) in 15 ml methanol with an ethereal solution of diazomethane (obtained from 4 g N-nitrosomethylurea), for 2 hr at room temp, followed by addition of one drop of acetic acid and evaporation *in vacuo*, furnished 420 mg *16β-carbomethoxy-17α-(iso)-Δ⁵-pregnene-3β-ol-20-one* (IIc). Recrystallization from ether–methanol yielded a pure IIc[4], m.p. 205–207°; $[\alpha]_D$ −115° (*c*, 1; chloroform). IR λ_{max}^{KBr} 3 μ (OH), 3·8 μ (OH, bonded), 5·88 μ (20-ketone), 5·93 μ (carboxyl), and 6·05 μ (w). This compound was identical (mixed m.p. and IR spectra) with an authentic sample[4].

The corresponding acetate (IId), prepared by the usual acetic anhydride–pyridine technique gave, after recrystallization from acetone–hexane, pure *16β-carbomethoxy-17α-(iso)-Δ⁵-pregnene-3β-ol-20-one 3-acetate* (IId), m.p. 155–157°; $[\alpha]_D$ −105° (*c*, 1; chloroform). IR $\lambda_{max}^{CHCl_3}$ 5·73 and 8·03 μ (acetate), 5·78 μ (ester) and 5·85 μ (20-ketone).

16β-Carboxy-17α-(iso)-Δ⁵-pregnene-3β-ol-20-one 3-acetate (IIb)

To a solution of 2·3 g acid (IIa)[4] in 10 ml anhydrous pyridine, 4 ml freshly distilled acetic anhydride were added and the reaction mixture allowed to stand overnight at room temp. Water was then added and the product extracted with ether. The ethereal fraction was washed first with 10% hydrochloric acid, then with water and evaporated *in vacuo*. The crude product was recrystallized from methylene chloride–acetone to yield 2·11 g acetate (IIb), m.p. 190–192°. Three further recrystallizations gave *16β-carboxy-17α-(iso)-Δ⁵-pregnene-3β-ol-20-one 3-acetate* (IIb), m.p. 208–210°; $[\alpha]_D$ −95° (*c*, 0·5; chloroform). IR λ_{max}^{KBr} 2·93 μ (OH), 5·78 μ and 8 μ (acetate), 5·85 μ (s) (carbonyl and carboxyl). (Found: C, 71·31; H, 8·69; O, 19·76. $C_{34}H_{54}O_5$ requires: C, 71·61; H, 8·51; O, 19·88%).

16β-Carbox-(N-diethyl)-amido-17α-(iso)-Δ⁵-pregnene-3β-ol-20-one 3-acetate (IIg)

To a solution of 1 g acetate (IIb) dissolved in 30 ml anhydrous benzene, 0·88 g freshly distilled thionyl chloride were slowly added at 0°. This solution was then heated under reflux for 2 hr and the excess of thionyl chloride distilled off and the solution evaporated to dryness *in vacuo*. 30 ml anhydrous benzene were added to the acid chloride of (IIb) and then 5 ml freshly distilled diethylamine were added, dropwise, at 0°. The reaction mixture was allowed to stand at room temp for 60 hr. A sodium bicarbonate solution was then added and the organic material extracted with ether. The organic layer was washed with water to neutrality, then dried (Na_2SO_4), filtered and evaporated *in vacuo*. The resulting crude material (795 mg) showed m.p. 132–134°. Further recrystallization from methanol–water furnished *16β-carbox-(N-diethyl)-amido-17α-(iso)-Δ⁵-pregnene-3β-ol-20-one 3-acetate* (IIg); m.p. 134–136°; $[\alpha]_D$ −72° (*c*, 0·7; chloroform). UV λ_{max}^{EtOH} 284–286 mμ (log ε 1·73). IR λ_{max}^{KBr} 5·74 μ and 8 μ (acetate), 5·84 μ (20-ketone), 6·09 μ (amide). (Found: C, 73·30; H, 9·50; O, 14·00; N, 3·27. $C_{36}H_{55}O_4N$ requires: C, 73·48; H, 9·47; O, 13·99; N, 3·06%).

16β-Carboxamido-17α-(iso)-Δ⁵-pregnene-3β-ol-20-one 3-acetate (IIe)

To a solution of 2 g acid chloride of IIb in 30 ml anhydrous benzene, 50 ml ammonium hydroxide were added with stirring at 0°. The reaction mixture was allowed to stand overnight at room temp. The precipitate was filtered off and washed with water. Recrystallization of this compound from ethyl alcohol–water gave 1·37 g (IIe), m.p. 199–203°. The *16β-carboxamido-17α-(iso)-Δ⁵-pregnene-3β-ol-20-one 3-acetate* (IIe), was obtained by further recrystallization from methanol–water, as long prismatic needles, m.p. 210–212°; $[\alpha]_D$ −110° (*c*, 1; chloroform). UV λ_{max}^{EtOH} 284–286 mμ (log ε 1·60). IR λ_{max}^{KBr} 2·94, 3·03 and 3·14 μ (NH_2 free and bonded), 5·77 and 8 μ (acetate), 5·85 μ (20-ketone), 5·97 and 6·17 μ (amide). (Found: C, 71·43; H, 8·84; O, 15·91; N, 3·56. $C_{34}H_{53}O_4N$ requires: C, 71·79; H, 8·79; O, 15·94; N, 3·49%).

16β-Carboxamido-17α-(iso)-Δ⁵-pregnene-3β-ol-20-one (IIf)

The acetate–amide (IIe; 500 mg) was dissolved in 31 ml methanol and a solution of 315 mg potassium bicarbonate in 0·5 ml water added and the reaction mixture refluxed for 1 hr. Then it was poured into water, the precipitate was filtered off and washed with water and dried, m.p. 215–220°. After two recrystallizations from acetone, 330 mg were obtained, m.p. 250–257°. One further recrystallization from acetone furnished *16β-carboxamido-17α-(iso)-Δ⁵-pregnene-3β-ol-20-one* (IIf); m.p. 266–268° (dec.); $[\alpha]_D$ −87° (*c*, 1; methanol). IR λ_{max}^{KBr} 2·94, 3·0, 3·08 and 3·2 μ (OH, NH_2, free and bonded), 5·88 μ (20-ketone), 5·98 μ and 6·17 μ (amide). (Found: C, 72·79; H, 9·16; O, 13·60; N, 3·75. $C_{22}H_{33}O_3N$ requires: C, 73·50; H, 9·25; O, 13·35; N, 3·90%).

16β-Carbox-(N,N-diethylethylenediamine)-amido-17α-(iso)-Δ⁵-pregnene-3β-ol-20-one 3-acetate methyl iodide (IIh)

Freshly distilled N,N-diethylethylenediamine (3 g) was added dropwise, at 0°, to a solution of 2 g acid chloride of IIb in 30 ml anhydrous benzene. The reaction mixture was allowed to stand 60 hr at room temp. Further treatment, as for the amide (IXd) followed by reaction with methyl iodide, yielded crystalline material which was filtered after 23 days, washed and dried. Several recrystallizations from acetone yielded *16β-carbox-(N,N-diethylethylenediamine)-amido-17α-(iso)-Δ⁵-pregnene-3β-ol-20-one 3-acetate methyl iodide* (IIh; 50 mg): m.p. 202–204°; $[\alpha]_D$ −90° (*c*, 0·2; methanol). IR λ_{max}^{KBr} 2·95 μ (NH), 5·78 μ and 8·03 μ (acetate), 5·88 μ (w) (20-ketone), 6·01 μ (amide). (Found: C, 58·38; H, 8·15; O, 10·27; N, 4·49; I, 18·71. $C_{31}H_{51}O_4N_2I$ requires: C, 57·93; H, 8·00; O, 9·98; N, 4·36; I, 19·74%).

16α-Cyano-Δ⁵-pregnene-3,20-dione

A mixture of 1 g adduct (I)[4] in 40 ml acetone (distilled over potassium permanganate) was treated, under nitrogen, at 0°, with 2 ml 8N chromic acid solution[37] and the mixture stirred for 1 additional min at 0°. Then water was added and an excess of a 10% sodium carbonate solution. Further extraction with chloroform followed by washing and drying (Na_2SO_4) affordedt he crude product, m.p. 172–175°. By further recrystallization from methylene chloride–methanol, *16α-cyano-Δ⁵-pregnene-3,20-dione* was obtained, as prisms; m.p. 186–188°; $[\alpha]_D$ +43° (*c*, 1; chloroform). UV λ_{max}^{EtOH} 288 mμ (log ε 1·90). IR λ_{max}^{KBr} 4·48 μ (C≡N), 5·85 μ (s) (3- and 20-ketone). (Found: C, 77·62; H, 8·54; O, 9·65; N, 4·20. $C_{22}H_{29}O_2N$ requires: C, 77·84; H, 8·61; O, 9·43; N, 4·13%).

Mild alkaline treatment of this unsaturated ketone provided the corresponding *16α-cyano-progesterone*,[4] as long needles: m.p. 232–234°; $[\alpha]_D$ +135° (*c*, 1; chloroform). UV λ_{max}^{EtOH} 240 mμ (log ε 4·18). IR λ_{max}^{KBr} 4·42 μ (C≡N), 5·82 μ (20-ketone), 5·95 μ and 6·16 μ (Δ⁴-3-ketone). (Found: C, 77·78; H, 8·68; $C_{22}H_{29}O_2N$ requires: C, 77·84; H, 8·61%).

16β-Carbomethoxy-17α-(iso)-progesterone (VIIIa)

This compound was prepared according to an earlier procedure[4] and exhibited m.p. 155–157°; $[\alpha]_D$ +18° (*c*, 0·35; chloroform) and $[\alpha]_D$ +11° (*c*, 1; methanol). UV λ_{max}^{EtOH} 240 mμ (log ε 4·25). IR λ_{max}^{KBr} 5·78 μ (ester), 5·85 μ (20-ketone), 5·99 and 6·18 μ (Δ⁴-3-ketone).

16β-Carboxy-17α-(iso)-progesterone (VIIIb)

Alkaline hydrolysis of the above ester (VIIIa) afforded the known acid:[4] m.p. 249–251°; $[\alpha]_D$ +15° (*c*, 0·5; chloroform). UV λ_{max}^{EtOH} 241 mμ (log ε 4·21). IR λ_{max}^{KBr} 2·9 and 3·6 μ (OH, free and bonded), 5·86 μ (20-ketone), 5·95 and 6·07 μ (Δ⁴-3-ketone).

16β-Carboxamido-17α-(iso)-progesterone (VIIIc)

To a solution of 2·4 g 16β-carboxy-isoprogesterone (VIIIb) in 360 ml ethyl alcohol were added dropwise 67·5 ml 0·1N NaOH until neutrality. This solution was then evaporated *in vacuo* and dried at 110° for 17 hr.[16] After cooling, 50 ml anhydrous benzene were added and then 25 drops anhydrous pyridine. The reaction flask was cooled to 0° and 10 ml oxalyl chloride were added with stirring. The reaction was then stirred for 3·5 hr at room temp and the solution evaporated to dryness, *in vacuo*, below 15°. To the residual acid chloride 60 ml anhydrous benzene were added. Then to this solution, cooled at 0°, 80 ml ammonia were carefully added. The reaction mixture was kept for 3 hr at 0°

[37] K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.* **39** (1946); see also C. Djerassi, R. R. Engle and A. Bowers, *J. Org. Chem.* **21**, 1547 (1956).

under stirring and then left overnight at room temp. Water was added, then ethyl acetate and the solution extracted. The organic layer was washed with water, dried (Na_2SO_4) and the solvents evaporated *in vacuo*. The crude neutral product (800 mg) was then chromatographed over 15 g silica gel (B.D.H. Laboratory, England). Elution of the column with chloroform–methanol (97–3) afforded 450 mg crystalline material, m.p. 233–241°. Three recrystallizations from methanol–water gave 16*β-carboxamido*-17α-(*iso*)-*progesterone* (VIIIc), as long fine needles, m.p. 259–261; $[\alpha]_D$ +12° (*c*, 0·5; chloroform). UV λ_{max}^{EtOH} 240 μ (log ε 4·22). IR λ_{max}^{KBr} 2·98 μ and 3·07 μ (NH_2), 5·9 μ (20-ketone), 5·95 μ (amide), 6·01 and 6·19 μ (Δ^4-3-ketone). Found: C, 73·43; H, 8·74; N, 4·09; $C_{22}H_{31}O_3N$ requires: C, 73·91; H, 8·74; N, 3·92%).

16*β-Hydroxymethyl*-17α-(*iso*)-Δ^5-*pregnene*-3*β*,20*β-diol* (XVIa)

16*β*-Carbomethoxy-17α-(iso)-Δ^5-pregnene-3*β*,20*β*-diol (VIId,[4] 1 g) reduced with lithium aluminum hydride in tetrahydrofuran, following the technique described below, and after crystallization from methanol yielded 420 mg triol (XVIa), m.p. 262–264°. The analytical sample (from methanol) of 16*β-hydroxymethyl*-17α-(*iso*)-Δ^5-*pregnene*-3*β*,20*β-diol* (XVIa), crystallized as small prisms: m.p. 265–266°; $[\alpha]_D$ −76° (*c*, 0·45; pyridine). IR λ_{max}^{KBr} 3·1 μ (s) (OH). (Found: C, 75·99; H, 10·09; O, 13·58. $C_{22}H_{36}O_3$ requires: C, 75·81; H, 10·41; O, 13·77%).

Acetylation (acetic anhydride–pyridine) afforded 16*β-hydroxymethyl*-17α-(*iso*)-Δ^5-*pregnene*-3*β*,20*β-diol* 3,16,20-*triacetate* (XVIb) as an amorphous material, after chromatography and sublimation *in vacuo* (0·1 mm Hg) at 120°: m.p. 45–50°; $[\alpha]_D$ −45° (*c*, 0·6; chloroform). IR $\lambda_{max}^{CHCl_3}$ 5·78 μ and 7·99 μ (s) (acetate). (Found: C, 70·99; H, 8·76; O, 20·02. $C_{28}H_{42}O_6$ requires: C, 70·85; H, 8·92; O, 20·23%).

16*β-Carboxy*-Δ^5-*pregnene*-3*β*,20*β-diol*-16,20-*lactone* (IVa)

A mixture of 5 g cyano-diol (III),[6] 6 g potassium hydroxide and 150 ml ethyleneglycol containing 6 ml water was heated under reflux for 1–3/4 hr. After cooling and acidification with dil hydrochloric acid (10%), a white precipitate formed which was recrystallized from methanol to yield 4·5 g lactone (IVa), m.p. 238–240° undepressed upon admixture with an authentic sample of IVa.[6] Identity was also confirmed by IR spectral comparison.

16α-*Carboxy*-Δ^5-*pregnene*-3*β*,20*β-diol* (Va)

The lactone (IVa; 450 mg) was dissolved in 20 ml ethyleneglycol and 450 mg potassium hydroxide in 2 ml water added. The mixture was refluxed for 30 hr, cooled, water added and then 10% hydrochloric acid to acidic pH. The acid precipitated. Extraction with ethyl acetate, followed by washing with water, drying (Na_2SO_4) and evaporation under red. press., gave a crystalline substance which recrystallized from methanol to afford 16α-*carboxy*-Δ^5-*pregnene*-3*β*,20*β-diol* (Va; 320 mg): m.p. 289–293°; $[\alpha]_D$ −77° (*c*, 0·5; dioxane). IR λ_{max}^{KBr} 2·95 μ (OH), 5·84 μ (carboxyl). These physical constants are in agreement with the data published by Mazur and Cella.[6] The diacetate (Vb) has also been reported by these authors.

16α-*Carbomethoxy*-Δ^5-*pregnene*-3*β*,20*β-diol* (Vd)

A 500 ml ethereal diazomethane solution (obtained from 12 g N-nitrosomethylurea) was added, at room temp, to a solution of 7 g acid (Va) in 30 ml methanol. The reaction mixture was then allowed to stand 5 hr at room temp. A few drops of acetic acid were then added to destroy the excess diazomethane and the solution concentrated *in vacuo*. After recrystallization from methanol 6·15 g 16α-*carbomethoxy*-Δ^5-*pregnene*-3*β*,20*β-diol* (Vd) resulted: m.p. 178–179°. Further recrystallizations from methanol yielded the analytical sample: m.p. 180–182°; $[\alpha]_D$ −75° (*c*, 0·2; chloroform). IR $\lambda_{max}^{CHCl_3}$ 2·97 μ (OH), 5·81 μ (ester). (Found: C, 72·94; H, 9·54; $C_{23}H_{36}O_4$ requires: C, 73·36; H, 9·64%).

16α-*Carbomethoxy*-Δ^5-*pregnene*-3*β*,20*β-diol- diacetate* (Ve)

Acetylation of the ester-diol (Vd) with acetic anhydride, in pyridine, for 1 hr on the steam-bath, gave the diacetate-ester (Ve). Recrystallization from acetone–methanol provided 16α-*carbomethoxy*-Δ^5-*pregnene*-3*β*,20*β-diol diacetate* (Ve): m.p. 187–189°; $[\alpha]_D$ −65° (*c*, 0·2; chloroform). IR λ_{max}^{KBr} 5·78 μ and 8·02 μ (acetate), 5·81 μ (ester). (Found: C, 69·96; H, 8·76. $C_{27}H_{40}O_6$ requires: C, 70·40; H, 8·75%).

16α-Carboxamido-Δ⁵-pregnene-3β,20β-diol diacetate (Vc)

To a solution of 1·2 g diacetate (Vb)[6] in 25 ml anhydrous benzene, 2 ml freshly distilled thionyl chloride were added and the mixture refluxed for 2 hr and the solution then evaporated to dryness *in vacuo*. The residue was dissolved in 30 ml benzene and a stream of gaseous ammonia passed through for 5 min. The reaction mixture was then allowed to stand overnight at room temp. The solvents were eliminated by steam distillation and the amide (Vc) precipitated. The crystalline material was washed with water and dried. Further recrystallization from methanol gave 760 mg prismatic needles, m.p. 203°. The *16α-carboxamido-Δ⁵-pregnene-3β,20β-diol diacetate* (Vc), had: m.p. 203–204°; $[\alpha]_D$ −56° (*c*, 1; chloroform). IR λ_{max}^{KBr} 2·8, 3·0 and 3·15 μ (NH_2 free and bonded), 5·78 μ and 8 μ (s) (acetate), 6·0 μ and 6·1 μ (amide). (Found: C, 70·35; H, 8·84; O, 18·18; N, 3·04. $C_{26}H_{39}O_5N$ requires: C, 70·08; H, 8·82; O, 17·95; N, 3·14%).

16α-Aminomethyl-Δ⁵-pregnene-3β,20β-diol (VIa)

(a) *From 16α-cyano-Δ⁵-pregnene-3β-ol-20-one* (I). A solution of 2·5 g cyano adduct (I)[4] in 280 ml anhydrous tetrahydrofuran was refluxed with 1·8 g lithium aluminum hydride, for 10 hr, then 5 ml ethyl alcohol were added dropwise to the ice-cooled reaction mixture, and then 5 ml water. The solution was then dried (Na_2SO_4) and, after filtration, the volume concentrated under red. press. The residue was crystallized from ether and 1·89 g material, m.p. 240°, obtained. Several recrystallizations from methanol provided *16α-aminomethyl-Δ⁵-pregnene-3β,20β-diol* (VIa), as small prisms: m.p. 248–250°; $[\alpha]_D$ −83° (*c*, 0·3; ethanol). IR λ_{max}^{KBr} 3·0, 3·05 and 3·12 μ (OH and NH_2, free and bonded), 6·25 μ (NH_2). (Found: C, 75·83; H, 10·69; N, 4·27. $C_{22}H_{37}O_2N$ requires: C, 76·03; H, 10·73; N, 4·03%).

(b) *From 16α-carboxamido-Δ⁵-pregnene-3β,20β-diol diacetate* (Vc). The diacetyl-amide (Vc; 1·5 g) was dissolved in 200 ml anhydrous tetrahydrofuran and 1·5 g lithium aluminum hydride was added and the mixture refluxed for 18 hr. The reaction flask was ice-cooled and 20 ml ethyl acetate added dropwise to destroy the excess reagent. Water was added (10 ml) and after stirring the reaction mixture was filtered. The clear filtrate was dried (Na_2SO_4) and evaporated. The semi-solid residue was crystallized from methanol–ether affording 320 mg small prisms, m.p. 248–250°. This compound was identical, by mixed m.p. and direct comparison of IR spectra, with the amine obtained in (a).

16α-Aminomethyl-Δ⁵-pregnene-3β,20β-diol 3,20-*diacetate* 16-*acetamide* (VIb)

Treatment of VIa with acetic anhydride in pyridine, 1 hr on the steam bath, gave the *16α-aminomethyl-Δ⁵-pregnene-3β,20β-diol* 3,20-*diacetate* 16-*acetamide* (VIb); m.p. 183–186°; $[\alpha]_D$ −67° (*c*, 1; chloroform). IR λ_{max}^{KBr} 3·08 μ and 3·17 μ (NH, bonded), 5·78 μ, 6·09 μ and 8·05 μ (acetate, amide). (Found: C, 70·65; H, 8·92; N, 2·95. $C_{28}H_{43}O_5N$ requires: C, 71·00; H, 9·15; N, 2·96%). The same compound (VIb) was obtained from the amine (VIa) prepared either as in (a) or as in (b) above.

16α-Hydroxymethyl-Δ⁵-pregnene-3β,20β-diol (XVIIa)

The ester-diol (Vd; 1 g) was reduced by lithium aluminum hydride in tetrahydrofuran. After isolation of the compound, recrystallization from methanol gave 480 mg, m.p. 227–229°. The *16α-hydroxymethyl-Δ⁵-pregnene-3β,20β-diol* (XVIIa), was obtained as small prisms, m.p. 231–234°; $[\alpha]_D$ −86° (*c*, 0·4; dioxane) and $[\alpha]_D$ −72° (*c*, 0·3; ethanol). IR λ_{max}^{KBr} 3·07 μ (s) (OH). (Found: C, 75·53; H, 10·39; $C_{22}H_{36}O_3$ requires: C, 75·81; H, 10·41%).

Acetylation of XVIIa by the acetic anhydride-pyridine procedure, 1 hr on the steam bath, gave the *16α-hydroxymethyl-Δ⁵-pregnene-3β,20β-diol* 3,16,20-*triacetate* (XVIIb), m.p. 166–168°, $[\alpha]_D$ −69° (*c*, 0·9; chloroform). IR λ_{max}^{KBr} 5·78 μ and 8·05 μ (s) (acetate). (Found: C, 70·68; H, 8·90; $C_{28}H_{42}O_6$ requires: C, 70·85; H, 8·92%).

16α-Carbomethoxy-progesterone (XIIa)

From a solution of 3 g 16α-carbomethoxy-Δ⁵-pregnene-3β,20β-diol (Vd) in 130 ml anhydrous toluene, 15 ml were distilled to eliminate moisture. 35 ml freshly distilled cyclohexanone were added and then a solution of 1 g aluminum isopropoxide in 20 ml anhydrous toluene. The reaction mixture was refluxed for 1 hr. After cooling to room temp the organic layer was washed with a 5% hydrochloric acid solution and with water to neutrality. The solvents were then eliminated by steam distillation and the oily residue extracted with chloroform. This extract was then washed with water, dried (Na_2SO_4) and evaporated *in vacuo*. The oily residue (3·12 g) was dissolved in 35 ml acetic acid.

The mixture was then cooled in an ice-bath and a solution of 2 g chromic anhydride in 4 ml water and 16 ml acetic acid added, with stirring, over a period of 20 min. After the addition, the mixture was allowed to stand at 15° for 1 additional hr. The reaction mixture was then poured into 200 ml ice-water. Extraction with ether, followed by washing with water, then with 5% sodium carbonate and again with water, drying (Na_2SO_4) and evaporation gave crude XIIa. Recrystallization from acetone–hexane yielded 1·06 g crystalline material, m.p. 141–143°. Further recrystallization from acetone–hexane gave the 16α-*carbomethoxy-progesterone* (XIIa), as large prisms: m.p. 148–150°; $[\alpha]_D$ +136° (*c*, 1; chloroform). UV λ_{max}^{EtOH} 240 mμ (log ε 4·25). IR λ_{max}^{KBr} 5·82 μ (ester), 5·89 μ (20-ketone), 6·04 and 6·21 μ (Δ⁴-3-ketone). (Found: C, 74·22; H, 8·32; O, 17·14. $C_{23}H_{32}O_4$ requires: C, 74·16; H, 8·66; O, 17·18%).

16α-*Carboxy-progesterone* (XIIb)

To 20 ml methanol containing 500 mg 16α-carbomethoxy-progesterone (XIIa), 500 mg potassium hydroxide in 2 ml water were added. This mixture was refluxed for 1/2 hr and then neutralized with acetic acid. The volume was reduced *in vacuo*, then diluted with water and extracted with chloroform, washed with water, dried (Na_2SO_4) and evaporated under red. press. The residue was recrystallized from ether to furnish 380 mg prismatic crystals, m.p. 175–178°. Recrystallization from acetone–ether provided 16α-*carboxy-progesterone* (XIIb): m.p. 182–184°; $[\alpha]_D$ +129° (*c*, 0·75; methanol). UV λ_{max}^{EtOH} 240 mμ (log ε 4·22). IR λ_{max}^{KBr} 2·98 μ (OH), 5·87 μ (20-ketone), 5·98 μ and 6·15 μ (Δ⁴-3-ketone). (Found: C, 73·82; H, 9·07; O, 17·44. $C_{23}H_{30}O_4$ requires: C, 73·71; H, 8·44; O, 17·85%).

Esterification of XIIb (200 mg) with diazomethane gave 145 mg 16α-carbomethoxy-progesterone (XIIa), m.p. 145–147°, identical, by mixed m.p. and superimposable IR spectra, with the above progesterone (XIIa).

16β-*Carboxy*-(5αH)-*pregnane*-3β,20β-*diol*-16,20-*lactone* 3-*acetate* (XXb)

The lactone (IVb; 190 mg) was dissolved in 30 ml ethyl acetate. This solution was then stirred under hydrogen atmosphere in presence of 50 mg previously reduced platinum oxide in 10 ml ethyl acetate. The hydrogen up-take was stopped after 15 ml were absorbed and the catalyst filtered off. The ethyl acetate was removed by vacuum distillation affording the crude lactone (XXb): m.p. 197–200° (160 mg). This compound was chromatographed onto 10 g neutral alumina and eluted with hexane–benzene (85–15). Recrystallization from chloroform–hexane yielded 16β-*carboxy*-(5αH)-*pregnane*-3β,20β-*diol*-16,20-*lactone* 3-*acetate* (XXb), as dimorphic crystals: m.p. 208–209°, 258–261°, the transformation of which could be observed readily during m.p. determination; $[\alpha]_D$ +6° (*c*, 1; chloroform). IR λ_{max}^{KBr} 5·66 μ (γ-lactone), 5·75 μ and 7·98 μ (acetate). (Found: C, 74·20; H, 9·18; O, 16·59. $C_{24}H_{36}O_4$ requires: C, 74·19; H, 9·34; O, 16·47%).

16β-*Hydroxymethyl*-Δ⁵-*pregnene*-3β,20β-*diol* (XIa)

The lactone (IVa[6]; 1 g) was dissolved in 100 ml anhydrous tetrahydrofuran and a solution of 1 g lithium aluminum hydride in 20 ml tetrahydrofuran added, with magnetic stirring, over a period of 15 min. The reaction mixture was then allowed to reflux for 1 hr and then 80 ml tetrahydrofuran distilled off, the reaction mixture cooled in an ice-bath, the excess lithium aluminum hydride destroyed with ethyl alcohol, and the mixture poured into 150 ml water. After acidification with a 5% hydrochloric acid solution, the precipitate was filtered off and crystallized from methanol, giving 550 mg, m.p. 245–250° (dec). The 16β-*hydroxymethyl*-Δ⁵-*pregnene*-3β,20β-*diol* (XIa) was obtained by several recrystallizations from methanol as small prisms, m.p. 279–285° (dec); $[\alpha]_D$ −26° (*c*, 0·2; pyridine). IR λ_{max}^{KBr} 3·1 μ (s) (OH). (Found: C, 75·75; H, 10·37; O, 13·87. $C_{22}H_{36}O_2$ requires: C, 75·81; H, 10·41; O, 13·77%).

Acetylation of XIa with acetic anhydride in pyridine, 1 hr on the steam-bath, gave 16β-*hydroxymethyl*-Δ⁵-*pregnene*-3β,20β-*diol* 3,16,20-*triacetate* (XIb) which after recrystallization from acetone–methanol had m.p. 167–168°; $[\alpha]_D$ +4° (*c*, 0·3; methanol). IR $\lambda_{max}^{CHCl_3}$ 5·8 and 8 μ (s) (acetate). (Found: C, 71·24; H, 8·91; O, 20·00. $C_{28}H_{42}O_6$ requires: C, 70·85; H, 8·92; O, 20·23%).

16α-*Carboxy*-17α-(*iso*)-Δ⁵,²⁰-*pregnadiene*-3β,20-*diol* 16,20-*lactone* 3-*acetate* (XIII)

The acid (IIa; 3·5 g) was dissolved in 25 ml anhydrous pyridine and 10 ml freshly distilled acetic anhydride added and heated on the steam-bath for 5 hr and then left overnight at room temp. Ice-water was then added and the solution extracted 3 times with ethyl acetate. The organic layer was

washed with 10% hydrochloric acid, water, sodium bicarbonate solution and finally with water. The organic phase was dried (Na_2SO_4), filtered and the solvent evaporated *in vacuo*. The crude crystalline material, m.p. 200–222° was decolorized with charcoal and after 2 recrystallizations from methylene chloride–methanol 1·6 g m.p. 238–242° was obtained. The 16α-*carboxy*-17α-(*iso*)-$\Delta^{5,20}$-*pregnadiene*-3β,20-*diol* 16,20-*lactone* 3-*acetate* (XIII) was obtained by sublimation under 0·5 mm Hg, ca. 200°: m.p. 241–243° (dec.); $[\alpha]_D$ −67° (*c*, 0·7; chloroform). UV no absorption between 216 mμ and 320 mμ. IR λ_{max}^{KBr} 5·59 μ (γ-lactone), 5·78 μ and 8·02 μ (acetate), 6·0 μ and 11·36 μ (C═CH_2). (Found: C, 74·85; H, 8·39. $C_{24}H_{32}O_4$ requires: C, 74·97; H, 8·39%).

Strong alkaline treatment of the enol lactone (XIII)

To 1 g enol lactone (XIII), dissolved in 25 ml methanol, 2 g potassium hydroxide and 3 ml water were added. This solution was refluxed for 1 hr and then left at room temp overnight. Acidification and then addition of water gave a precipitate which was washed and recrystallized from methanol and water, giving 850 mg of an acid, m.p. 224–226°. By further recrystallizations, IIa was obtained: m.p. 229–231°, identical with the previously described compound[4] (by mixed m.p., IR spectra comparison and same rotatory dispersion curves).

16α-*Carboxy*-17α-(*iso*)-Δ⁵-*pregnene*-3β,20β-*diol*-16,20-*lactone* 3-*acetate* (XVIIIb)

The enol lactone (XIII; 500 mg) was dissolved in 50 ml ethyl acetate. This solution was stirred under hydrogen atmosphere in the presence of 200 mg 10% palladium on carbon until 1 equiv. hydrogen was absorbed. The catalyst was filtered off, the ethyl acetate removed *in vacuo*, affording the crude lactone (XVIIIb), m.p. 180–186° (420 mg). This was then chromatographed over 20 g neutral alumina. Elution with hexane–benzene (60–40) gave a compound, m.p. 200–205°. Recrystallization from methylene chloride–methanol yielded the 16α-*carboxy*-17α-(*iso*)-Δ⁵-*pregnene*-3β,20β-*diol*-16,20-*lactone* 3-*acetate* (XVIIIb): m.p. 231–233°; $[\alpha]_D$ −143° (*c*, 1; chloroform). Tetranitromethane test: positive. IR λ_{max}^{KBr} 5·66 μ (γ-lactone), 5·78 μ and 8·04 μ (acetate). (Found: C, 74·57; H, 8·64; O, 16·57. $C_{24}H_{34}O_4$ requires: C, 74·58; H, 8·87; O, 16·55%).

16α-*Carboxy*-17α-(*iso*)-Δ⁵-*pregnene*-3β,20β-*diol*-16,20-*lactone* (XVIIIa)

The above lactone (XVIIIb; 150 mg) was dissolved in 40 ml methanol containing 300 mg potassium bicarbonate in 5 ml water. This solution was refluxed for 1 hr and was then diluted with water and acidified with 5% hydrochloric acid. After extraction, the crystalline material after evaporation of solvent was recrystallized in acetone–ether to afford 95 mg XVIIIa, m.p. 202–205°. Further recrystallization from acetone–ether provided the 16α-*carboxy*-17α-(*iso*)-Δ⁵-*pregnene*-3β,20β-*diol*-16,20-*lactone* (XVIIIa), as prismatic needles, m.p. 208°; $[\alpha]_D$ −128° (*c*, 0·3; methanol). IR λ_{max}^{KBr} 3 μ (OH), 5·65 μ (γ-lactone). (Found: C, 76·69; H, 9·47; O, 14·08. $C_{22}H_{32}O_5$ requires: C, 76·47; H, 9·76; O, 13·77%).

Reacetylation of 40 mg of XVIIIa with 1 ml acetic anhydride in 1 ml pyridine for 1 hr on the steam bath furnished 35 mg of the original acetate-lactone (XVIIIb), m.p. 224–226° (no depression by mixed m.p. with an authentic sample of XVIIIb).

Alkaline treatment and reacetylation of the lactone (XVIIIb)

The lactone (XVIIIb; 150 mg) was dissolved in 50 ml methanol containing 1 g potassium hydroxide. The mixture was refluxed for 1/2 hr and then left 10 min at room temp. Water was added and the mixture extracted twice with ethyl acetate. The aqueous alkaline solution was acidified with 10% hydrochloric acid and then extracted 3 times with ethyl acetate. The organic layer was washed with water, dried (Na_2SO_4) and evaporated *in vacuo*. The residue was acetylated overnight at room temp, with acetic anhydride–pyridine, to afford crystalline material which was chromatographed over 10 g neutral alumina. Elution with benzene yielded XVIIIb, which when recrystallized from methylene chloride–hexane, m.p. 224–226°. The mixed m.p. with an authentic sample of XVIIIb was undepressed and the IR spectra were superimposable.

16α-*Carboxy*-(5αH)-17α-(*iso*)-*pregnane*-3β,20β-*diol*-16,20-*lactone* 3-*acetate* (XIX)

The enol lactone (XIII; 400 mg) was first hydrogenated with palladium on charcoal in ethyl acetate. The catalyst was filtered off and the filtrate added to a previously reduced solution of 100 mg platinum oxide in 10 ml ethyl acetate. After uptake of 1 equiv. hydrogen the catalyst was filtered off and the filtrate evaporated *in vacuo*. The crude product (m.p. 177–181°) was chromatographed over

15 g alumina. Elution with hexane–benzene (50–50) gave XIX. The 16α-*carboxy*-(5αH)-17α-(*iso*)-*pregnane*-3β,20β-*diol*-16,20-*lactone* 3-*acetate* (XIX) was obtained by recrystallization from chloroform–hexane, m.p. 226–228°; $[\alpha]_D$ −63° (*c*, 0·9; chloroform). IR λ_{max}^{KBr} 5·67 μ (γ-lactone), 5·76 μ and 8·01 μ (acetate). (Found: C, 74·28; H, 9·33; O, 16·60. $C_{24}H_{36}O_4$ requires: C, 74·19; H, 9·34; O, 16·47%).

16α-*Hydroxymethyl*-17α-(*iso*)-Δ⁵-*pregnene*-3β,20α(?)-*diol* (XXIa)

The enol lactone (XIII; 200 mg) was dissolved in 30 ml anhydrous tetrahydrofuran and 400 mg lithium aluminum hydride were added. The reaction mixture was refluxed for 18 hr, the solution cooled, ethyl acetate added dropwise and then water and 5% hydrochloric acid solution added until the solution was acid. Several extractions with ethyl acetate, followed by washing with water, drying (Na_2SO_4) and evaporation *in vacuo* provided 160 mg crude XXIa, m.p. 265–270°. Further recrystallization from methanol gave 16α-*hydroxymethyl*-17α-(*iso*)-Δ⁵-*pregnene*-3β,20α(?)-*diol* (XXIa), as fine needles, m.p. 307–309° (dec.); $[\alpha]_D$ −117° (*c*, 0·5; pyridine). IR λ_{max}^{KBr} 3·1 μ (s) (OH). (Found: C, 76·10; H, 10·29; $C_{22}H_{36}O_3$ requires: C, 75·81; H, 10·41%).

Acetylation of 50 mg of XXIa in acetic anhydride and pyridine at room temp overnight, afforded amorphous material, which could not be crystallized even after chromatography: $[\alpha]_D$ −70° (*c*, 1; chloroform). IR $\lambda_{maxm}^{CHCl_3}$ 5·78 μ and 8 μ (s) (acetate).

16α-*Carboxy*-17α-(*iso*)-Δ⁵-*pregnene*-3β-*ol*-20-*one* 3-*acetate* (XIVb).

Enol lactone (XIII, 100 mg) dissolved in 30 ml dioxane, 70 mg potassium bicarbonate in 10 ml water were added and the solution refluxed for 2 hr. The reaction mixture was cooled and water added, and then 10% hydrochloric solution until acid. The solution was then extracted several times with ethyl acetate. The organic layer was washed with water to neutrality, dried (Na_2SO_4) and evaporated *in vacuo* yielding crude material m.p. 204–208°. The 16α-*carboxy*-17α-(*iso*)-Δ⁵-*pregnene*-3β-*ol*-20-*one* 3-*acetate* (XIVb) was obtained by repeated crystallizations from methanol–water: m.p. 221–224°; $[\alpha]_D$ −121° (*c*, 0·5; methanol). UV λ_{max}^{EtOH} 278–282 mμ (log ε 1·88). IR λ_{max}^{KBr} 2·95 μ (OH), 5·70 μ and 8 μ (acetate), 5·76 μ (carboxy), 5·86 μ (20-ketone). (Found: C, 71·41; H, 8·60; O, 19·63. $C_{24}H_{34}O_5$ requires: C, 71·61; H, 8·51; O, 19·88%).

16α-*Carbomethoxy*-17α-(*iso*)-Δ⁵-*pregnene*-3β-*ol*-20-*one* (XIVa)

To a suspension of 500 mg XIII in 60 ml methanol, a solution of 320 mg potassium bicarbonate in 5 ml water was added. This mixture was heated under reflux for 15 min and the resultant homogeneous solution allowed to stand overnight at room temp. The solution was acidified with acetic acid and concentrated *in vacuo*. Water was added and the precipitate filtered off and chromatographed over 20 g neutral alumina. Elution with benzene yielded 265 mg crude XIVa, m.p. 188–190°. Recrystallization from acetone–hexane provided 16α-*carbomethoxy*-17α-(*iso*)-Δ⁵-*pregnene*-3β-*ol*-20-*one* (XIVa), as long needles: m.p. 192–193°; $[\alpha]_D$ −150° (*c*, 0·8; chloroform). UV λ_{max}^{EtOH} 288 mμ (log ε 1·75). IR λ_{max}^{KBr} 2·86 μ (OH), 5·73 μ (ester), 5·88 μ (20-ketone). (Found: C, 73·58; H, 9·39; OCH_3, 8·28. $C_{23}H_{34}O_4$ requires: C, 73·76; H, 9·15; OCH_3, 8·65%).

Strong alkaline treatnemt of the ester (XIVa)

The ester (XIVa; 250 mg) was refluxed for 1 hr in 10 ml methanol containing 250 mg sodium hydroxide. Water was added and then 20% hydrochloric acid solution until acid. The precipitate was recrystallized from acetone–ether, yielding 170 mg IIa, m.p. 223–228°. Further recrystallization from methanol gave a sample m.p. 232–234° which was identical with an authentic sample of IIa[4]. (Mixed m.p., IR spectra and rotatory dispersion curves superimposable).

16α-*Carbomethoxy*-17α-(*iso*)-Δ⁵-*pregnene*-3β-*ol*-20-*one* 3-*acetate* (XIVc)

(a) *From the ester* (XIVa). A solution of 100 mg of XIVa in 2 ml pyridine was acetylated overnight at room temp with 2 ml acetic anhydride. Water was added and the solution extracted several times with ethyl acetate. The organic layer was washed successively with 10% hydrochloric acid solution, water, 5% sodium carbonate solution and with water. After drying (Na_2SO_4), the solvent was distilled *in vacuo*. The residue was chromatographed over 6 g neutral alumina. Elution with hexane–benzene (70-30) afforded 70 mg m.p. 217–219°. The 16α-*carbomethoxy*-17α-(*iso*)-Δ⁵-*pregnene*-3β-*ol*-20-*one* 3-*acetate* (XIVc) was obtained by recrystallization from acetone–hexane, as plates: m.p. 219–221°, $[\alpha]_D$ −146° (*c*, 1·2; chloroform). UV λ_{max}^{EtOH} 286 mμ (log ε 1·73). IR λ_{max}^{KBr} 5·74 μ,

5·78 μ and 8·06 μ (acetate and ester bands), 5·86 μ (20-ketone). (Found: C, 71·79; H, 8·84; O, 19·27. $C_{25}H_{36}O_5$ requires: C, 72·08; H, 8·71; O, 19·21%).

(b) *From the enol lactone* (XIII). The same acetate-ester (XIVc) was obtained when the enol lactone (XIII; 200 mg) was treated in methanol (25 ml), 10 min at reflux with potassium bicarbonate (120 mg) followed by direct extraction in acid medium and recrystallization, m.p. 218–220°; $[\alpha]_D$ −145° (*c*, 1; chloroform). The mixed m.p. did not give any depression and the IR spectra were identical.

(c) *From the acid* (XIVb). Methylation of XIVb with diazomethane, followed by evaporation of the solvent and chromatography, gave, by elution with hexane–benzene (95-5), a crystalline compound m.p. 215–218°. Recrystallization from methylene chloride–hexane yielded the acetate–ester, m.p. 219–220°. This substance was identical with XIVc obtained previously (mixed m.p. and IR spectra superimposable).

16α-*Carbomethoxy*-17α-(*iso*)-*progesterone* (XV)

A solution of 500 mg XIVa in 80 ml toluene was heated and 15 ml solvent allowed to distill off in order to eliminate moisture. Then 10 ml cyclohexanone and a solution of 300 mg aluminum isopropoxide in 15 ml toluene were added and the mixture refluxed for 45 min. The reaction flask was cooled to room temp, water was added and then 10% hydrochloric acid solution until acid. Usual extraction procedure followed by one crystallization from acetone–ether furnished the isoprogesterone (XV); m.p. 196–197°. Further recrystallization afforded the 16α-*carbomethoxy*-17α-(*iso*)-*progesterone* (XV) as bright plates, m.p. 204–206°; $[\alpha]_D$ −38° *c*, 1; methanol). UV λ_{max}^{EtOH} 240 mμ (log ε 4·24). IR λ_{max}^{KBr} 5·76 μ (ester), 5·87 μ (20-ketone), 5·94 μ and 6·18 μ (Δ^4-3-ketone). (Found: C, 74·16; H, 8·69; O, 17·31. $C_{23}H_{32}O_4$ requires: C, 74·16; H, 8·66; O, 17·18%).

Strong alkaline treatment of the isoprogesterone (XV)

A solution of 100 mg isoprogesterone (XV) in 10 ml methanol containing 100 mg potassium hydroxide was refluxed for 1/2 hr. Water was added and then 10% hydrochloric acid solution until acid. The precipitate was washed thoroughly with water and recrystallized from ether–methanol yielding 55 mg of 16β-carboxy-isoprogesterone (VIIIb), m.p. 245–248°. The identity of these substances was established by mixed m.p. and comparison of the IR spectra and rotatory dispersion curves.

Reduction of the acid (XIVb) *to the lactone* (XVIIIb)

The acid (XIVb; 130 mg) was dissolved in 30 ml isopropanol[28] and 200 mg sodium borohydride added, and the solution heated under reflux for 1 hr. Water was added and 10% hydrochloric acid solution until acid. The organic substance was extracted several times with ethyl acetate. The latter was separated, washed with water, dried (Na_2SO_4) and evaporated *in vacuo*. The residue in 5 ml methanol was treated with 1 drop conc hydrochloric acid. The solvent was then evaporated to dryness *in vacuo*. This crude material, which showed a γ-lactone band in the IR, was dissolved in 3 ml pyridine and 2 ml acetic anhydride added. The mixture was allowed to stand overnight at room temp. Usual extraction procedure yielded a crude product which was chromatographed onto 6 g neutral alumina. Elution with hezane–benzene (50-50) gave 55 mg m.p. 198–200°. Recrystallization from acetone–hexane provided 16α-*carboxy*-17α-(*iso*)-Δ^5-*pregnene*-3β,20β-*diol*-16,20-*lactone* 3-*acetate* (XVIIIb); m.p. 228–231°; $[\alpha]_D$ −140° (*c*, 0·3; chloroform).

This compound was identical with the lactone (XVIIIb) obtained by catalytic hydrogenation of XIII. The mixed m.p. gave no depression and the IR spectra were the same.

Catalytic reduction of the acid (XIVb) *to the lactone* (XIX)

Hydrogen uptake corresponding to 2 equivs was stopped after 12 hr when 100 mg of XIVb were shaken in 20 ml ethyl acetate with 50 mg platinum oxide catalyst in an atmosphere of hydrogen. The catalyst was filtered off, 2 drops conc hydrochloric acid added and the filtrate evaporated to dryness. The residue was then passed over 3 g neutral alumina. Elution with hexane–benzene (90-10) and recrystallization from acetone–hexane provided 45 mg 16α-*carboxy*-(5αH)-17α-(*iso*)-*pregnene*-3β,20β-*diol*-16,20-*lactone* 3-*acetate* (XIX): m.p. 225–228°; $[\alpha]_D$ −64° (*c*, 0·2; chloroform).

This compound was identical with the lactone (XIX) by mixed m.p. and IR spectra comparison.

16α-Hydroxymethyl-17α-(iso)-Δ⁵-pregnene-3β,20β(?)-diol (XXIIa)

The ester (XIVc; 250 mg) dissolved in 30 ml tetrahydrofuran and, after addition of 250 mg lithium aluminum hydride, was heated under reflux for 3 hr. The reaction flask was cooled and ethyl acetate added, then water and finally 5% hydrochloric acid solution. The precipitate was filtered off and washed with water and dried. Recrystallization from methanol–ether afforded 110 mg m.p. 204–207°. Further recrystallization from methanol–ether yielded *16α-hydroxymethyl-17α-(iso)-Δ⁵-pregnene-3β,20β-(?)-diol* (XXIIa), as small prisms, m.p. 214–219°[38]; $[\alpha]_D$ −103° (*c*, 1; pyridine). IR λ_{max}^{KBr} 3·1 μ (s) (OH). (Found: C, 75·78; H, 10·30; $C_{23}H_{36}O_3$ requires: C, 75·81; H, 10·41%).

Acetylation of XXIIa furnished an amorphous triacetate, unchanged by chromatography: $[\alpha]$ −74° (*c*, 1; chloroform). IR $\lambda_{max}^{CHCl_3}$ 5·79 μ and 8 μ (s) (acetate).

16β-Carboxy-Δ⁵,²⁰-pregnadiene-3β,20-diol 16,20-*lactone* 3-*acetate* (XXIII) and *16β-Carboxy-Δ⁵-pregnene-3β,20ξ-diol* 16,20-*lactone* 3,20-*diacetate* (XXIV)

The 16β-carboxy-Δ⁵-pregnene-3β-ol-20-one (IXa; 1 g) was heated under reflux for 3 hr with 4 ml acetic anhydride and 4 ml anhydrous pyridine. Ice-water (60 ml) was added and the mixture extracted several times with ether. The organic layer was washed successively with dil hydrochloric acid solution (20%), water, sodium hydroxide solution (5%) and water, and was finally dried (Na_2SO_4). Evaporation of the solvent *in vacuo*, followed by crystallization from ether–hexane provided 360 mg of XXIV, m.p. 167–170°. Further recrystallization from ether–hexane furnished *16β-carboxy-Δ⁵-pregnene-3β,20ξ-diol* 16,20-*lactone* 3,20-*diacetate* (XXIV): m.p. 174–176°; $[\alpha]_D$ −70° (*c*, 0·5; chloroform). λ_{max}^{KBr} 5·56 μ (γ-lactone), 5·76 and 8·06 μ (s) (acetate). (Found: C, 70·14; H, 7·97; O, 21·76. $C_{36}H_{36}O_6$ requires: C, 70·24; H, 8·16; O, 21·60.)

The mother liquors were concentrated to dryness (610 mg) and chromatographed onto 15 g neutral alumina. Elution with hexane–benzene (8-2) afforded the enol-lactone (XXIII). Recrystallization from acetone–hexane gave 410 mg of *16β-carboxy-Δ⁵,²⁰-pregnadiene-3β,20-diol* 16,20-*lactone* 3-*acetate* (XXIII), as prismatic needles: m.p. 173–176°; $[\alpha]_D$ −104° (*c*, 1; chloroform). No UV absorption between 216 and 320 mμ λ_{max}^{KBr} 5·56 μ (γ-lactone), 5·80 and 8·04 μ (acetate), 5·97 and 11·65 μ (*exo*-methylene). (Found: C, 74·92; H, 8·44; 0, 16·87. $C_{24}H_{32}O_H$ requires: C, 74·97; H, 8·39; O, 16·65%).

Hydrogenation of the enol lactone (XXIII)

Hydrogen uptake corresponding to 2 equiv was stopped after 2 hr, when 200 mg enol lactone (XXIII) were shaken in 20 ml acetic acid with 60 mg platinum oxide catalyst in an atmosphere of hydrogen. The catalyst was filtered off, chloroform was added to the filtrate washed with a dil solution of sodium hydroxide (5%), then water, and finally dried (Na_2SO_4). Evaporation to dryness afforded a crude material which was chromatographed onto 6 g neutral alumina. Elution with hexane–benzene (30-70), followed by recrystallization from acetone–hexane, yielded 145 mg *16β-carboxy-(5αH)-pregnane-3β,20β-diol*-16,20-*lactone* 3-*acetate* (XXb): m.p. 205–207°; $[\alpha]_D$ +4° (*c*, 0·3; chloroform).

This compound was identical, by mixed m.p. and superimposable IR spectra, with the above lactone (XXb).

16β-Carboxy-(5αH)-pregnane-3β,20β-diol-16,20-*lactone* (XXa)

Alkaline hydrolysis of 80 mg of XXb was carried out for 40 min at reflux in 10 ml methanol containing 200 mg potassium hydroxide and 1 ml water. Water and dil hydrochloric acid (20%) were added and the precipitate collected, washed and dried. Recrystallization from methanol–ether afforded 45 mg *16β-carboxy-(5αH)-pregnane-3β,20β-diol*-16,20-*lactone* (XXa): m.p. 232–234°; $[\alpha]_D$ +12° (*c*, 0·2; chloroform). λ_{max}^{KBr} 2·90 μ (OH), 5·66 μ (γ-lactone). (Found: C, 76·16; H, 9·73. $C_{22}H_{34}O_3$ requires: C, 76·26; H, 9·89%).

Reacetylation of 25 mg of hydroxy-lactone (XXa) provided the acetoxy-lactone (XXb), m.p. 198–200°; $[\alpha]_D$ +10° (*c*, 0·6; chloroform). This compound was identical (by mixed m.p. and IR spectra comparison) with the above acetoxy-lactone (XXb).

[38] The m.p. of the triols (XIa) and (XXIIa) were broad even after numerous recrystallizations. This is attributable to the hydrogen bonding existing in these substances.

Reduction of the acetoxy-lactone (XXIV) *with lithium aluminum hydride*

The acetoxy-lactone (130 mg) was dissolved in 20 ml anhydrous tetrahydrofuran, 200 mg powdered lithium aluminum hydride were added and the mixture refluxed for 3 hr. Usual extraction followed by recrystallization from methanol afforded 40 mg 16*β-hydroxymethyl-*Δ^5*-pregnene-3β,20β-diol* (XIa): m.p. 275–279°, which was identical with the previously prepared XIa (mixed m.p. and same infrared spectra).

Alkaline hydrolysis of the acetoxy-lactone (XXIV)

To a solution of 150 mg acetoxy-lactone (XXIV) in 20 ml methanol, 150 mg potassium bicarbonate in 3 ml water were added. This mixture was then heated under reflux for 30 min; to the cooled solution 1 drop acetic acid was added and the solvents evaporated *in vacuo*. The residue was then dissolved in methanol, the inorganic salt eliminated by filtration and the methanolic solution concentrated. Recrystallization from methanol provided 25 mg 16*β-carboxy-*Δ^5*-pregnene-3β-ol-20-one* (IXa): m.p. 253°. A mixed m.p. with an authentic sample of IXa did not give any depression and the IR spectra were identical. The mother liquors were then refluxed 1 hr in 20 ml methanol containing 300 mg sodium hydroxide. Usual extraction procedure, followed by crystallization, provided 35 mg 16*β*-carboxy-17α-(iso)-compound (IIa), m.p. 224–226°, undepressed by mixed m.p. with an authentic sample of IIa and the IR spectra were identical.

16α-*Acetyl-*Δ^5*-pregnene-3β,20β-diol* (XXVa)

(a) *From the cyano-diol* (III). A solution of 6 g cyano-compound (III) in 700 ml toluene was prepared and 50 ml was distilled to eliminate moisture. A 200 ml ethereal solution of methyl magnesium iodide (prepared from 25 g methyl iodide) was added to this toluene solution containing the diol (III). The reaction mixture was then heated under reflux for 22 hr. After ice-cooling, water was added and the organic layer washed with 5% hydrochloric acid and then with water, dried (Na_2SO_4) and evaporated *in vacuo*. The oily residue (5·32 g) was refluxed for 1 hr with the same weight of Girard T reagent[39] dissolved in 70 ml absolute alcohol and 7 ml acetic acid. The ketonic fraction was then extracted with ether. By evaporation of the solvent, 3·89 g m.p. 178–180° were obtained. Further recrystallizations from acetone–ether gave 16α-*acetyl-*Δ^5*-pregnene-3β,20β-diol* (XXVa) as needles, m.p. 189–190°; $[\alpha]_D$ −86° (*c*, 0·5; dioxane). IR λ_{max}^{KBr} 2·96 μ (OH), 5·86 μ (s) (16-acetyl). (Found: C, 76·44; H, 9·88; O, 13·67. $C_{23}H_{36}O_3$ requires: C, 76·62; H, 10·07; O, 13·31%).

The non-ketonic fraction was not investigated.

(b) *From the lactone* (IVa). A solution of 3 g IVa was prepared with 1 l. toluene. About 100 ml toluene were allowed to distill in order to eliminate moisture. To this solution, cooled to room temp, 300 ml ethereal methylmagnesium iodide solution (prepared from 15 g methyl iodide) were added. Work-up in the normal manner afforded 1·25 g 16α-acetyl-3,20 diol (XXVa): m.p. 176–179°. Several recrystallizations from acetone–ether gave 920 mg needles, m.p. 186–188°. This compound was identical with that obtained in (a) as shown by mixed m.p. and IR spectra.

Acetic anhydride–pyridine acetylation, performed by heating 1 hr on the steam-bath, afforded the 16α-*acetyl-*Δ^5*-pregnene-3β,20β-diol 3,20-diacetate* (XXVb): m.p. 198–199°; $[\alpha]_D$ −52° (*c*, 0·35; chloroform). IR $\lambda_{max}^{CHCl_3}$ 5·78 μ and 8 μ (acetate), 5·84 μ (acetyl). (Found: C, 72·82; H, 9·08. $C_{27}H_{40}O_5$ requires: C, 72·94; H, 9·07%).

16α-*Acetyl-progesterone* (XXVI)

Using exactly the same procedure as described above for the carbomethoxy-progesterone, 1·23 g acetyl-progesterone (XXVI) was prepared. Crystallization from acetone–hexane gave m.p. 167–168°. The 16α-*acetyl-progesterone* (XXVI) was obtained by further recrystallization, as prismatic needles: m.p. 170–174°; $[\alpha]_D$ +158° (*c*, 1; chloroform). UV λ_{max}^{EtOH} 241 mμ (log ε 4·22). IR $\lambda_{max}^{CHCl_3}$ 5·89 μ (16- and 20-ketone), 6·02 and 6·19 μ (Δ^4-3-ketone). (Found: C, 77·53; H, 8·94; O, 13·67. $C_{23}H_{32}O_3$ requires: C, 77·49; H, 9·05; O, 13·46%)

16*β-Acetyl-*17α-(*iso*)-Δ^5*-pregne3ne-β,20β-diol* (XXVII)

The diacetate (VIIb[4]; 3 g) was dissolved in 60 ml anhydrous benzene, 10 ml benzene were then distilled and after cooling 10 ml thionyl chloride added and the reaction mixture refluxed for 2 hr.

[39] A. Girard and G. Sandulesco, *Helv. Chim. Acta* **19**, 1095 (1936)

The solution was then evaporated to dryness *in vacuo* and 30 ml anhydrous benzene added. To an ethereal solution of methylmagnesium-bromide (15 ml, 3 moles), 60 ml benzene were first added, and then slowly, with stirring, 10 g anhydrous cadmium chloride. This solution was allowed to stand 30 min at room temp. Then the above prepared acid chloride solution was added to the dimethyl-cadmium mixture and the whole reaction mixture heated under reflux for 4 hr. Water was added, followed by addition of 50% hydrochloric acid solution until acid. The benzene layer was separated, washed with water and dried (Na_2SO_4). After evaporation of the solvent the residue was treated with 60 ml absolute ethyl alcohol, 6 ml acetic acid and 3 g Girard T reagent[39] and refluxed for 1 hr. The ketonic fraction (1·9 g) was hydrolyzed with 50 ml methanol containing 3 g potassium hydroxide 1 hr at reflux. Water was added and the precipitate removed by filtration. Recrystallization from methanol–ether furnished a crystalline product: m.p. 180–182° (1·1 g). Further recrystallization from methanol–ether provided 16*β-acetyl*-17α-(*iso*)-Δ⁵-*pregnene*-3*β*,20*β*-*diol* (XXVII), as small prisms: m.p. 193–194°; $[\alpha]_D$ −73° (*c*, 1; methanol). IR λ_{max}^{KBr} 2·92 μ (s) (OH), 5·88 μ (s) (carbonyl). (Found: C, 76·38; H, 9·98; O, 13·61. $C_{23}H_{36}O_3$ requires: C, 76·62; H, 10·07; O, 13·31%).

16*β-Acetyl*-17α-(*iso*)-*progesterone* (XXVIII)

A solution of 1 g 16*β*-acetyl-diol (XXV) submitted to Oppenauer oxidation as described above, yielded by the usual extraction procedure followed by one crystallization from chloroform–hexane 220 mg m.p. 162–164°. Further recrystallization from chloroform–hexane gave 16*β-acetyl*-17α-(*iso*)-*progesterone* (XXVIII) as needles: m.p. 168–169°; $[\alpha]_D$ −18° (*c*, 0·5; chloroform). UV λ_{max}^{EtOH} 241 mμ (log ε 4·21). IR λ_{max}^{KBr} 5·86 μ (16- and 20-ketone) 6·02 and 6·18 μ (Δ⁴-3-ketone). (Found: C, 77·43; H, 8·87; O, 13·61. $C_{22}H_{32}O_3$ requires: C, 77·49; H, 9·05; O, 13·46%).

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