Amino- and Dienamino-derivatives formed from Adrenocortical Steroids and Heterocyclic Bases †

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Pyrrolidine, morpholine, and piperidine react directly with the 20-oxo-17α,21-dihydroxy-side-chain of corticosteroids to give 21-amino-derivatives. I.r. and n.m.r. data indicate the presence of an internal hydrogen bond between the 17α-hydroxy-group and the C-21 nitrogen atom. The reaction at the 4-en-3-one system leads, as expected, to 3-amino-3,5-dienes. Reactivity at C-3 follows the order pyrrolidine > morpholine > piperidine and can be explained on the basis of resonance theory and steric effects. It is possible to prepare either 21-amino- or 3,21-diamino-derivatives. An *s-trans*-structure is postulated for the 3,5-diene system; a cross-conjugated system is excluded on the basis of n.m.r. data. Corticosteroids without a 17α-hydroxy-group react at C-21 only, under more drastic conditions. A possible explanation of the function of the 17-hydroxy-group is advanced.

AMINO-, enamino-, dienamino-, and conjugated azodiene derivatives of steroidal carbonyl compounds have been synthesized and studied,[1-6] but the direct reaction between heterocyclic bases and active corticoids [17α,21-dihydroxypregn-4-ene-3,11,20-trione (cortisone); 17α,11β,21-trihydroxypregn-4-ene-3,20-dione (cortisol); 17α,21-dihydroxypregn-4-ene-3,20-dione (cortexolone)] has not been investigated. All previously reported [5,6] 21-amino-steroids were obtained from the 21-halogeno-derivatives. Leukart's reaction, conducted on steroids with an α-ketol chain at C-17 but without a 17α-hydroxy-group, led to 20-amino-steroids.[7,8] 3-Dienamino-derivatives of steroidal carbonyl compounds, which are interesting both from the point of view of selective protection of carbonyl groups [9] and as intermediates,[10,11] have been studied in greater detail,[7,8,12] but only a few 3-pyrrolidino-derivatives of corticosteroids are known.

We have found that cortisone, cortisol, and cortexolone

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[10] G. I. Fujimoto and R. W. Ledeen, *J. Org. Chem.*, 1964, **29**, 2059.
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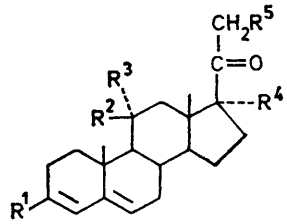
[12] J. L. Johnson, M. E. Herr, J. C. Babcock, A. F. Fonken, J. E. Stafford, and F. W. Heyl, *J. Amer. Chem. Soc.*, 1956, **78**, 430.

(but not corticosteroids lacking a 17α-hydroxy-group) react rapidly, in benzene solution, with heterocyclic bases (with azeotropic removal of water) to give 21-amino-derivatives. With pyrrolidine, which also reacts readily with the 4-en-3-one system, 3,21-diamino-derivatives are obtained, but with morpholine or piperidine, which are less reactive, it is possible to obtain 21-amino-derivatives without protecting position 3. With pyrrolidine, 21-acetoxy-cortisone gives the 3,21-dipyrrolidino-derivative under the conditions used by us, whereas not only 21-acetoxy-cortisone but also cortisone in methanol (toluene-*p*-sulphonic acid catalyst) react only at position 3 (in agreement with the literature [7,8]). Under much more drastic conditions cortexone (lacking a 17α-hydroxy-group) reacts at the 21-position, but the yields are much lower.

Reaction at Position 3.—I.r. absorptions (see Experimental section) in the double-bond region for compounds (I)—(IX) (Table), which are all 3-pyrrolidino-derivatives to H-4 and H-6 of an exocyclic (*trans*) diene system (Table). This assignment is also supported by literature data.[14] Compounds (II)—(IX) give H-4 and H-6 signals in agreement with those of compound (I); thus the cross-conjugated homoannular diene structure is also excluded for these compounds.

The u.v. spectrum of 17α-hydroxy-3,21-dimorpholino-pregna-3,5-diene-11,20-dione (X) shows a blue shift of >10 nm and smaller ε values with respect to the 3-pyrrolidino-derivatives (I)—(IX). The energy necessary for the six-membered heterocycles to reach the principal excited level, in which an exocyclic double bond is present, must, in fact, be greater.[12,15] The n.m.r. signals for H-4 and H-6 of the conjugated diene system are found at lower field in compound (X) and in 17α-hydroxy-3,21-dipiperidinopregna-3,5-diene-11,20-dione (XII). Since the electronic delocalization depends on the character of the exocyclic double bond, these two protons are less shielded than in structures (I)—(IX)



						¹H N.m.r. (τ values; Me_4Si internal standard; $CDCl_3$)								
	Parent steroid [a]	R¹	R²R³	R⁴	R⁵	H-4	H-6	H-11	17α-OH	21-H_2	21-OH	$-CH_2-CH_2-N$-3(C)	$-CH_2-CH_2-N$-21(C)	$-CH_2-CH_2-O-$
(I)	Cortisone [b] / 21-Iodocortisone	P	O	OH	P	5·22(s)	4·92(m)		4·20(s) *	6·55(q) †		6·80(m)	7·35(m)	
		P	O	OH	P	5·27(s)	4·97(m)		4·30(s) *	6·6(q) †		6·9(m)	7·4(m)	
(II)	Cortisone	P	O	OH	OH	5·27(s)	4·96(m)		?	5·54(q)	?	6·85(m)		
(III)	Cortisol [c]	P	OH,H	OH	P	5·20(s)	4·99(m)	5·45(m)	5·45(s)	6·48(q) †		6·80(m)	7·35(m)	
(IV)	Cortexolone [d]	P	H,H	OH	P	5·20(s)	4·91(m)		4·55(s) *	6·55(q) †		6·84(m)	7·36(m)	
(V)	21-Iodo-corticosterone	P	OH,H	H	P	5·27(s)	5·08(m)	5·63(m)		6·70(s)		6·87(m)	7·43(m)	
(VI)	Corticosterone [e]	P	OH,H	H	OH	5·45(s)	5·28(m)	5·78(m)		5·98(s)	5·98(s) ‡	6·68(m)		
(VII)	Cortexone	P	H,H	H	OH	5·21(s)	5·01(m)			5·78(s)	5·55(s)	*ca.* 6·85(m)		
(VIII)	17α-Hydroxy-progesterone	P	H,H	OH	H	5·18(s)	4·91(m)		6·6(s)			6·79(m)		
(IX)	Progesterone	P	H,H	H	H	5·22(s)	4·98(m)					6·88(m)		
(X)	Cortisone	M	O	OH	M	4·91(s)	4·80(m)		4·5(s) *	6·67(d)		7·07(m)	7·07(m)	6·21(m)
(XI)	Cortisone	*f*	O	OH	M	4·25(s)			?	6·67(d)			7·43(m)	6·25(m)
(XII)	Cortisone	Pi	O	OH	Pi	4·90(s)	4·83(m)		3·0(s) *	6·79(q) †		7·05(m)	7·50(m)	
(XIII)	Cortisone	*f*	O	OH	Pi	4·42(s)			3·32(s)	6·88(q)			7·57(m)	
(XIV)	Cortisone	M	O	OH	Pi	5·04(s)	4·93(m)		4·5(s) *	6·88(q) †		7·13(m)	7·55(m)	6·31(m)
(XV)	Cortexolone	*f*	O	OH	Pi	4·24(s)			*ca.* 5·3(s) *	6·72(q)			7·50(m)	

P = Pyrrolidine; Pi = piperidine; M = morpholine.

* Very broad. † Partially hidden by skeletal proton resonances. ‡ Hidden by 21-H_2 (tentatively assigned on the basis of integral ratio).

[a] Trivial names from ref. 13. [b] τ 4·37 (H-4), 5·4 (17α-OH), 5·66 (21-H_2), 4·45 (21-OH) [$(CD_3)_2SO$]. [c] τ 4·45 (H-4), 5·56 (17α-OH), 5·72—5·79 (H-11 and 21-H_2), 4·90 (21-OH) [$(CD_3)_2SO$]. [d] τ 4·38 (H-4), *ca.* 5·6 (17α-OH), 5·6 (21-H_2), 4·83 (21-OH) [$(CD_3)_2SO$]. [e] τ 4·3 (H-4), 5·6 (H-11), 5·82 (21-H_2) ($CDCl_3$). [f] 4-En-3-one system.

derived from Δ^4-3-oxo-steroids, were characteristic of dienamines [9,12] ($\nu_{max.}$ 1650—1630 and 1620—1600 cm^{-1}). The electronic spectra of solutions in methanol showed maxima in the 275—277 nm range (ε 19,000—23,000). The high values of ε suggest that the compounds are transoid heteroannular dienes (*s-trans*).[12,13] From i.r. and u.v. spectra and rotations [12] it is not possible to exclude the presence of the homoannular cross-conjugated diene in tautomeric equilibrium. However n.m.r. data exclude the latter form. The ¹H n.m.r. spectrum of 17α-hydroxy-3,21-dipyrrolidinopregna-3,5-diene-11,20-dione (I) shows a sharp signal at τ 5·22 and a broad low-field signal at τ 4·92 which we have assigned owing to the smaller interaction with the nitrogen lone pair in the case of the six-membered bases. The H-2 signal is also absent for compounds (X) and (XII), and the cross-conjugated form can be excluded. As in analogous cases,[14] the absence of the homoannular isomer is probably to be attributed to resonance and steric effects. Models indicate that the exocyclic diene structure is favoured and that resonance stabilization is greater for *s-trans*-isomers than for cross-conjugated isomers. The differing reactivities of the bases examined towards position 3 can be explained as follows. Pyrrolidine is the most active five-membered

[13] L. F. Fieser and M. Fieser, ' Steroids,' Reinhold, New York, 1969, pp. 15—25.

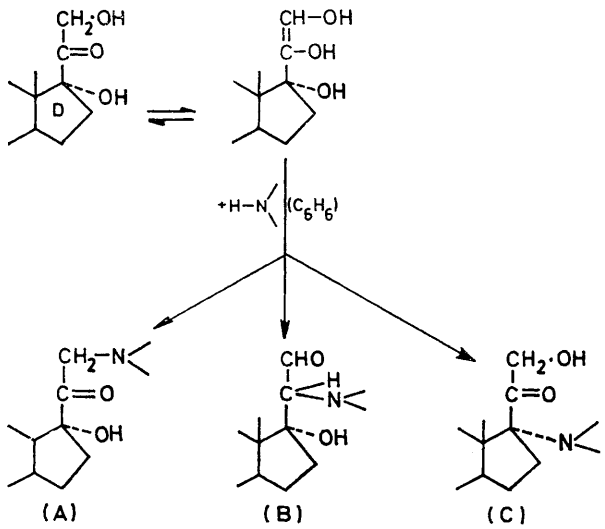
[14] N. F. Firrell and P. W. Hickmott, *J. Chem. Soc.* (*B*), 1969, 293.

[15] H. C. Brown, *J. Org. Chem.*, 1957, **22**, 439.

base because the product is more highly stabilized by resonance and because the formation of the exocyclic double bond, which must be present in the transitions state between the carbinolamine intermediate and the 3-dienamine, requires less energy. The higher reactivity of morpholine with respect to piperidine, can probably be attributed to the difference in steric requirement.

Catalysis with toluene-*p*-sulphonic acid is sufficient to give compound (X), but compound (XII) can be obtained in good yield only under more drastic conditions from 17α-hydroxy-21-piperidinopregn-4-ene-3,11,20-trione (XIII). Compound (XIII) readily gave 17α-hydroxy-3-morpholino-21-piperidinopregna-3,5-diene-11,20-dione (XIV). In all the 3-dienamino-derivatives a shift of about 0·2 p.p.m. to higher field of the 10-methyl resonances was noted.

Reaction at the Side Chain.—For the side-chain reaction it is possible to postulate several mechanisms, which may give 21-amino-17α-hydroxy-20-oxo-derivatives (A); 20-amino-17α-hydroxy-21-oxo-derivatives (B); or 17α-amino-21-hydroxy-20-oxo-derivatives (C) (Scheme 1). Derivatives of type (B) can be excluded



SCHEME 1

because of the presence in the i.r. spectra of all compounds substituted in the side chain of the C-20 carbonyl absorption, and also because no signal is found below τ 3 in the n.m.r. spectra corresponding to C*H*=O. To ascertain whether these compounds have structures of type (A) or of type (C), 11β,21-dihydroxypregn-4-ene-3,20-dione (corticosterone) and 21-hydroxypregn-4-ene-3,20-dione (cortexone), both lacking a 17α-hydroxy-group, and 17α-hydroxypregn-4-ene-3,20-dione (17α-hydroxy-progesterone) were treated with pyrrolidine under the same conditions used for making compounds (I), (III), and (IV). However we were only able to isolate the 3-dienamines (VI)—(VIII). Under more drastic conditions (piperidine both as solvent and as reagent) 21-piperidinopregn-4-ene-3,20-dione (XVI) was obtained from cortexone. The fact that under our conditions 21-acetoxycortisone reacted with pyrrolidine to give the disubstituted compound (at C-3 and on the side chain), was a preliminary indication that these compounds have structure (A). To establish this beyond doubt the reaction was carried out by an alternative route; that is, with 17α-hydroxy-21-iodopregn-4-ene-3,11,20-trione (21-iodocortisone) and 11β-hydroxy-21-iodopregn-4-ene-3,20-dione (21-iodocorticosterone), prepared from 21-methanesulphonates by treatment with sodium iodide.[16-18] 21-Iodocortisone gave compound (I) identical with that obtained *via* the direct route. Similarly, 21-iodocorticosterone gave 11β-hydroxy-3,21-dipyrrolidinopregna-3,5-dien-20-one (V).

That reaction takes place at C-21 is also supported by the n.m.r. spectra, on the basis of Shoolery's rules.[19,20] For C-21 methylenic protons, the calculated τ value is 5·51 for the system RCO–CH_2–OH and 6·5 for RCO–CH_2–NR_2. The experimental values are *ca.* 5·8 (singlet) for 21-hydroxy-20-oxo-steroids and *ca.* 5·61 (quartet or doublets, *J* 20 Hz) for 17α,21-dihydroxy-20-oxo-steroids.[21] These are the positions in which the C-21 proton resonances are found in the spectra of 17α,21-dihydroxy-3-pyrrolidinopregna-3,5-diene-11,20-dione (II) and compounds (VI) and (VII) substituted only at C-3. In all compounds substituted in the side chain, the C-21 proton resonances are displaced by *ca.* 1 p.p.m. to higher field, in agreement with the prediction for C(21)–N linked compounds. The assignment of the C-21 proton signals in the 21-amino-derivatives is more or less easy according to the nature of the base at C-3. In fact, the resonances of CH_2 groups adjacent to the C-3 nitrogen atom and conjugated with the diene system, are centered around τ 7. The analogous methylenic groups of the bases bound at C-21 occur at τ *ca.* 7·5 (Table). In 3-pyrrolidinopregna-3,5-dien-20-one (IX) and compound (VIII), where 21-methylene protons are absent, only a triplet is found at about τ 6·85, and similar results are found for compounds (II), (VI), and (VII). The morpholine CH_2 protons, adjacent to the heterocyclic oxygen atom in 17α-hydroxy-3,21-dimorpholinopregna-3,5-diene-11,20-dione (X) and in 17α-hydroxy-21-morpholinopregn-4-ene-3,11,20-trione (XI) resonate at about τ 6·25.

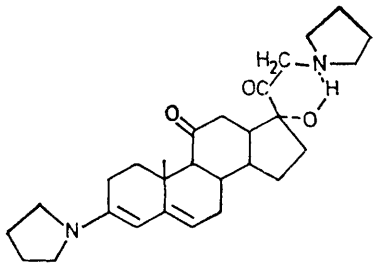
The assignments of the N–C(21)H_2 signals and other assignments (Table) are supported by integration and by comparison with the n.m.r. spectra of the parent steroids (some of which are reported in the literature [21,22]

[16] P. Borrevang, *Acta Chem. Scand.*, 1955, **9**, 587.
[17] J. E. Fried and A. Borman, *Vitamins and Hormones*, 1958, **16**, 304.
[18] J. P. Conbere and K. Pfister, U.S.P. 2,870,177 (*Chem. Abs.*, 1959, **53**, 11,453b).
[19] R. M. Silverstain and G. C. Bassler, 'Spectrometric Identification of Organic Compounds,' Wiley, New York, 1967, pp. 141—143.
[20] J. A. Pople, W. G. Schneider, and H. J. Bernstein, 'High Resolution Nuclear Magnetic Resonance,' McGraw-Hill, New York, 1959, p. 119.
[21] W. Neudert and H. Röpke, 'Steroid Spektrenatlas,' Springer-Verlag, Berlin–Heidelberg–New York, 1965.
[22] J. N. Shoolery and M. T. Rogers, *J. Amer. Chem. Soc.*, 1958, **80**, 5121.

and others in the Table). The n.m.r. spectrum of 17α-hydroxy-21-piperidinopregn-4-ene-3,20-dione (XV) shows clearly the quartet due to the 21-methylene protons.

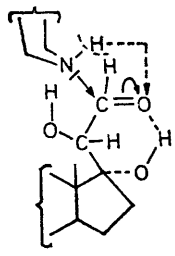
Contrary to what is found for substitution at C-3, substitution at C-21 does not cause noticeable displacements of the 10-methyl resonances. In the i.r. spectrum of 17α-hydroxy-3,21-dipyrrolidinopregna-3,5-dien-20-one (IV), as well as in those of compounds (I), (Ia), and (XII), the signals relating to the 17α- and 21-hydroxy-groups of the parent steroids are absent, and instead are found broad absorptions between 3300 and 2500 cm^{-1} (KBr), which persist even in methylene dichloride and chloroform solutions. Similar results are found for compounds (XIII), (XIV), and (XV) (all 21-piperidino-derivatives), and for (X) and (XI) (21-morpholino-derivatives) (Experimental section). These data, which are in agreement with a strong internal hydrogen bond, are confirmed by the n.m.r. data. For all 21-amino-derivatives of 17α-hydroxy-steroids, in fact, a very broad signal between τ 3 and 4·5 is found, which shows both concentration and temperature dependence and exchange with deuterium oxide. The C-20 carbonyl stretching frequency in the 21-amino-derivatives has been assigned on the basis of its lower intensity, with respect to the 11-carbonyl absorption and of the dependence of its frequency upon the 21-substituent.[23]

In conclusion, chemical and spectroscopic data show that all the 3,21-disubstituted derivatives must be formulated as exocyclic *trans*-diene systems and as chelates [as shown for compound (I) in Scheme 2].



SCHEME 2

The strong internal hydrogen bond is present in all 21-amino-derivatives. That the presence of the 17α-



SCHEME 3

hydroxy-group favours reaction at C-21 is probably not only because the final product is stabilized by the hydrogen bond, but also because this hydroxy-group could play an important part in the reaction mechanism, which could involve the intermediate shown in Scheme 3.

EXPERIMENTAL

Compounds (I), (III), (IV), (VI)—(XI), and (XIII)—(XV) were prepared by refluxing the corresponding steroids in benzene with an excess of pyrrolidine, morpholine, or piperidine all freshly distilled from sodium hydroxide (pyrrolidine, b.p. 87—88°; morpholine, b.p. 128—129°; piperidine, b.p. 105—107°). During the reaction the mixture was continually flushed with dry nitrogen and stirred, and the water formed was removed azeotropically with a Dean–Stark apparatus. The reaction was allowed to proceed until no more water was collected. Compounds (VIII), (IX), (X), and (XIV) required small additional amounts of toluene-*p*-sulphonic acid as catalyst. Dienamines (I) [method (*b*)] and (V) were obtained by adding an excess of pyrrolidine to the 21-iodo-derivatives dissolved in anhydrous acetone (distilled from phosphoric anhydride; b.p. 56°) with anhydrous sodium sulphate as drying agent, under dry nitrogen and with vigorous stirring. ^1H N.m.r. spectra were obtained with a Varian A-60 or a Jeol C60-HL apparatus, for solutions in deuteriochloroform or [$^2H_6$]dimethyl sulphoxide (tetramethylsilane as internal standard). I.r. spectra were obtained with a Perkin-Elmer 457 spectrometer, for potassium bromide discs or Nujol mulls unless otherwise stated. U.v. spectra were recorded for methanolic solutions with a Cary 14 spectrophotometer.

17α-*Hydroxy*-3,21-*dipyrrolidinopregna*-3,5-*diene*-11,20-*dione* (I).—(*a*) To cortisone (3 g, 8·5 mmol) suspended in benzene (35 ml), pyrrolidine (3 ml, 36 mmol) was added in three portions. During the reaction the solution was twice concentrated under reduced pressure and cooled with ice. The precipitate was washed with cold benzene, ether–methanol, and ether to give the *product* (1·55 g, 40%), m.p. 197—199° (decomp.) (Found: C, 74·45; H, 9·2; N, 6·15. $C_{29}H_{42}N_2O_3$ requires: C, 74·1; H, 9·0; N, 6·0%); $\lambda_{max.}$ 275 nm (ε 20,350), $\nu_{max.}$ 3060 (17α-OH), 1716 [C(20)=O], 1703 [C(11)=O], and 1640 and 1610 cm^{-1} (3,5-diene).

(*b*) To cortisone 21-iodide (0·4 g, 0·85 mmol) in acetone (25 ml), pyrrolidine (0·75 ml, 6·6 mmol) was added. After 45 min the solution was concentrated under diminished pressure and cooled. The crude product was washed with acetone, water, acetone again, and then with ether, to give the diamine (I) (0·060 g, 15%), m.p. 201—204° (decomp.) (Found: C, 74·2; H, 9·1; N, 5·7%); u.v. and i.r. data as for the product from (*a*).

17α,21-*Dihydroxy*-3-*pyrrolidinopregna*-3,5-*diene*-11,20-*dione* (II).—We followed the method used for the 3-pyrrolidino-diene of androstenedione.[12] To a supersaturated solution of cortisone (1·5 g, 4·2 mmol) in methanol (34 ml) at 35°, toluene-*p*-sulphonic acid (0·01 g) and pyrrolidine (0·85 ml, 10·1 mmol) in methanol (2 ml) were added, and the resulting solution was stirred for 50 min. The mixture was twice concentrated under diminished pressure causing the *product* (II), which rapidly decomposes, to precipitate (1·2 g, 70%). Repeated crystallization by adding distilled water to an acetone solution and then washing the solid with cold water gave material of m.p. 132—134° (decomp.) (Found: C, 71·25; H, 8·3; N, 3·3. $C_{25}H_{35}NO_4$ requires

[23] C. N. R. Rao, 'Chemical Application of Infrared Spectroscopy,' Academic Press, New York and London, 1963, pp. 192—200 and 417—419.

C, 72·6; H, 8·5; N, 3·4%); $\lambda_{max.}$ 274 nm (ε 19,151), $\nu_{max.}$ 3430 (17α- and 21-OH), 1706 [C(20)=O and C(11)=O], and 1640 and 1610 cm^{-1} (3,5-diene).

11β,17α-*Dihydroxy*-3,21-*dipyrrolidinopregna*-3,5-*dien*-20-*one* (III).—To cortisol (2 g, 5·5 mmol) in benzene (22 ml), pyrrolidine (2·05 ml, 24·1 mmol) was added in several portions. After 35 min repeated concentration under reduced pressure gave a precipitate, which decomposed on exposure to the atmosphere. The crude product was purified by washing with cold benzene and repeating the procedure with ether after centrifugation. Further washing with ether gave a light yellow *product*, m.p. 195—198° (decomp.) (Found: C, 73·5; H, 9·6; N, 5·95. $C_{29}H_{44}N_2O_3$ requires C, 74·2; H, 9·7; N, 9·0%); $\lambda_{max.}$ 276 nm (ε 23,170), $\nu_{max.}$ 3510 (11β-OH), 3150 (17α-OH), 1698 [C(20)=O], and 1639 and 1608 cm^{-1} (3,5-diene).

3,21-*Dipyrrolidinopregna*-3,5-*dien*-20-*one* (IV).—To cortexolone (0·5 g, 1·44 mmol) suspended in benzene (22 ml), pyrrolidine (0·72 ml, 8·5 mmol) was added. After about 30 min the mixture was cooled and a crystalline *solid* precipitated, which was filtered off and washed with acetone and then with ether (0·13 g, 20%), m.p. 195—198° (decomp.) (Found: C, 76·1; H, 9·7; N, 5·95. $C_{29}H_{44}N_2O_2$ requires C, 76·2; H, 9·7; N, 6·2%); $\lambda_{max.}$ 276 nm (ε 21,078), $\nu_{max.}$ 3100 (17α-OH), 1710 [C(20)=O], and 1637 and 1605 cm^{-1} (3,5-diene).

11β-*Hydroxy*-3,5-*dipyrrolidinopregna*-3,5-*dien*-20-*one* (V).—To corticosterone 21-iodide (0·8 g, 1·75 mmol) in acetone (50 ml), pyrrolidine (1·15 ml, 13·4 mmol) was added. Method (*b*) for compound (I) gave the *product* (0·26 g, 37%), m.p. 196—198° (decomp.) (Found: C, 77·65; H, 9·9; N, 5·65. $C_{29}H_{44}N_2O_2$ requires C, 76·95; H, 9·8; N, 6·2%); $\lambda_{max.}$ 277 nm (ε 20,404), $\nu_{max.}$ 3480 (11α-OH), 1704 [C(20)=O], and 1628 and 1600 cm^{-1} (3,5-diene).

11β,21-*Dihydroxy*-3-*pyrrolidinopregna*-3,5-*dien*-20-*one* (VI).—To corticosterone (2 g, 5·77 mmol) suspended in benzene (30 ml), pyrrolidine (3 ml, 34·7 mmol) was added. The steroid rapidly dissolved and in a short time a crystalline product began to precipitate. After concentration of the solution this was collected and washed with methanol and ether, giving the *amine* (VI) (1·6 g, 63%), m.p. 180—183° (decomp.) (Found: C, 75·2; H, 9·4; N, 3·4. $C_{25}H_{37}NO_3$ requires C, 75·15; H, 9·3; N, 3·5%); $\lambda_{max.}$ 277 nm (ε 20,530), $\nu_{max.}$ 3480 (11β-OH), 3450 (21-OH), 1708 [C(20)=O], and 1630 and 1600 cm^{-1} (3,5-diene).

21-*Hydroxy*-3-*pyrrolidinopregna*-3,5-*dien*-20-*one* (VII).—To cortexone (0·5 g, 1·51 mmol) suspended in benzene (25 ml), pyrrolidine (0·75 ml, 8·95 mmol) was added. The solution was then concentrated under reduced pressure and cooled, and the crystalline *product* was filtered off and washed with methanol and ether; m.p. 158—160° (decomp.) (Found: C, 78·4; H, 9·8; N, 3·5. $C_{25}H_{37}NO_2$ requires C, 78·3; H, 9·7; N, 3·65%); $\lambda_{max.}$ 275 nm (ε 22,128), $\nu_{max.}$ 3520 (21-OH), 1709 [C(20)=O], and 1636 and 1606 cm^{-1} (3,5-diene).

17α-*Hydroxy*-3-*pyrrolidinopregna*-3,5-*dien*-20-*one* (VIII).—To the parent steroid (2 g, 6·05 mmol) in benzene (35 ml), pyrrolidine (3 ml, 3·52 mmol) and toluene-*p*-sulphonic acid (10 mg) were added. The solution was concentrated and cooled to yield yellow *crystals*, which were washed with acetone–methanol and ether (yield 1 g, 43%), m.p. 185—189° (decomp.) (Found: C, 78·35; H, 9·7; N, 3·55. $C_{25}H_{37}NO_2$ requires C, 78·3; H, 9·3; N, 3·65%); $\lambda_{max.}$ 277 nm (ε 22,272), $\nu_{max.}$ 3442 (17α-OH), 1695 [C(20)=O], and 1637 and 1611 cm^{-1} (3,5-diene).

3-*Pyrrolidinopregna*-3,5-*dien*-20-*one* (IX).[12]—This product had m.p. 184—186° (decomp.) (from methylene dichloride–methanol) (lit.,[12] 175—177°) (Found: C, 82·1; H, 10·4; N, 3·7. Calc. for $C_{25}H_{37}NO$: C, 81·7; H, 10·15; N, 3·8%); u.v. and i.r. spectra as reported.

17α-*Hydroxy*-21-*methoxysulphonylpregn*-4-*ene*-3,11,20-*trione*.—This material had m.p. 200—203° (decomp.) (from benzene) (lit.,[16–18] 195—196°) (Found: C, 60·4; H, 7·0; Calc. for $C_{22}H_{30}O_7S$: C, 60·3; H, 6·9%); $\nu_{max.}$ 3500 (17α-OH), 1740 [C(20)=O], 1700 [C(11)=O], 1648 [C(3)=O], 1612 (4-ene), and 1358 and 1169 cm^{-1} (SO_2).

17α-*Hydroxy*-21-*iodopregn*-4-*ene*-3,11,20-*trione*.—This material had m.p. 172—175° (decomp.) (from ethyl acetate) (lit.,[16–18] 170—175°) (Found: C, 53·4; H, 5·9. Calc. for $C_{21}H_{27}IO_4$: C, 53·6; H, 5·8%); $\nu_{max.}$ 3310 (17α-OH), 1712 [C(20)=O], 1700 [C(11)=O], 1643 [C(3)=O], and 1610 cm^{-1} (4-ene).

11β-*Hydroxy*-21-*methylsulphonylpregn*-4-*ene*-3,20-*dione*.[24]—The reaction was performed as for cortisone 21-methanesulphonate. To corticosterone (2·3 g, 6·65 mmol) dissolved in dry pyridine (17 ml), methanesulphonyl chloride (1·1 ml, 13·3 mmol) was added. The solution was poured into ice–water to yield a crude *product* that was recrystallized from ethanol–water; yield 1·97 g (80%), m.p. 164—166° (decomp.) (Found: C, 62·25; H, 7·6. $C_{22}H_{32}O_6S$ requires C, 61·9; H, 7·6%); $\nu_{max.}$ 3350 (11β-OH), 1730 [C(20)=O], 1645 [C(3)=O], and 1608 cm^{-1} (4-ene).

11β-*Hydroxy*-21-*iodopregn*-4-*ene*-3,20-*dione*.[24]—To corticosterone 21-methanesulphonate (1·92 g, 4·53 mmol) in dry acetone (65 ml), sodium iodide (1·36 g, 9·5 mmol) was added. The reaction was conducted as for the cortisone 21-iodide. The crude *product* was washed with cold water (yield 2·05 g, 99·5%); m.p. 136—137° (Found: C, 55·6; H, 6·6. $C_{21}H_{29}IO_3$ requires C, 55·3; H, 6·4%); $\nu_{max.}$ 3400 (11β-OH), 1711 [C(20)=O], 1646 [C(3)=O], 1610 cm^{-1} (4-ene).

17α-*Hydroxy*-3,21-*dimorpholinopregna*-3,5-*diene*-11,20-*dione* (X).—To cortisone (3 g, 8·35 mmol) in benzene (35 ml), morpholine (3·5 ml, 50 mmol) was added. Evaporation under reduced pressure left a yellow oil. Crystallization from absolute ethanol and washing with ether gave a crystalline *solid* (1·2 g, 28%), m.p. 191—195° (decomp.). Attempts to remove water of crystallization were unsuccessful and led to the decomposition (Found: C, 67·4; H, 8·6; N, 5·9. $C_{29}H_{42}N_2O_5,H_2O$ requires C, 67·4; H, 8·6; N, 5·5%); $\lambda_{max.}$ 263 nm (ε 19,132), $\nu_{max.}$ 3520 * (H–O–H), 3250 (17α-OH), 1710 [C(20)=O], 1700 [C(11)=O], 1640 and 1607 cm^{-1} (3,5-diene).

17α-*Hydroxy*-21-*morpholinopregn*-4-*ene*-3,11,20-*trione* (XI).—To cortisone (3 g, 8·35 mmol) in benzene (35 ml), morpholine (7 ml, 79·2 mmol) was added. The solution was concentrated under diminished pressure and cooled to give a yellow crystalline *product*, which after recrystallization from methanol gave the *amine* (XI) (1·25 g, 34%). Attempts at removal of water of crystallization were unsuccessful; m.p. 198—201° (decomp.) (Found: C, 67·25; H, 8·3; N, 3·5. $C_{25}H_{35}NO_5,H_2O$ requires C, 67·1; H, 8·3; N, 3·15%); $\lambda_{max.}$ 240 nm (ε 16,344), $\nu_{max.}$ 3540 * (H–O–H), 3300 (17α-OH), 1710 [C(20)=O], 1700 [C(11)=O], 1660 [C(3)=O], and 1616 cm^{-1} (4-ene).

* This band changes in very dilute CCl_4 solution (2 cm cell) into absorptions at *ca.* 3700 and 3610 cm^{-1}, due to H_2O stretching.

[24] P. Tannhauser, R. I. Pratt, and E. V. Jensen, *J. Amer. Chem. Soc.*, 1956, **78**, 2658; J. Fried, personal communication.

17α-*Hydroxy*-3,21-*dipiperidinopregna*-3,5-*diene*-11,20-*dione* (XII).—To compound (XIII) (0·5 g, 1·17 mmol) in dry piperidine (30 ml) were added anhydrous sodium sulphate (3—4 g) (in a Soxhlet thimble) and toluene-*p*-sulphonic acid (0·01 g). The mixture was heated at 110° while flushing with nitrogen and occasionally shaking. After 8 h the reaction was stopped and benzene (30 ml) was added twice to wash the thimble. Concentration and addition of light petroleum (b.p. 80—100°) precipitated the *diamine* (XII) (0·385 g, 65%), m.p. 178—181° (decomp.) (from light petroleum) (Found: C, 75·5; H, 5·5; N, 9·4. $C_{31}H_{46}N_2O_3$ requires C, 75·3; H, 5·7; N, 9·4%); $\lambda_{max.}$ 265 nm (ε 17,888), $\nu_{max.}$ 3000 (17α-OH), 1717 [C(20)=O], 1705 [C(11)=O], and 1640 and 1602 cm^{-1} (3,5-diene).

17α-*Hydroxy*-21-*piperidinopregn*-4-*ene*-3,11,20-*trione* (XIII).—To cortisone (3 g, 8·35 mmol) suspended in benzene (35 ml), piperidine (7 ml, 71 mmol) was added in two portions. The solution was heated at 100° and, after 6 h, twice evaporated under diminished pressure, giving a light yellow *solid* (1·8 g, 50%) that crystallized from light petroleum (b.p. 80—100°); m.p. 170—175° (decomp.) (Found: C, 73·3; H, 8·9; N, 3·25. $C_{26}H_{37}NO_4$ requires C, 74·04; H, 8·7; N, 3·3%); $\lambda_{max.}$ 239 nm (ε 15,874), $\nu_{max.}$ 3400 * (17α-OH), 1718 [C(20)=O], 1706 [C(11)=O], 1652 [C(3)=O], and 1618 cm^{-1} (4-ene).

17α-*Hydroxy*-3-*morpholino*-21-*piperidinopregna*-3,5-*diene*-11,20-*dione* (XIV).—To compound (XIII) (1·4 g, 3·28 mmol) suspended in benzene (35 ml) were added toluene-*p*-sulphonic acid and morpholine (2 ml, 49·2 mmol) in two portions, while heating at 100°. After 6 h the solution was twice concentrated under reduced pressure. The crude product (0·77 g, 43%) was washed with ether, crystallized from light petroleum (b.p. 80—100°), and dried (1 h at 100° and 15 mmHg); m.p. 203—207° (decomp.) (Found: C, 72·75; H, 8·75; N, 5·5. $C_{30}H_{44}N_2O_4$ requires C, 72·55; H, 8·9; N, 5·6%); $\lambda_{max.}$ 264 nm (ε 20,178), $\nu_{max.}$ 3540 † (H–O–H), 3240 ‡ (17α-OH), 1710 [C(20)=O], 1700 [C(11)=O], and 1645 and 1610 cm^{-1} (3,5-diene).

17α-*Hydroxy*-21-*piperidinopregn*-4-*ene*-3,20-*dione* (XV).—To cortexolone (2 g, 5·77 mmol) suspended in benzene (35 ml), piperidine (5·3 ml, 52 mmol) was added in four portions during heating for 6 h at 100°. The solution was twice concentrated under diminished pressure. Addition of ether caused some unchanged cortexolone to precipitate. The *product* (XV) crystallized from the remining solution after 1 day at room temperature (yield 0·45 g, 20%), m.p. 171—175° (decomp.) [from light petroleum (b.p. 80—100°)] (Found: C, 75·4; H, 9·55; N, 3·2. $C_{26}H_{39}NO_3$ requires C, 75·5; H, 9·5; N, 3·4%); $\lambda_{max.}$ 242 nm (ε 16,775), $\nu_{max.}$ 3410 ‡ (17α-OH), 1710 [C(20)=O], 1645 [C(3)=O], and 1612 cm^{-1} (4-ene).

21-*Piperidinopregn*-4-*ene*-3,20-*dione* (XVI).—Cortexone (1 g, 3·3 mmol) in piperidine (2 ml) was heated for 2 h at 110—115° in the presence of anhydrous sodium sulphate and under nitrogen. The solution was filtered and evaporated to dryness. The residue was twice chromatographed on 2 mm silica gel plates (propanol as eluant). The broadest band was extracted with methanol. The oily product was treated with ether and the residue was filtered off. Removal of the ether left a small amount of a crude *product* which, recrystallized from light petroleum (b.p. 80—100°), had m.p. 130—138° (Found: C, 77·7; H, 9·8; N, 3·2. $C_{26}H_{39}NO_2$ requires C, 78·5; H, 9·9; N, 3·57%); $\lambda_{max.}$ 240 nm, $\nu_{max.}$ ($CHCl_3$) 1710 [C(20)=O], 1660 [C(3)=O], and 1610 cm^{-1} (4-ene), τ *ca.* 7 (21-H_2) (in spectrum of reaction mixture).

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* $\nu_{max.}$ 3000 cm^{-1} in $CHCl_3$.
† This disappears upon drying.
‡ $\nu_{max.}$ *ca.* 3000 cm^{-1} in $CHCl_3$.