Tetrahedron, 1963, Vol. 19, pp. 51 to 64. Pergamon Press Ltd. Printed in Northern Ireland

OPTICAL ROTATORY DISPERSION STUDY OF 16-SUBSTITUTED PREGNENE AND ISOPREGNENE DERIVATIVES[1]

PIERRE CRABBÉ
Research Laboratories, Syntex, S.A., Mexico

(*Received* 17 *April* 1962)

Abstract—The rotatory dispersion technique was successfully applied for the assignment of configuration to various 16-substituted pregnene and 17α-(iso)-pregnene 20-ketones. Some useful generalizations were deduced from the examination of the rotatory dispersion curves of compounds belonging either to the Δ^4-3-ketone or to the Δ^5-3-alcohol series.

THE current use of optical rotatory dispersion for structure elucidation and configurational assignment is mainly the result of the extensive studies by Djerassi and his school.[2] Although Djerassi's work has been largely concerned with cyclic ketones, valuable information about the configuration of the substituents attached to an asymmetric center situated in the vicinity of an aliphatic carbonyl has also been gained by this new method.[3] Thus rotatory dispersion has been employed successfully to determine the configuration of the 17-acetyl side chain of the steroid nucleus, the 17β-oriented side chain of a pregnane derivative giving a strong positive Cotton effect, while the 17α-oriented side chain shows a negative Cotton effect.[4]

Application of this elegant technique has afforded a convenient method of establishing the stereochemistry at C-16 and C-17 in most of the 20-ketones obtained in the course of our investigation of 16-substituted pregnenes and 17α-(iso)-pregnenes.[5]

The sign of the Cotton effect and the amplitude of the peak associated with the rotatory dispersion curve of the 16α-cyano compound (I; (Fig. 1) are in agreement with the 17β-acetyl configuration assigned to this adduct,[6–8] the curves of I and of 16α-methyl-Δ^5-pregnene-3β-ol-20-one (II)[9] being practically superimposable. For the same reason the β-configuration is attributed to the 17-acetyl side chain of the amide (VII).[5]

During the hydrolysis of the 16α-cyano-17β-acetyl compound (I) to the acid IIIa, an inversion of configuration takes place at C-17 as well as at C-16. The inversion of

---

[1] Steroids CCIV. Part CCIII, P. Crabbé, L. M. Guerrero, J. Romo and F. Sanchez-Viesca, *Tetrahedron* **19**, 25 (1963).

[2a] C. Djerassi, *Optical Rotatory Dispersion* McGraw-Hill, New York (1960); [b] W. Klyne, *Advances in Organic Chemistry* Vol. 1; p. 239. T. A. Raphael, E. C. Taylor and H. Wynberg, Interscience, New York (1960).

[3] See ref. 2[a], p. 106.

[4] C. Djerassi, *Bull. Soc. Chim. Fr.* 741 (1957); see also ref. 2*a*, pp. 51–52.

[5a] ref. 1; [b] P. Crabbé and J. Romo, *Chem. & Ind.* 408 (1962); [c] *Ciencia* **22**, 29 (1962).

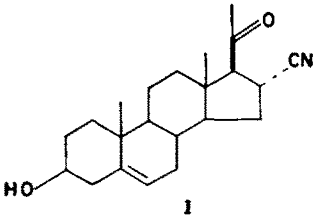
[6] J. Romo, *Tetrahedron* **3**, 37 (1958).

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

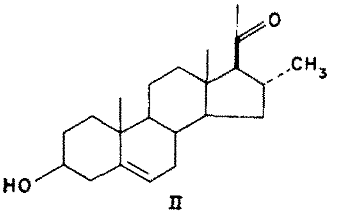
[8] R. H. Mazur and J. A. Cella, *Tetrahedron* **7**, 130 (1959).

[9a] R. E. Marker and H. M. Crooks, *J. Amer. Chem. Soc.* **64**, 1280 (1942); [b] K. Heusler, J. Kebrle, C. Meystre, H. Ueberwasser, P. Wieland, G. Anner and A. Wettstein, *Helv. Chim. Acta.* **42**, 2043 (1959).

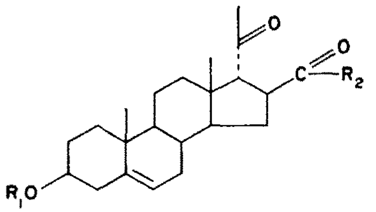
the Cotton effect observed in passing from I to IIIa supports the 17α-configuration assigned to this acid (IIIa).[5,8,10] In all cases where the stereochemistry is known to be 16β,17α,[5] the Cotton effect of the rotatory dispersion curve is negative. Thus, in Fig. I the curve of the acetate-ester (IIId) resembles the curve of 16β-methyl-17α-(iso)-Δ^5-pregnene-3β-ol-20-one (IV).[11]



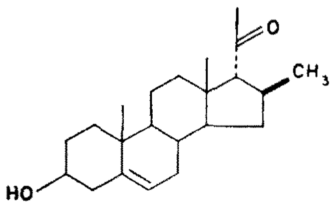
I



II



III 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: $R_1 = Ac$; $R_2 = NH[CH_2]_2NEt_2 , CH_3^{\bullet} I^{\bullet}$



IV

In the 16β,17β-series, although the rotatory dispersion curve of the 16β-carboxy-17β-acetyl compound (Va) shows a positive Cotton effect (Fig. 2), as does the nitrile (I), it is notable that the intensity of the peak associated with the curve of the acid (Va) is considerably lower than that of the other 17β-acetyl compounds (I and II), as shown in Fig. I. This can be attributed to the partial hydrogen-bond formation between the hydrogen of the hydroxyl group of the 16-carboxylic acid and the oxygen of the 20-ketone in the free acid (Va). Indeed, the rotatory dispersion curve of the corresponding acetate-ester (Vc) presents a much stronger positive Cotton effect (Fig. 2) reminiscent of the curves of the ketones I and II. The three 20-keto-compounds belonging to the 16α,17α-series (VIa, b, c) are typified by a strongly negative Cotton effect, illustrated in Fig. 2 by the curve of the acetate-ester (VIc) which is almost the mirror image of the curve of the acetate-ester (Vc).

It is now possible to differentiate between 16-substituted 17α- and 17β-acetyl epimers, the former presenting a negative Cotton effect, the latter a positive Cotton effect. Furthermore, in the 17α-series, the 16α-substituted carboxy-derivatives show a

---

[10] W. A. Struck and R. L. Houtman, *J. Org. Chem.* **26**, 3883 (1961).

[11] J. Romo, J. Lepe and M. Romero, *Bol. Inst. Quim., Mexico* **4**, 125 (1952).

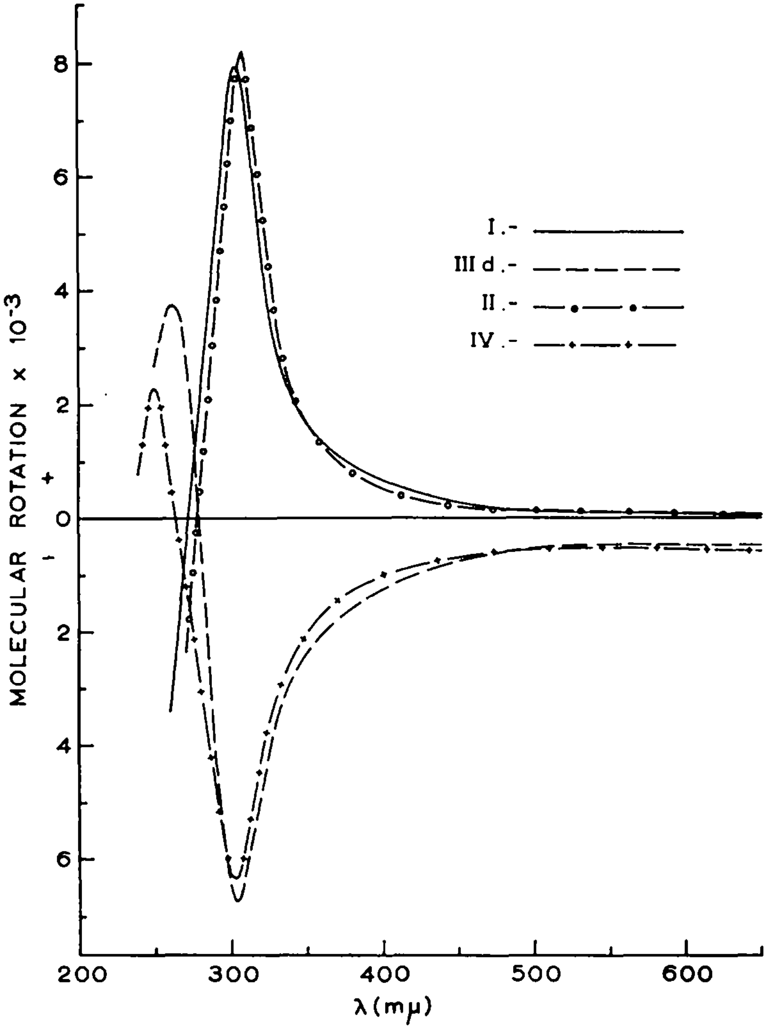
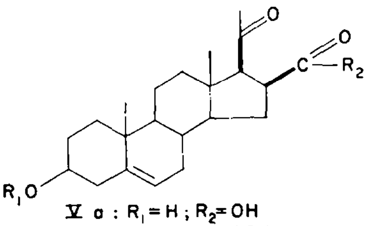


FIG. 1. Optical rotatory dispersion curves of 16α-cyano-Δ^5-pregnene-3β-ol-20-one (I), 16α-methyl-Δ^5-pregnene-3β-ol-20-one (II), 16β-carbomethoxy-17α-(iso)-Δ^5-pregnene-3β-ol-20-one 3-acetate (IIId), and 16β-methyl-17α-(iso)-Δ^5-pregnene-3β-ol-20-one (IV).

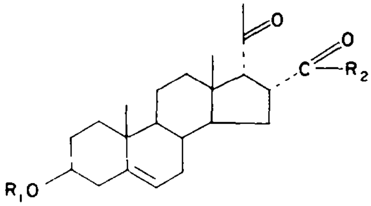
much stronger negative Cotton effect than the corresponding 16β-carboxy-17α-acetyl stereoisomers.[12] Finally, although the rotatory dispersion curves of some 16β,17β-substituted compounds, such as the acetoxy-ester (Vc; Fig. 2) or the ester (Vb), are very similar to the curves of the 16α-substituted-17β-acetyl compounds such as I and II (Fig. 1), by choosing the appropriate derivative for rotatory dispersion measurements,

---

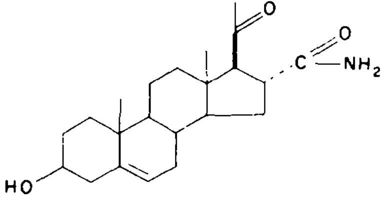
[12] Whether the substituent at C-16 is a carbomethoxy or a methyl grouping, neither in the *trans*, nor in the *cis*-series is it possible to detect any (hemi)-ketal formation with methanol under acidic conditions; C. Djerassi, L. A. Mitcher and B. J. Mitcher, *J. Amer. Chem. Soc.* **81**, 947 (1959); see also ref. 2*a*, p. 144.



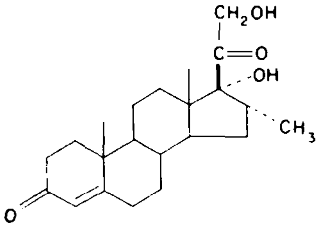
V a : $R_1 = H ; R_2 = OH$
b : $R_1 = H ; R_2 = OCH_3$
c : $R_1 = Ac ; R_2 = OCH_3$
d : $R_1 = Ac ; R_2 = NH[CH_2]_2NEt_2$
$CH_3^{\oplus} I^{\ominus}$



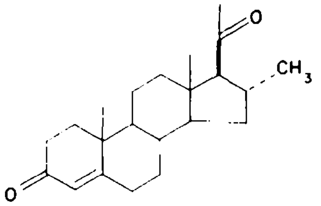
VI a : $R_1 = Ac , R_2 = OH$
b : $R_1 = H ; R_2 = OCH_3$
c : $R_1 = Ac ; R_2 = OCH_3$



VII



VIII



IX

as for example the free acid (Va), it is possible to differentiate between both substitution patterns (16α and 16β).[13]

Rotatory dispersion also provides an elegant tool for studying the stability of these various epimeric compounds. Apart from determining the stereochemistry of the reaction products isolated from the equilibration experiments described previously,[5] it is possible to draw some conclusions regarding their configurational stability by measuring the rotatory dispersion curves of the different epimers (I and VII, III, V and VI) in alkaline medium. Addition of 2% methanolic potassium hydroxide to the cyano-adduct (I) causes a decrease in the intensity of the peak, indicative of a partial epimerization occurring at C-17.[14] Under similar conditions, the intensity of the peak

---

[13] Although rotatory dispersion sometimes permits assignment of configuration of α-substituted carboxylic acids [see for instance: [a] B. Sjöberg, A. Fredga and C. Djerassi, *J. Amer. Chem. Soc.* **81**, 5002 (1959); [b] C. Djerassi and K. Undheim, *ibid.* **82**, 5755 (1960); [c] B. Sjöberg, *Acta Chem. Scand.* **14**, 273 (1960) and *Arkiv Kemi* **15**, 451, 473 and 481 (1960); [d] C. Djerassi, K. Undheim, R. C. Sheppard, W. G. Terry and B. Sjöberg, *Acta Chem. Scand.* **15**, 903 (1961); [e] C. Djerassi, E. Lund, E. Bunnenberg and J. C. Sheehan, *J. Org. Chem.* **26**, 4509 (1961)] these methods could not be applied to our problem because of the presence of other asymmetric centers and possible epimerization during the preparation of the appropriate derivatives.

[14] L. F. Fieser and M. Fieser, *Steroids* p. 566. Reinhold, New York (1959).

of the rotatory dispersion curve of the amide (VII) is not altered. As far as the two 17-epimeric amides (IIIh and Vd) are concerned, it appears that the 17β-epimer (Vd) is thermodynamically the more stable compound. This is shown by taking the rotatory

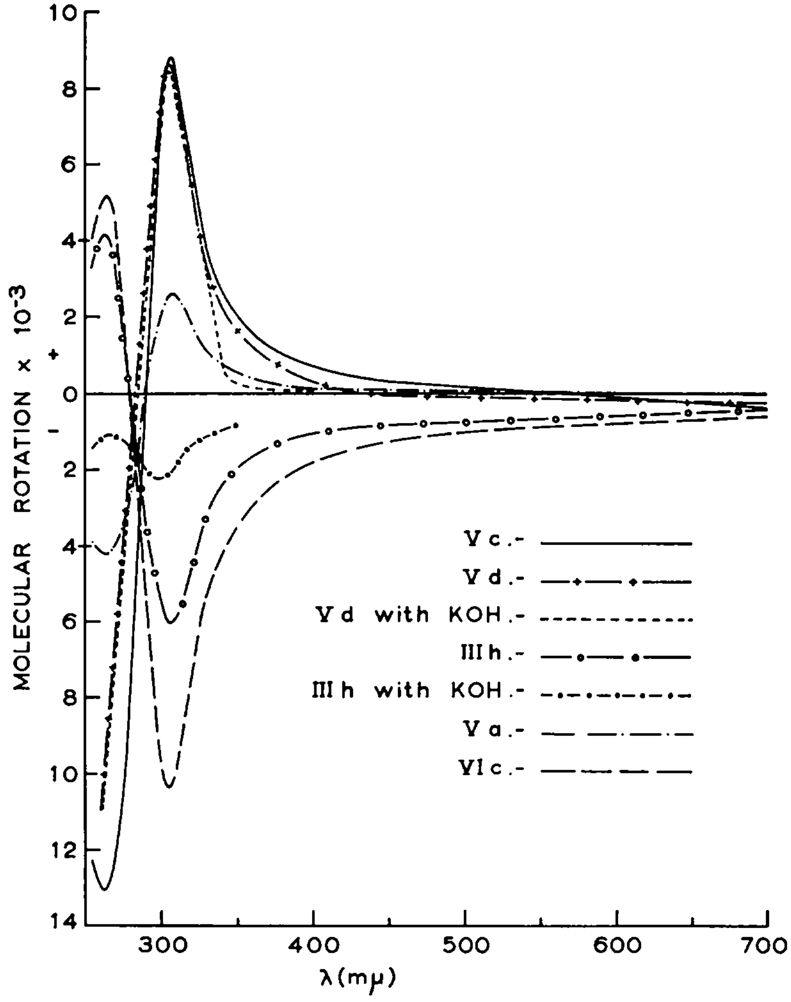
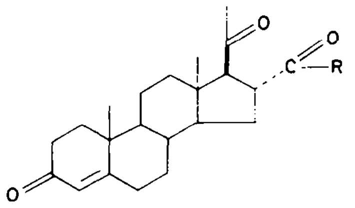


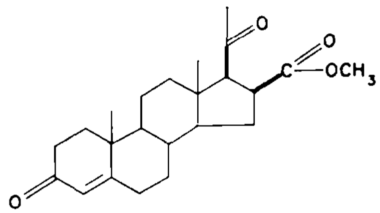
FIG. 2. Optical rotatory dispersion curves of 16β-carbox-(N,N,-diethylethylenediamine)-amido-17α-(iso)-Δ^5-pregnene-3β-ol-20-one 3-acetate methyl iodide (IIIh), (in neutral and alkaline medium), 16β-carboxy-Δ^5-pregnene-3β-ol-20-one (Va), 16β-carbomethoxy-Δ^5-pregnene-3β-ol-20-one 3-acetate (Vc), 16β-carbox-(N,N-diethylethylenediamine)-amido-Δ^5-pregnene-3β-ol-20-one 3-acetate methyl iodide (Vd) (in neutral and alkaline medium) and 16α-carbomethoxy-17α-(iso)-Δ^5-pregnene-3β-ol-20-one 3-acetate (VIc).

dispersion curve of the 17α-acetyl-amide (IIIh) in methanol with one drop of 10% potassium hydroxide solution. Under these conditions there is observed a substantial decrease in the depth of the trough (Fig. 2). Under the same alkaline conditions the rotatory dispersion curve of the 17β-acetyl-amide (Vd) is not appreciably altered, indicating that the 17β-epimer (Vd) is thermodynamically the more stable. However, as anticipated, the rotatory dispersion curve of the methyl-ester (Vc) shows in alkaline medium a weakly negative Cotton effect (see Experimental) apparently due to significant epimerization of the 17β-acetyl side chain to its 17α-epimer (IIId). Finally, while the rotatory dispersion curves of most of the compounds belonging to the 16β,17α-series (III) are not affected by alkaline treatment (see Experimental), except for the amide (IIIh; *vide supra*), a decrease of the negative Cotton effect of the rotatory dispersion curve of the 16α,17α-ester (VIc) is observed under identical conditions.

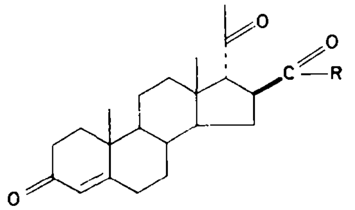
That the 16β-ester-17α-acetyl compound (IIId) is thermodynamically more stable than its 17β-stereoisomer (Vc) is confirmed by thermal epimerization.[15] When both IIId and Vc are submitted separately to gas chromatography at 260° and the collected material submitted to rotatory dispersion measurements, the 17β-epimer (Vc) is found to have isomerized completely into the ester (IIId).



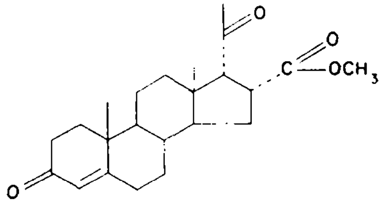
X a : R = OCH_3
b : R = OH



XI



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



XIII

The presence of a Δ^4-3-ketone chromophore in the molecule does not prevent differentiation between 16-substituted progesterones and 17α-(iso)-progesterones.[10] Besides the Δ^4-3-ketone multiple Cotton effects around 370 mμ, slightly shifted towards higher wavelengths (Fig. 3), the rotatory dispersion curves of the substituted progesterones (17β-acetyl side chain) show a strong positive Cotton effect in the 300 mμ region.[16] This peak is not apparent in the rotatory dispersion curves of the substituted 17α-(iso)-progesterones which explains why the fine structure characteristic

---

[15] The author is indebted to Dr. J. C. Matthews of these laboratories for these experimental results.

[16a] E. W. Foltz, A. E. Lippman and C. Djerassi, *J. Amer. Chem. Soc.* 77, 4359 (1955); [b] C. Djerassi, R. Riniker and B. Riniker, *Ibid.* 78, 6377 (1956).

of α, β-unsaturated ketones is better resolved in the 17α-compounds.[10] Typical examples of this strong positive Cotton effect are provided by the rotatory dispersion curves of compounds VIII to XI, as shown in Fig. 3.

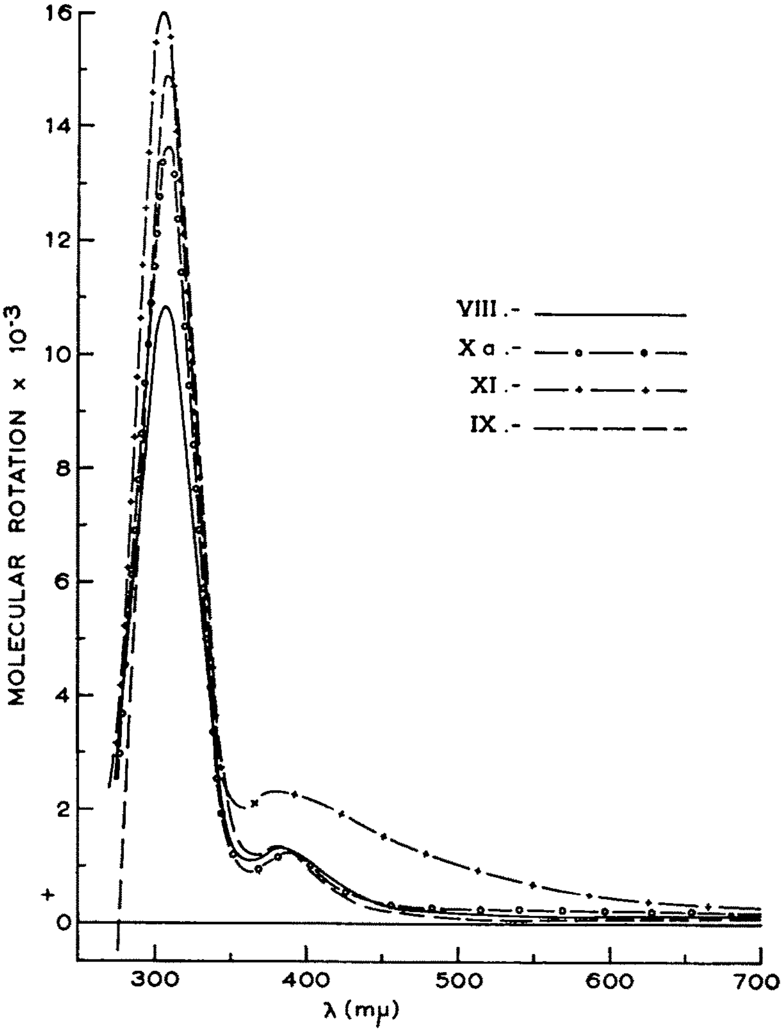


Fig. 3. Optical rotatory dispersion curves of 16α-methyl-Δ^4-pregnene-17α,21-diol-3 20-dione (VIII), 16α-methyl-progesterone (IX), 16α-carbomethoxy-progesterone (Xa), 16β-carbomethoxy-progesterone (XI).

Turning now to the 16-substituted 17α-(iso)-progesterones, it is immediately apparent that the multiple Cotton effects at 350 mμ associated with the Δ^4-3-keto-system are the main feature of the rotatory dispersion curves of these compounds. This is shown in Fig. 4, in the case of the 16β-carbomethoxy-17α-(iso)-progesterone (XIIa), the corresponding acid (XIIb) and its amide (XIIc). Apart from the Δ^4-3-keto absorption bands at ca. 350 mμ, the rotatory dispersion curves present a typical trough around 300 mμ. From the amplitude of this trough, the configuration of the substituent at C-16 can be deduced. Fig. IV clearly indicates the difference between the rotatory dispersion curves of the 16α-carbomethoxy-17α-(iso)-progesterone (XIII) and the 16β-carbomethoxy-17α-(iso)-progesterones (XIIa, b, c). Hence among the Δ^4-3-ketones, differentiation between 16α- and 16β-substituted isoprogesterones can readily be made, while the exact assignment of configuration at C-16 is much more delicate in the progesterone series (see however ref. 10).

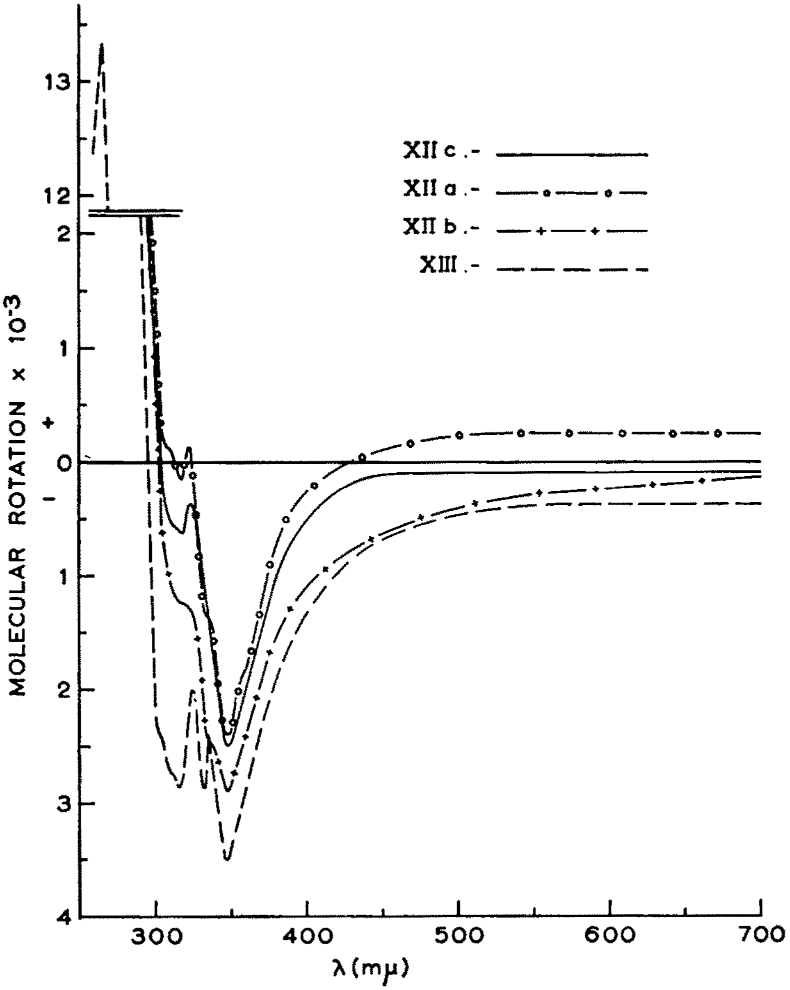
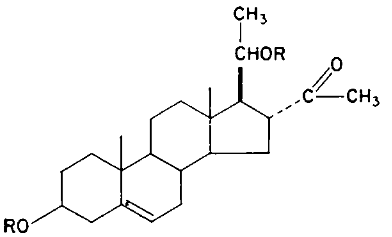
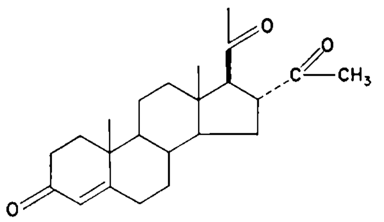


FIG. 4. Optical rotatory dispersion curves of 16β-carbomethoxy-17α-(iso)-progesterone (XIIa), 16β-carboxy-17α-(iso)-progesterone (XIIb), 16β-carboxamido-17α-(iso)-progesterone (XIIc) and 16α-carbomethoxy-17α-(iso)-progesterone (XIII).

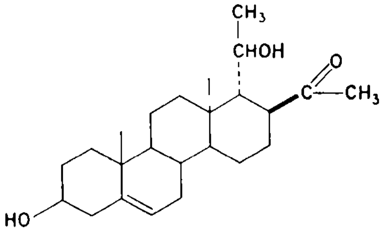
The stereochemical stability of the progesterones (Xa) and (XI) and of the isoprogesterones (XIIa and XIII) has also been examined by vapor phase chromatography technique, followed by rotatory dispersion measurements.[15] From these experiments one can draw the following conclusions: (a) the *trans*-16-carbomethoxy-progesterone (Xa) and 17α-(iso)-progesterone (XIIa) are not affected by this thermal treatment; (b) the configuration of the 16β-carbomethoxy-progesterone (XI) undergoes inversion at C-17 to yield the isoprogesterone (XIIa), characterized by the absence of positive Cotton effect in the 300 mμ region; and (c) the 16α-carbomethoxy-17α-(iso)-progesterone (XIII) is epimerized to the 16α-carbomethoxy-progesterone (Xa), as shown by the typical peak which appears at 297·5 mμ in the rotatory dispersion curve of the compound collected after vapor phase chromatography. Hence, while strong alkaline treatment of the 16α-carbomethoxy-17α-(iso)-progesterone (XIII) yields the 16β-carboxy-17α-(iso)-progesterone (XIIb),[5] involving inversion at C-16, the above mentioned thermal epimerization which gives the progesterone (Xa) involves inversion at C-17. This experiment again strongly supports the assumption that the 16,17-*trans*-configurations are more stable and also suggests that when accessible (as under strongly enolising conditions) the all-*trans* system (16β,17α) is thermodynamically the most stable of the four possible epimers.



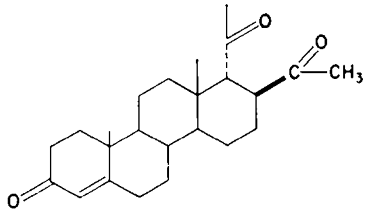
XIV a : R=H
b : R=Ac



XV



XVI



XVII

The problem of the configuration at C-16 of the acetyl-progesterone (XV) and isoprogesterone (XVII) may now be considered. It has already been shown[5] that the same acetyl-diol (XIVa) is obtained by Grignard reaction with methyl-magnesium iodide either on the 16α-cyano-Δ^5-pregnene-3β,20β-diol[8] or on the 16β-carboxy-Δ^5-pregnene-3β,20β-diol-16,20-lactone.[8] This implies that epimerization occurred at C-16 during the work up of one of these reaction products. Moreover, since no (hemi)-ketal formation is detectable by rotatory dispersion method,[12] an observation which is supported by the strong carbonyl band apparent in the IR spectrum, the 16,17-*trans*-configuration is assigned to this substance (XIVa). The 16α-configuration can therefore be deduced for the acetyl side chain in the diol (XIVa) and its di-acetate

(XIVb) (Fig. V). The Oppenauer oxidation product (XV) obtained from the diol (XIVa) belongs to the 17β-acetyl series. The rotatory dispersion curve of this substance (XV) reveals besides the Δ^4-3-ketone fine structure a positive Cotton effect at 305 mμ, typical of the 17β-acetyl side chain (*vide supra*). As could be anticipated from the small positive Cotton effect associated with the 16α-acetyl function (Fig. 5), the rotatory dispersion curve of this 16α-acetyl-progesterone (XV) is very similar to the curve of the 16-carbomethoxy-progesterones (Xa and XI; Fig. 3).

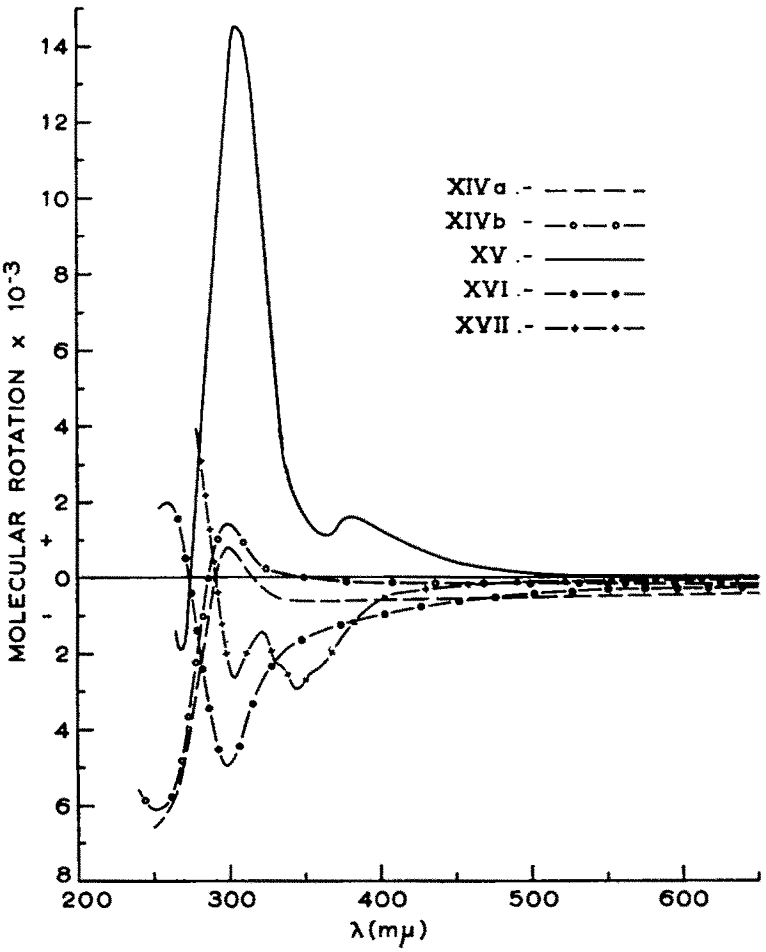


FIG. 5. Optical rotatory dispersion curves of 16α-acetyl-Δ^5-pregnene-3β,20β-diol (XIVa), 16α-acetyl-Δ^5-pregnene-3β,20β-diol diacetate (XIVb), 16α-acetyl-progesterone (XV), 16β-acetyl-17α-(iso)-Δ^5-pregnene-3β,20β-diol (XVI) and 16β-acetyl-17α-(iso)-progesterone (XVII).

As far as the 16β-acetyl-17α-(iso)-Δ^5-pregnene-3β,20β-diol (XVI) is concerned, assignment of the 16β-configuration to the acetyl group results from the same kind of argument as developed above for the 16α-acetyl compounds (XIVa, b and XV). This acetyl-diol (XVI) possesses a rotatory dispersion curve which does not show any marked change when taken in methanolic hydrochloric acid.[12] Furthermore, the strong negative Cotton effect observed in the rotatory dispersion curve of this diol (XVI), which is of *opposite* sign to that associated with the 16α-acetyl configuration (Fig. 5), seems to indicate a 16β-acetyl-stereochemistry. The Oppenauer oxidation product of the diol (XVI), namely the 16β-acetyl-17α-(iso)-progesterone (XVII), has a rotatory dispersion curve shown in Fig. 5 which is in agreement with the configuration assigned to this compound. The absence of positive Cotton effect around 300 mμ supports the 17α-acetyl configuration while the amplitude of the trough at 305 mμ is in agreement with a 16β-acetyl stereochemistry.

EXPERIMENTAL

All compounds are from Syntex collection. The preparation of most of these substances is described in the previous papers.[5] For the other compounds an appropriate reference is mentioned.

The rotatory dispersion curves, obtained through the courtesy of Dr. J. Matthews and his staff, were measured with an automatic recorder Rudolph photoelectric spectropolarimeter.

All rotations are reported and plotted as molecular rotations $[\Phi]$.[17]

16α-*Cyano*-Δ^5-*pregnene-3β-ol-20-one* (I; Fig. 1). Methanol, (*c:* 0·056): $[\Phi]_{700}$ +73°; $[\Phi]_{589}$ +79°; $[\Phi]_{302\cdot5}$ +7930° $[\Phi]_{260}$ −3410°. Alkaline study (with one drop of 2% methanolic KOH): $[\Phi]_{302\cdot5}$ +7250°.

16α-*Methyl*-Δ^5-*pregnene-3β-ol-20-one* (II[9]; Fig. 1). Methanol, (*c:* 0·049): $[\Phi]_{700}$ +54°; $[\Phi]_{589}$ +34°; $[\Phi]_{307\cdot5}$ +8200°; $[\Phi]_{270}$ −2352°. Acid study:[12] $[\Phi]_{307\cdot5}$ +8200°.

16β-*Carboxy*-17α-(*iso*)-Δ^5-*pregnene-3β-ol-20-one* (IIIa). Methanol, (*c:* 0·050): $[\Phi]_{700}$ −187°; $[\Phi]_{589}$ −252°; $[\Phi]_{302\cdot5}$ −6380°; $[\Phi]_{257\cdot5}$ +4075°; $[\Phi]_{250}$ +3465°. Acid study:[12] $[\Phi]_{302\cdot5}$ −6380°.

16β-*Carboxy*-17α-(*iso*)-Δ^5-*pregnene-3β-ol-20-one 3-acetate* (IIIb). Methanol, (*c:* 0·048): $[\Phi]_{700}$ −282°; $[\Phi]_{589}$ −333°; $[\Phi]_{302\cdot5}$ −6315°; $[\Phi]_{262\cdot5}$ +4400°; $[\Phi]_{235}$ +102°.

16β-*Carbomethoxy*-17α-(*iso*)-Δ^5-*pregnene-3β-ol-20-one* (IIIc). Methanol, (*c:* 0·055): $[\Phi]_{700}$ −404°; $[\Phi]_{589}$ −453°; $[\Phi]_{302\cdot5}$ −6540°; $[\Phi]_{257\cdot5}$ +4120°; $[\Phi]_{250}$ +3315°. Acid study:[12] $[\Phi]_{302\cdot5}$ −6320°. Alkaline study (with one drop of 5% methanolic KOH): $[\Phi]_{302\cdot5}$ −6240°.

16β-*Carbomethoxy*-17α-(*iso*)-Δ^5-*pregnene-3β-ol-20-one 3-acetate* (IIId; Fig. 1). Methanol, (*c:* 0·047): $[\Phi]_{700}$ −413°; $[\Phi]_{589}$ −554°; $[\Phi]_{305}$ −6690°; $[\Phi]_{262\cdot5}$ +3735°; $[\Phi]_{250}$ +2670°. Acid study:[12] $[\Phi]_{305}$ −6675°. Alkaline study (with one drop of 5% methanolic KOH): $[\Phi]_{305}$ −6660°.

16β-*Carboxamido*-17α-(*iso*)-Δ^5-*pregnene-3β-ol-20-one 3-acetate* (IIIe). Methanol, (*c:* 0·05): $[\Phi]_{700}$ −238°; $[\Phi]_{589}$ −202°; $[\Phi]_{305}$ −6020°; $[\Phi]_{262\cdot5}$ +4540°; $[\Phi]_{245}$ +2240°. Alkaline study (with one drop of 5% methanolic KOH): $[\Phi]_{302\cdot5}$ −6320°.

16β-*Carboxamido*-17α-(*iso*)-Δ^5-*pregnene-3β-ol-20-one* (IIIf). Methanol, (*c:* 0·044): $[\Phi]_{700}$ −538°; $[\Phi]_{589}$ −545°; $[\Phi]_{300}$ −5705°; $[\Phi]_{260}$ +3725°; $[\Phi]_{255}$ +3475°. Alakline study (with one drop of 5% methanolic KOH): $[\Phi]_{300}$ −5700°.

16β-*Carbox*-(N-*diethyl*)-*amido*-17α-(*iso*)-Δ^5-*pregnene-3β-ol-20-one 3-acetate* (IIIg). Methanol, (*c:* 0·053): $[\Phi]_{700}$ −68°; $[\Phi]_{589}$ −169°; $[\Phi]_{305}$ −7150°; $[\Phi]_{257\cdot5}$ +7435°; $[\Phi]_{245}$ +4740°.

16β-*Carbox*-(N,N-*diethylethylenediamine*)-*amido*-17α-(*iso*)-Δ^5-*pregnene-3β-ol-20-one 3-acetate methyl iodide* (IIIh; Fig. 2). Methanol, (*c:* 0·06): $[\Phi]_{700}$ −480°; $[\Phi]_{589}$ −662°; $[\Phi]_{305}$ −6000°; $[\Phi]_{262\cdot5}$ +4080°; $[\Phi]_{255}$ +3285°. Alkaline study (with one drop of 10% methanolic KOH): $[\Phi]_{310}$ −1937°; $[\Phi]_{305}$ −2130°; $[\Phi]_{300}$ −2213°; $[\Phi]_{297\cdot5}$ −2240°; $[\Phi]_{295}$ −2210°; $[\Phi]_{290}$ −1918°. Stronger alkaline conditions led to a precipitate.

16β-*Methyl*-17α-(*iso*)-Δ^5-*pregnene-3β-ol-20-one* (IV;[11] Fig. 1). Methanol, (*c:* 0·06): $[\Phi]_{700}$ −635°; $[\Phi]_{589}$ −515°; $[\Phi]_{302\cdot5}$ −6350°; $[\Phi]_{250}$ +2268°; $[\Phi]_{240}$ +782°.

16β-*Carboxy*-Δ^5-*pregnene-3β-ol-20-one* (Va; Fig. 2). Methanol, (*c:* 0·053): $[\Phi]_{700}$ −67°; $[\Phi]_{589}$ −40°; $[\Phi]_{307\cdot5}$ +2595°; $[\Phi]_{265}$ −4180°; $[\Phi]_{255}$ −3885°. Acid study:[12] $[\Phi]_{315}$ −242°; $[\Phi]_{305}$ −126°; $[\Phi]_{295}$ −227°. Alkaline study (with one drop of 5% methanolic KOH): $[\Phi]_{307\cdot5}$ +788° (sodium salt).

16β-*Carbomethoxy*-Δ^5-*pregnene-3β-ol-20-one* (Vb). Methanol, (*c:* 0·053): $[\Phi]_{700}$ −337°; $[\Phi]_{589}$ −168°; $[\Phi]_{307\cdot5}$ +8320°; $[\Phi]_{250}$ −3142°.

16β-*Carbomethoxy*-Δ^5-*pregnene-3β-ol-20-one 3-acetate* (Vc; Fig. 2). Methanol, (*c:* 0·025): $[\Phi]_{700}$ −404°; $[\Phi]_{589}$ −146°; $[\Phi]_{307\cdot5}$ +8810°; $[\Phi]_{262\cdot5}$ −13080°; $[\Phi]_{255}$ −12300°. Acid study:[12] $[\Phi]_{307\cdot5}$ +8760°. Alkaline study (with one drop of 5% methanolic KOH): $[\Phi]_{305}$ −1420°.

[17] See ref. 2*a*, p. 17 and ref. 2*b*, p. 250.

16β-*Carbox*-(N,N-*diethylethylenediamine*)-*amido*-Δ^5-*pregnene*-3β-*ol*-20-*one* 3-*acetate methyl iodide* (Vd; Fig. 2). Methanol, (*c*: 0·062): $[\Phi]_{700}$ +462°; $[\Phi]_{589}$ −288°; $[\Phi]_{305}$ +8680°; $[\Phi]_{260}$ −1095°. Alkaline study (with one drop of 10% methanolic KOH): $[\Phi]_{320}$ +5230°; $[\Phi]_{310}$ +7760°; $[\Phi]_{307\cdot5}$ +8310°; $[\Phi]_{305}$ +8410°; $[\Phi]_{302\cdot5}$ +8110°; $[\Phi]_{300}$ +7480°.

16α-*Carboxy*-17α-(*iso*)-Δ^5-*pregnene*-3β-*ol*-20-*one* 3-*acetate* (VIa). Methanol, (*c*: 0·039): $[\Phi]_{700}$ +153°; $[\Phi]_{589}$ −21°; $[\Phi]_{300}$ −8260°; $[\Phi]_{255}$ +3895°. Acid study:[12] $[\Phi]_{300}$ −8130°.

16α-*Carbomethoxy*-17α-(*iso*)-Δ^5-*pregnene*-3β-*ol*-20-*one* (VIb). Methanol, (*c*: 0·047): $[\Phi]_{700}$ −195°; $[\Phi]_{589}$ −210°; $[\Phi]_{302\cdot5}$ −9500°; $[\Phi]_{260}$ −3480°.

16α-*Carbomethoxy*-17α-(*iso*)-Δ^5-*pregnene*-3β-*ol*-20-*one* 3-*acetate* (VIc; Fig. 2). Methanol, (*c*: 0·034): $[\Phi]_{700}$ −634°; $[\Phi]_{589}$ −755°; $[\Phi]_{305}$ −10350°; $[\Phi]_{265}$ +5140°; $[\Phi]_{255}$ +4050°. Acid study:[12] $[\Phi]_{305}$ −10700°. Alkaline study (with one drop of 5% methanolic KOH): $[\Phi]_{310}$ −6830°; $[\Phi]_{307\cdot5}$ −7100°; $[\Phi]_{305}$ −7250°; $[\Phi]_{302\cdot5}$ −7100°; $[\Phi]_{300}$ −6700°.

16α-*Carboxamido*-Δ^5-*pregnene*-3β-*ol*-20-*one* (VII). Methanol, (*c*: 0·060): $[\Phi]_{700}$ +93°; $[\Phi]_{589}$ +118°; $[\Phi]_{302\cdot5}$ +8420°; $[\Phi]_{265}$ −1905°. Alkaline study (with one drop of 5% methanolic KOH): $[\Phi]_{302\cdot5}$ +8450°.

16α-*Methyl*-Δ^4-*pregnene*-17α,21-*diol*-3,20-*dione* (VIII;[18] Fig. 3). Dioxane, (*c*: 0·048): $[\Phi]_{700}$ +80°; $[\Phi]_{589}$ +83°; $[\Phi]_{400}$ +1149°; $[\Phi]_{390}$ +1260°; $[\Phi]_{385}$ +1300°; $[\Phi]_{382\cdot5}$ +1308°; $[\Phi]_{380}$ +1305°; $[\Phi]_{377\cdot5}$ +1285°; $[\Phi]_{375}$ +1246°; $[\Phi]_{370}$ +1142°; $[\Phi]_{367\cdot5}$ +1080°; $[\Phi]_{365}$ +1068°; $[\Phi]_{362\cdot5}$ +1088°; $[\Phi]_{360}$ +1120°; $[\Phi]_{350}$ +1344°; $[\Phi]_{307\cdot5}$ +10840°; $[\Phi]_{275}$ +2517°.

16α-*Methyl-progesterone* (IX;[19] Fig. 3). Dioxane, (*c*: 0·029): $[\Phi]_{700}$ −45°; $[\Phi]_{589}$ +102°; $[\Phi]_{400}$ +1047°; $[\Phi]_{395}$ +1228°; $[\Phi]_{392\cdot5}$ +1250°; $[\Phi]_{390}$ +1240°; $[\Phi]_{387\cdot5}$ +1240°; $[\Phi]_{385}$ +1238°; $[\Phi]_{382\cdot5}$ +1210°; $[\Phi]_{380}$ +1194°; $[\Phi]_{377\cdot5}$ +1115°; $[\Phi]_{375}$ +1072°; $[\Phi]_{372\cdot5}$ +1037°; $[\Phi]_{370}$ +1000°; $[\Phi]_{367\cdot5}$ +948°; $[\Phi]_{365}$ +925°; $[\Phi]_{362\cdot5}$ +913°; $[\Phi]_{360}$ +1025°; $[\Phi]_{350}$ +1295°; $[\Phi]_{310}$ +13930°; $[\Phi]_{307\cdot5}$ +13930°; $[\Phi]_{270}$ +1510°.

16α-*Carbomethoxy-progesterone* (Xa; Fig. 3). Dioxane, (*c*: 0·03): $[\Phi]_{700}$ +37°; $[\Phi]_{589}$ +99°; $[\Phi]_{400}$ +930°; $[\Phi]_{390}$ +1278°; $[\Phi]_{385}$ +1328°; $[\Phi]_{382\cdot5}$ +1338°; $[\Phi]_{380}$ +1338°; $[\Phi]_{377\cdot5}$ +1328°; $[\Phi]_{375}$ +1290°; $[\Phi]_{372\cdot5}$ +1254°; $[\Phi]_{370}$ +1214°; $[\Phi]_{367\cdot5}$ +1192°; $[\Phi]_{365}$ +1240°; $[\Phi]_{362\cdot5}$ +1238°; $[\Phi]_{360}$ +1302°; $[\Phi]_{355}$ +1413°; $[\Phi]_{350}$ +1838°; $[\Phi]_{307\cdot5}$ +14870°; $[\Phi]_{270}$ −917°.

16α-*Carboxy-progesterone* (Xb). Dioxane, (*c*: 0·028): $[\Phi]_{700}$ +165°; $[\Phi]_{589}$ +242°; $[\Phi]_{400}$ +1335°; $[\Phi]_{390}$ +1452°; $[\Phi]_{385}$ +1492°; $[\Phi]_{382\cdot5}$ +1518°: $[\Phi]_{380}$ +1530°; $[\Phi]_{377\cdot5}$ +1530°; $[\Phi]_{375}$ +1503°; $[\Phi]_{372\cdot5}$ +1462°; $[\Phi]_{370}$ +1397°; $[\Phi]_{367\cdot5}$ +1364°; $[\Phi]_{365}$ +1340°; $[\Phi]_{362\cdot5}$ +1397°; $[\Phi]_{360}$ +1488°; $[\Phi]_{350}$ +1720°; $[\Phi]_{305}$ +14400°; $[\Phi]_{270}$ −243°; $[\Phi]_{260}$ +1600°.

16β-*Carbomethoxy-progesterone* (XI; Fig. 3). Dioxane, (*c*: 0·025): $[\Phi]_{700}$ +187°; $[\Phi]_{589}$ +199°; $[\Phi]_{400}$ +1980°; $[\Phi]_{395}$ +2250°; $[\Phi]_{390}$ +2290°; $[\Phi]_{387\cdot5}$ +2310°; $[\Phi]_{385}$ +2340°; $[\Phi]_{382\cdot5}$ +2350°; $[\Phi]_{380}$ +2340°; $[\Phi]_{377\cdot5}$ +2340°; $[\Phi]_{375}$ +2325°; $[\Phi]_{372\cdot5}$ +2285°; $[\Phi]_{370}$ +2230°; $[\Phi]_{367\cdot5}$ +2135°; $[\Phi]_{365}$ +2062°; $[\Phi]_{362\cdot5}$ +2015°; $[\Phi]_{360}$ +2015°; $[\Phi]_{357\cdot5}$ +2062°; $[\Phi]_{355}$ +2108°; $[\Phi]_{350}$ +2180°; $[\Phi]_{305}$ +16000°; $[\Phi]_{270}$ +2360°.

16β-*Carbomethoxy*-17α-(*iso*)-*progesterone* (XIIa; Fig. 4). Dioxane, (*c*: 0·026): $[\Phi]_{700}$ −235°; $[\Phi]_{589}$ −240°; $[\Phi]_{400}$ −249°; $[\Phi]_{390}$ −402°; $[\Phi]_{380}$ −677°; $[\Phi]_{370}$ −1230°; $[\Phi]_{360}$ −1855°; $[\Phi]_{355}$ −1990°; $[\Phi]_{352.5}$ −2118°; $[\Phi]_{350}$ −2370°; $[\Phi]_{347\cdot5}$ −2378°; $[\Phi]_{345}$ −2335°; $[\Phi]_{340}$ −1690°; $[\Phi]_{337\cdot5}$ −1424°; $[\Phi]_{335}$ −1384°; $[\Phi]_{332\cdot5}$ −1328°; $[\Phi]_{330}$ −1065°; $[\Phi]_{327\cdot5}$ −539°; $[\Phi]_{325}$ −69°; $[\Phi]_{322\cdot5}$ +124° ; $[\Phi]_{320}$ +14° ; $[\Phi]_{317\cdot5}$ −152° ; $[\Phi]_{315}$ −96° ; $[\Phi]_{312\cdot5}$ +28°; $[\Phi]_{310}$ +111°; $[\Phi]_{305}$+208°; $[\Phi]_{300}$ +1050°; $[\Phi]_{265}$ +13030°.

16β-*Carboxy*-17α-(*iso*)-*progesterone* (XIIb; Fig. 4). Dioxane, (*c*: 0·025): $[\Phi]_{700}$ −44°; $[\Phi]_{589}$ −245°; $[\Phi]_{400}$ −1107°; $[\Phi]_{390}$ −1244°; $[\Phi]_{380}$ −1470°; $[\Phi]_{370}$ −1957°; $[\Phi]_{360}$ −2387°; $[\Phi]_{355}$ −2605°; $[\Phi]_{352\cdot5}$ −2715°; $[\Phi]_{350}$ −2820°; $[\Phi]_{347\cdot5}$ −2880°; $[\Phi]_{345}$ −2870°; $[\Phi]_{340}$ −2575°; $[\Phi]_{335}$ −2430°; $[\Phi]_{330}$ −1755°; $[\Phi]_{325}$ −1322°; $[\Phi]_{320}$ −1282°; $[\Phi]_{315}$ −1223°; $[\Phi]_{310}$ −1058°; $[\Phi]_{305}$ −276°; $[\Phi]_{300}$ −633°: $[\Phi]_{290}$ +4180°; $[\Phi]_{265}$ +13330°; $[\Phi]_{260}$ +12370°.

16β-*Carboxamido*-17α-(*iso*)-*progesterone* (XIIc; Fig. 4). Dioxane, (*c*· 0·055): $[\Phi]_{700}$ −160°; $[\Phi]_{589}$ −199°; $[\Phi]_{400}$ −540°; $[\Phi]_{390}$ −702°; $[\Phi]_{380}$ −932°; $[\Phi]_{370}$ −1467°; $[\Phi]_{360}$ −1985°; $[\Phi]_{355}$ −2190°; $[\Phi]_{352\cdot5}$ −2300°; $[\Phi]_{350}$ −2460°; $[\Phi]_{347\cdot5}$ −2495°; $[\Phi]_{345}$ −2395°; $[\Phi]_{340}$ −1807°; $[\Phi]_{330}$ −960°; $[\Phi]_{327\cdot5}$ −534°; $[\Phi]_{325}$ −386°; $[\Phi]_{322\cdot5}$ −373°; $[\Phi]_{320}$ −522°; $[\Phi]_{317\cdot5}$ −624°; $[\Phi]_{315}$ −592°; $[\Phi]_{312\cdot5}$ −547°; $[\Phi]_{310}$ −528°; $[\Phi]_{305}$ −213°; $[\Phi]_{300}$ +875°; $[\Phi]_{280}$ +5570°.

---

[18] E. Batres, T. Cardenas, J. A. Edwards, G. Monroy, O. Mancera, C. Djerassi and H. J. Ringold, *J. Org. Chem.* **26**, 871 (1961).

[19] A. Wettstein, *Helv. Chim. Acta* **27**, 1803 (1944); see also ref. 11.

16α-*Carbomethoxy*-17α-(*iso*)-*progesterone* (XIII; Fig. 4). Dioxane, (*c:* 0·035): $[\Phi]_{700}$ − 148°; $[\Phi]_{589}$ −195°; $[\Phi]_{400}$ −1373°; $[\Phi]_{390}$ −1625°; $[\Phi]_{380}$ −1866°; $[\Phi]_{370}$ −2378°; $[\Phi]_{360}$ −2830°; $[\Phi]_{350}$ −3330°; $[\Phi]_{347\cdot5}$ −3500°; $[\Phi]_{345}$ −3476°; $[\Phi]_{340}$ −2975°; $[\Phi]_{337\cdot5}$ −2775°; $[\Phi]_{335}$ −2820°; $[\Phi]_{332\cdot5}$ −2865°; $[\Phi]_{330}$ −2730°; $[\Phi]_{327\cdot5}$ −2360°; $[\Phi]_{325}$ −2085°; $[\Phi]_{322\cdot5}$ −2145°; $[\Phi]_{320}$ −2470°; $[\Phi]_{317\cdot5}$ −2795°; $[\Phi]_{315}$ −2870°; $[\Phi]_{312\cdot5}$ −2774°; $[\Phi]_{310}$ −2715°; $[\Phi]_{307\cdot5}$ −2652°; $[\Phi]_{305}$ −2458°; $[\Phi]_{300}$ −1224°; $[\Phi]_{290}$ +2882°; $[\Phi]_{275}$ +8960°.

16α-*Acetyl*-Δ^5-*pregnene*-3β,-20β-*diol* (XIVa; Fig. 5). Methanol, (*c:* 0·055): $[\Phi]_{700}$ −146°; $[\Phi]_{589}$ −396°; $[\Phi]_{300}$ +719°; $[\Phi]_{250}$ −6570°; Acid study:[12] $[\Phi]_{297\cdot5}$ +788°.

16α-*Acetyl*-Δ^5-*pregnene*-3β,20β-*diol diacetate* (XIVb; Fig. 5). Methanol, (*c:* 0·058): $[\Phi]_{700}$ −68°; $[\Phi]_{589}$ −83°; $[\Phi]_{300}$ +1408°; $[\Phi]_{252\cdot5}$ −6105°; $[\Phi]_{240}$ −5570°.

16α-*Acetyl-progesterone* (XV; Fig. 5). Dioxane, (*c:* 0·027): $[\Phi]_{700}$ +65°; $[\Phi]_{589}$ +77°; $[\Phi]_{400}$ +1062°; $[\Phi]_{390}$ +1190°; $[\Phi]_{385}$ +1217°; $[\Phi]_{382\cdot5}$ +1243°; $[\Phi]_{380}$ +1255°; $[\Phi]_{377\cdot5}$ +1255°; $[\Phi]_{375}$ +1228°; $[\Phi]_{370}$ +1165°; $[\Phi]_{367\cdot5}$ +1114°; $[\Phi]_{365}$ +1126°; $[\Phi]_{362\cdot5}$ +1126°; $[\Phi]_{360}$ +1191°; $[\Phi]_{355}$ +1307°; $[\Phi]_{350}$ +1413°; $[\Phi]_{305}$ +14500°; $[\Phi]_{267\cdot5}$ −1875°; $[\Phi]_{265}$ −1425°.

16β-*Acetyl*-17α-(*iso*)-Δ^5-*pregnene*-3β,20β-*diol* (XVI; Fig. 5). Methanol, (*c:* 0·049): $[\Phi]_{700}$ −275°; $[\Phi]_{589}$ −332°; $[\Phi]_{300}$ −4970°; $[\Phi]_{260}$ +1953°; $[\Phi]_{255}$ +1803°; Acid study:[12] $[\Phi]_{297\cdot5}$ −4995°.

16β-*Acetyl*-17α-(*iso*)-*progesterone* (XVII; Fig. 5). Dioxane, (*c:* 0·051): $[\Phi]_{700}$ −75°; $[\Phi]_{589}$ −89°; $[\Phi]_{400}$ −584°; $[\Phi]_{390}$ −1067°; $[\Phi]_{380}$ −1357°; $[\Phi]_{370}$ −1892°; $[\Phi]_{365}$ −2235°; $[\Phi]_{360}$ −2435°; $[\Phi]_{355}$ −2550°; $[\Phi]_{350}$ −2825°; $[\Phi]_{347\cdot5}$ −2935°; $[\Phi]_{345}$ −2950°; $[\Phi]_{342\cdot5}$ −2815°; $[\Phi]_{340}$ −2610°; $[\Phi]_{337\cdot5}$ −2425°; $[\Phi]_{335}$ −2350°; $[\Phi]_{332\cdot5}$ −2315°; $[\Phi]_{330}$ −2160°; $[\Phi]_{325}$ −1507°; $[\Phi]_{322\cdot5}$ −1458°; $[\Phi]_{320}$ −1570°; $[\Phi]_{315}$ −1885°; $[\Phi]_{310}$ −2200°; $[\Phi]_{307\cdot5}$ −2470°; $[\Phi]_{305}$ −2635°; $[\Phi]_{302\cdot5}$ −2550°; $[\Phi]_{300}$ −2280°; $[\Phi]_{290}$ +708°; $[\Phi]_{280}$ +3920°.

Chromatography study of the configurational stability of compounds. (IIId), (Vc), (Xa), (XI), (XIIa) and (XIII).[20]

For these experiments a Barber-Colman, Model 10, gas chromatograph with radium β-ray ionizing detector was used, under the following conditions for the acetate-esters (IIId and Vc): column, 1% SE 31 silicone on 100–140 mesh Gas Chrom P, ¼″ × 6′ at 240°, cell 260° and 750 volts, flash heater 275°, Argon flow about 90 ml/min.

Each of the samples, 1·04 mg of the ester (IIId) and 1·12 mg of the ester (Vc) was dissolved in 0·20 ml acetone. Six injections of 10 microliters were then made and collected from the gas chromatograph of each solution. The collection was made in 1 mm bore metal tubing at room temp. The collected fractions were eluted into 2 ml calibrated test tubes with dioxane and made to the mark. The rotatory dispersion measurement of these solution was then made. Both curves were identical with the rotatory dispersion curve of the ester (IIId), reported in Fig. 1.

For the Δ^4-3-ketones (Xa, XI, XIIa, and XIII) the same technique was applied under the following conditions: column, 1% SE 30 silicone on 100–140 mesh Gas Chrom P (acid and base washed). ¼″ × 6′ at 240°, flash heater 295°, Argon flow about 70 ml/min. The effluents were collected in 1 mm bore stainless steel tubing, and eluted into 5 ml volumetric flasks with dioxane. The actual concentration was determined by UV and the solutions were submitted to rotatory dispersion measurements. The rotatory dispersion curves of the progesterone (Xa; Fig. 3) and of the isoprogesterone (XIIa; Fig. 4) were not affected by this gas chromatography treatment. But, after passing through the chromatography column, the sample of the progesterone (XI; Fig. 3) gave the same rotatory dispersion curve as the isoprogesterone (XIIa), i.e. the positive Cotton effect at 305 mμ had completely disappeared, the main feature of the curve now being the Δ^4-3-ketone multiple Cotton effects (Fig. 4). Furthermore after gas chromatography, the sample of isoprogesterone (XIII; Fig. 4) gave a rotatory dispersion curve identical with the curve of the progesterone (Xa), thus showing a positive Cotton effect as 305 mμ (see Fig. 3).

Acknowledgements—The author would like to thank Professor C. Djerassi, Stanford University, for reading the manuscript prior to publication and making helpful comments.

[20] This type of epimerization occurring during vapor-phase chromatography has also been observed in other series. These experiments will be discussed thoroughly by Dr. J. C. Matthews in a forthcoming paper.