Bull. Soc. Chim. Belges, **76**, pp. 566-578, 3 fig. (1967)

ISOLATION AND IDENTIFICATION OF THE AMINES RESULTING FROM CHEMICAL AND CATALYTIC REDUCTION OF 20-HYDROXYIMINO-STEROIDS (RESTATEMENT)

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Summary

Sodium-propanol reduction of 3β-hydroxy-5-pregnen-20-one oxime affords the two 20-amino epimers in a ratio 20 α to 20 β equal to 1.3, while hydrogenation with platinum in acetic acid gives a mixture of the two corresponding saturated amines in the ratio of 2:1.

Quantitative separation of 20-amino epimers is conveniently achieved by chromatography on silica gel.

Thin layer chromatography, optical rotatory dispersion, infrared absorption, nuclear magnetic resonance data are joined.

Introduction

It is actually well established (1) that chemical as well as catalytic reduction of 20-hydroxyimino steroids affords mixtures of the two epimeric amines; however, some affirmations (1) concerning these reductions are not based on quantitative work (2) (3) (4).

We here report new experimental results concerning the preparation of a few pairs of simple 20-amino steroids—three of these, (III), (V) and (Ve), are new compounds—the separation of the epimers, the determination of their ratio in the reaction mixture and their identification. Some of these results do not support previous statements.

(1) R. Goutarel, *Tetrahedron*, **14**, 126 (1961), read p. 130.

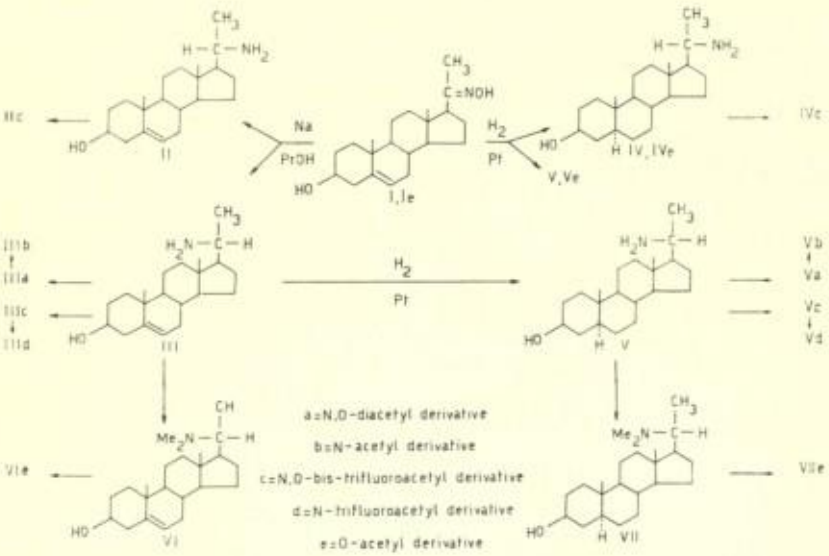
(2) V. Cerny, L. Labler, and F. Sorm, *Coll. Czech. Chem. Comm.*, **22**, 79 (1957).

(3) R.A. Lucas, D.F. Dickel, R.L. Dzieman, M.J. Ceglowski, B. L. Hensle, and H.B. Mac Phillamy, *J. Am. Chem. Soc.*, **82**, 5688 (1960).

(4) M.-M. Janot, F. Laine, Q. Khuong-Huu, and R. Goutarel, *Bull. Soc. Chim. Fr.*, 111 (1962).

RESULTS

We first reinvestigated the sodium-propanol reduction of 3β-hydroxy-5-pregnen-20-one oxime (I) described by Lucas and co-workers ([3]) and a second time applied by Wolf and co-workers ([5]).



Chromatography of the reaction mixture on a silica gel column according to a technique described by Sorm ([6]) repeatedly yielded in the following elution sequence: some starting material, 44% of the 20 β-amino epimer (III) and 54% of the 20 α-amino epimer (II)(*). The major

(*) It is scarcely possible to compare our result with that obtained by Sorm ([2]) and from which Goutarel ([1]) ([4]) inferred that sodium-ethanol reduction of 20-oximes of the 5α series predominantly involves formation of 20β primary amines; indeed, in the preparation described by Sorm, where 3β-acetoxy-5 α-pregnan-20-one oxime was reduced with sodium in ethanol and the isolated basic fraction successively dimethylated and acetylated, the overall yield in chromatographically pure 20β-dimethylamino epimer was 20%, in 20α-dimethylamino epimer 5%. In our opinion the complexity of the procedure applied by Sorm and the low yields of isolated products did not allow the inference of Goutarel.

([5]) H. WOLF, E. BUNNENBERG and C. DJERASSI, *Chem. Ber.*, **97**, 533 (1964).

([6]) L. LABLER and F. SORM, *Coll. Czech. Chem. Comm.*, **28**, 2345 (1963).

product proved identical with the alkaloid Holafebrine ([7]), 20 α-amino-5-pregnen-3 β-ol (II), by identity of melting point, optical rotation and infrared spectrum ([8]). To our knowledge, this synthetic correlation has not yet been reported in papers dealing with Holafebrine; configuration at C_{20} of the alkaloid had been established by identity with the Curtius degradation product of 3 β-hydroxy-23,24-dinorchol-5-en-22-oic acid ([9]).

Our minor product was found to differ from the only compound isolated by Lucas and co-workers in an identical reaction ([3]) and which they assumed to bear a 20 β-amino function, without providing any convincing experimental evidence.

Moreover, our two chromatographically pure amines, which proved to be isomeric, are easily distinguishable : melting points, optical rotations (Table II), infrared absorption spectra (fig. 2), polarities (Table I), solubilities as well as crystalline aspect are markedly different. These observations do not agree with the note published by Lucas and co-workers ([3]) pointing out that "it is very difficult, if not impossible, to distinguish" epimeric 20-amino steroids by their physical properties. These affirmations have been accepted by other authors ([10]) ([11]), without further confirmations.

Assignment of β-configuration at C_{20} of our minor product rests upon the following lines of evidences:

1° Eschweiler-Clarke methylation of the primary amine function of our amine led to the known 20 β-dimethylamino-5-pregnen-3 β-ol (VI) ([12]), the O-acetyl derivative of which also gave a correct centesimal analysis;

2° Catalytic hydrogenation of the 5,6-double bond of our product followed by dimethylation yielded 20 β-dimethylamino-5-α pregnan-3 β-ol (VII) earlier obtained as a chromatographically pure product by Sorm ([2]).

([7]) M.-M. Janot, X. Monseur, C. Conreur, and R. Goutarel, *Bull. Soc. Chim. Fr.*, 285 (1962).

([8]) R. Goutarel, Les Alcaloïdes stéroïdiques des Apocynacées, éd. Hermann, Paris-VI[e] (1964).

([9]) Bochmuhl, G. Ehrhart, and H. Ruschig, U.S. Patent 2.108.646; H. Ruschig, *Med. und Chem.*, **4**, 327 (1942), in *C.A.*, **38**, 4954 (1944).

([10]) J.J. Panouse, J. Schmitt, P.J. Cornu, A. Hallot, H. Pluchet, and P. Comoy, *Bull. Soc. Chim. Fr.*, 1753 (1962) read p. 1758.

([11]) D. Bertin and M. Legrand, *Compt. Rend. Acad. Sc.*, **256**, 1960 (1963).

([12]) J. Schmitt, J.P. Panouse, H. Pluchet, P. Comoy, A. Hallot, and P.J. Cornu, *Bull. Soc. Chim. Fr.*, 2240 (1963).

We further verified the catalytic reduction of (I) with Adams'catalyst in acetic acid ([4]). The two epimers were separated by chromatography on silica gel: pure 20β-amino-5α-pregnan-3β-ol (V) was obtained in 30% yield, the 20α-epimer (IV) in 66% yield. The former, which had not yet been isolated, is identical with the dihydro derivative of the unsaturated 20β-epimer (III) obtained in the above described sodium-propanol reduction of oxime (I); the latter is known to correspond to the alkaloid Funtuphyllamine A, 20 α-amino-5α-pregnan-3β-ol (IV).

Likewise, catalytic hydrogenation of 3β-acetoxy-5-pregnen-20-one oxime (Ie) allowed the simultaneous preparation of the acetates (Ve) in 30% yield and (IVe) in 65% yield; the former was till now unknown.

Ramirez and Stafiej ([13]) have reported quantitative results for the catalytic hydrogenation of 3β, 17α-dihydroxy-5α-pregnan-20-one oxime: they succeeded in isolating the 20α-amine in about 73% yield.

Note on the separation and identification of epimeric 20-amino steroids

In each investigated epimer pair, the 20β-epimer exhibits the larger solubility in the usual crystallisation solvents (*), e.g. methanol, benzene, ethylacetate; on simple recrystallisation of the reaction mixture, an important quantity of the 20α-epimer can be isolated in essentially pure state.

Although fractional precipitation of the hydrochlorides of 20-epimeric amines seems valuable ([13]), hydrochlorides of 20α-amines precipitating first (**), column chromatography on silica gel with solvents equilibrated on aqueous ammonia may be considered as a very sure quantitative separation method for epimeric 20-amino steroids: the first migrating 20β-epimer is obtained nearly quantitatively in pure state, a minor intermediate fraction is already enriched in α-epimer, the 20α-epimer is eluted at last.

(*) This fact along with the predominance of the α-epimer in the reaction mixture, explains why neither (V) nor (Ve) were earlier isolated.

(**) It is noteworthy that Lucas and co-workers ([3]) carried out such a fractionation of their reaction mixture.

([13]) R. Ramirez and S. Stafiej, *J. Am. Chem. Soc.*, 77, 134 (1955).

Czech authors ([14]) have reported the greater polarity of the 20α-epimer in 20-dimethylamino pairs. Our chromatographical results show this may be a general feature: the β-epimer of a 20-amino derivative pair always appeared to be less polar than the α-epimer; the former is first eluted from a chromatography column and migrates faster on a thin layer chromatogram (Table I); in case of epimer mixtures two distinct spots are obtained on the thin layer chromatogram.

TABLE I

R_F values of 20-amino steroids (100 γ) on silica gel thin layers (Solvent system : ether saturated with ammonia and methanol, 8.5:1.5, v/v).

Epimer pair	R_F		R_F/ R_F Holafebrine (II)	
	α	β	α	β
A : 20-amino-5α-pregnan-3β-ols	0.34	0.63(5)	1.05	1.95
A': 20-amino -5-pregnen-3β-ols	0.32(5)	0.61	1.00	1.85
B : 20-methylamino-5α-pregnan-3β-ols	0.32	0.64(5)	1.00	2.00
B' : 20-methylamino-5-pregnen-3β-ols	0.28	0.62	1.85	1.90
C : 20-dimethylamino-5α-pregnan-3β-ols	0.74(5)	0.88(5)	2.30	2.70
C' : 20-dimethylamino-5-pregnen-3β-ols	0.74	0.87(5)	2.25	2.65

Assignment of α- or β-configuration to epimeric 20-amino steroids seems also possible by comparison, for the *D* line of sodium, of the optical rotatory powers of the pure epimers: all known β-epimers are more levorotatory than their corresponding α-epimers ([15]). Table II shows that the molecular rotation increment for inversion $\beta \rightarrow \alpha$ at C_{20} seems to be comparable for the primary amino group, ($\Delta MD = 33°$), the monomethylamino group, ($\Delta MD = 74°$) and for the dimethylamino group, ($\Delta MD = 40°$).

Optical rotatory dispersion and circular dichroism data have been reported for the N-salicylidene ([11]) and N-phthalyl derivatives ([5]) of the

([14]) L. LABLER and V. CERNY, *Coll. Czech. Chem. Comm.*, **28**, 2932 (1963).

([15]) L. F. FIESER and M. FIESER, *Steroids*. Reinhold Publishing Corporation N.Y. 1959, p. 861; reported values are the reverse of the original literature values.

Epimer pair	Ref.	20α		20β		Δ*MD* α–β	*mp*		Δ*MD* introd. of 5-6	
		α*D*	*MD*	α*D*	*MD*		20α	20β	20α	20β
A 20-amino-5α-pregnan-3β-ols		+13.6	+43.5	+3	+9.6	33.9	173–175	177–177.4		
									−251.8	−250.6
A' 20-amino-5-pregnen-3β-ols		−65.6	−208.3	−76	−241	32.7	171–173	218.6 219.2		
	[3]			−60.4				170–172		
B 20-methylamino-5α-pregnan-3β-ols		+24	+80.1	+1	+3.3	76.8	213–214.8	171–171.2		
	[12]b			−38.2				175–177		
									−189.5	−181.0
B' 20-methylamino-5-pregnen-3β-ols		−33	−109.4	−53.6	−177.7	68.3	226.4 −228	183.4 −184		
	[12]b			−73.7				180–182		
C 20-dimethylamino-5α-pregnan-3β-ols		+24	+83.4	+12.5	43.5	39.9	171.6 −172	181.6 −182		
									−259.7	−261 2
C' 20-dimethylamino-5-pregnen-3β-ols		−51	−176.3	−63	−217.7	41.4	169.6 −170	180.4 −181.6		

[a] This figures were obtained for products prepared and identified in our laboratory. Literature values are indicated as far as they are rather different.

[b] We are tempted to consider our values as the right ones, the *MD*-increment for introduction of the 5-6 double bond being in accordance with those reported for similar structures: Holarrhenine (-181 [16]), Conessine (-169 [17]).

20-amino-5α-pregnan-3β-ol pair. The O.R.D. curves of the N-benzylidene derivatives of the epimeric 20-amino-5-pregnen-3β-ols show the expected characteristics: the 20β-epimer exhibits a negative Cotton effect, while the 20α-epimer exhibits a smaller Cotton effect of opposite sign.

French authors ([12]) have already reported significant differences in infrared spectra of 20-monomethylamino epimers.

Figure 2 allows the comparison of the infrared spectra of six pairs of steroids.

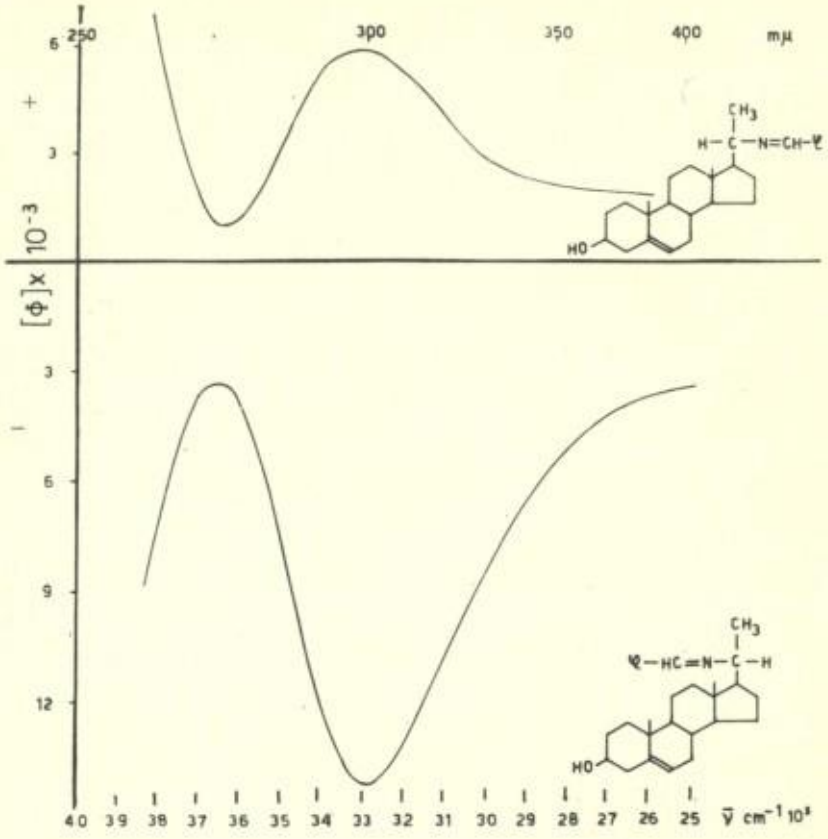


Fig. 1 — O.R.D. curves of N-benzylidene derivatives of 20-amino-5-pregnen-3β-ols (II) and (III), c 1,3 mg/10 ml dioxane.

(16) L. VAN HOVE, *Tetrahedron*, 7, 104 (1959).

(17) R.D. HAWORTH, J.MCKENNA, R.G. POWELL, and G.H. WHITFIELD, *J. Chem. Soc.*, 1115 (1953).

Comparison of the N.M.R. spectra gives following results: as previsible from the contributions of the 17β CH_3-CHOH side chain to the position of the resonance signal of the 18-methyl group ([18]) we find that for the 20-amino derivatives an analogous situation pertains: the 18-methyl resonance signal is systematically higher for the 20β-epimer than for the 20α-epimer but only for the primary amino group and the difference amounts to roughly 0.07-0.08 p.p.m., this value was slightly higher with the hydroxyl group at C_{20}: 0.09 p.p.m. An analogous finding has already been made for the amino group at C_{11} ([19]).

As can be seen from Table III, the 18-methyl resonance is nearly identical for the 20-monomethylamino and also for the 20-dimethylamino epimers. The resonance of the 21-methyl group, which exhibits a doublet with a coupling constant of about 6-6.5 c.p.s. and which is systematically higher by 0.1 p.p.m. for the α-epimer, constitutes an easy criterion for attribution of configuration at C_{20}. The absolute value is notably lower for 20-dimethylamino epimers but the difference between the resonance values remains unchanged.

TABLE III
N.M.R. data

(Resonance values are expressed in p.p.m. *Coupling constants are indicated between brackets and expressed in* c.p.s.*)*

Epimer pair	$C_{(18)}$ H_3 α	β	$C_{(19)}$ H_3 α	β	$C_{(21)}$ H_3 α	β	CH_3-N α	β
20-amino-5α-pregnan-3β-ols	0.65	0.72	0.80	0.80	1.10 (6.2)	1.00 (6.2)	–	–
20-amino-5-pregnen-3β-ols	0.68	0.75	1.01	1.02	1.12 (6.5)	1.02 (6.5)	–	–
20-methylamino-5α-pregnan-3β-ols	0.67	0.68	0.80	0.80	1.05 (6.2)	0.96 (6.2)	2.33	2.33
20-methylamino-5-pregnen-3β-ols	0.70	0.72	1.01	1.01	1.07 (6.5)	0.96 (5)	2.35	2.25
20-dimethylamino-5α-pregnan-3β-ols	0.66	0.65	0.81	0.80	0.87 (6.5)	0.75 (6.2)	2.17	2.11
20-dimethylamino-5-pregnen-3β-ols	0.68	0.69	1.02	0.12	0.89 (6.5)	0.78 (6.5)	2.17	2.13

([18]) R.F. ZURCHER, *Helv. Chim. Acta*, **46**, 2054 (1963).
([19]) R. RAUSSER, L. WEBER, E.B. HERSHBERG, and E.P. OLIVETO, *J. Org. Chem.*, **31**, 1342 (1966).

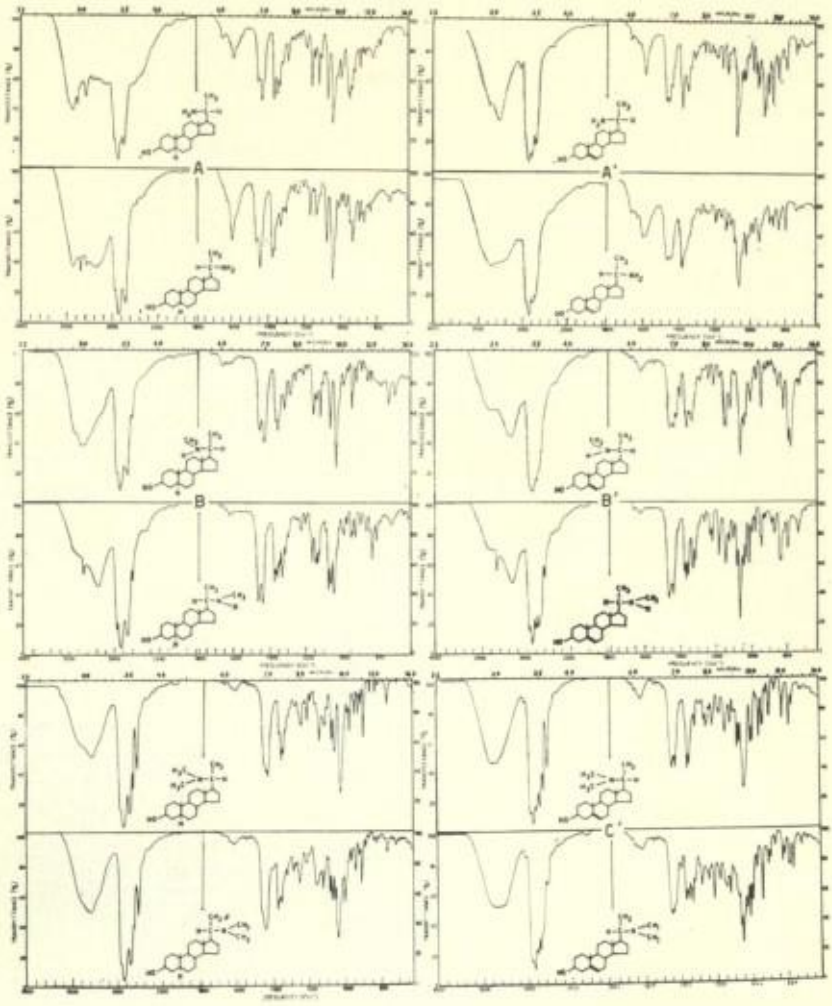


Fig. 2 — Infrared spectra.

A: 20-amino-5α-pregnan-3β-ol pair.
B: 20-monomethylamino-5α-pregnan-3β-ol pair.
C: 20-dimethylamino-5α-pregnan-3β-ol pair.

A': 20-amino-5-pregnen-3β-ol pair.
B': 20-monomethylamino-5-pregnen-3β-ol pair.
C': 20-dimethylamino-5-pregnen-3β-ol pair.

EXPERIMENTAL PART

GENERAL PROCEDURES

Melting points were taken in evacuated sealed capillaries with standardized Anschütz thermometers in a Hershberg's melting point apparatus.

Optical rotations were measured for the sodium D line on a Franz Schmidt and Haensch polarimeter on solutions contained in 2-dm tubes.

Infrared spectra were recorded on a Perkin Elmer 237 spectrophotometer. Products in the solid state were dispersed in KBr. Samples were previously pulverized and dried at 150°/0.1 mm Hg during 12 hrs.

Thin layer chromatography (t.l.c.) was carried out on Merck 7731 silica gel layers (thickness of the coating 0.2 mm) in an ammonia atmosphere. Products were detected using iodine vapor.

O.R.D. measurements were made on a Bellingham and Stanley/Bendix-Ericsson Polarmatic spectropolarimeter using a 1-cm cell and a mercury lamp.

N.M.R. spectra were recorded on a Varian A-60 spectrometer using solutions in deuteriochloroform and tetramethylsilane as an internal standard.

Elemental analyses were performed by Mrs S. Franck-Frederick, Free University Brussels and by A. Bernhardt, Mülheim, West-Germany.

Preparation of *N-p-nitrobenzylidene* and *N-benzylidene* derivatives: the freshly recrystallized (0.1 g) or redistilled (0.1 ml) aldehyde was added to a boiling solution of the primary amine (1 mmol) in methanol (10 ml). Condensation was complete within a few min. The derivative separated as a crystalline material, eventually upon concentration.

Acetylation of the amino alcohols was carried out by heating the solution in acetic anhydride and pyridine for an hour at 100°. The ester function was selectively hydrolyzed with aqueous methanolic sodium hydroxide at boiling temperature.

Trifluoroacetylation of the amino alcohols: freshly distilled trifluoroacetic anhydride (10 drops) was added to the water-free solutions of the amino alcohol (1 mmol) in benzene (8 ml). The mixture was heated to boiling point for half an hour under nitrogen. After elimination of the solvents under reduced pressure, the residue was recrystallized from absolute methanol. Dilution with water of the methanolic solution of the amido esters resulted within a few hours in the selective hydrolysis of the O-trifluoroacetyl function.

All these derivatives were recrystallized in methanol.

20 α-*amino*-5-*pregnen*-3 β-*ol* (II) *and* 20 β-*amino*-5-*pregnen*-3 β-*ol* (III)

Sodium (25 g) was added to a boiling solution of 7.3 g of 3β-hydroxy-5-pregnen-20-one oxime (I) in 250 ml of *n*-propanol over a period of 45 min.; reduction was carried out under nitrogen. Reflux was maintained until, after about 20 min., the last traces of sodium had disappeared. After cooling under nitrogen, the resulting slurry was treated with 500 ml of water. Extraction of the mixture with ether was repeated several times, the extracts were washed with water, dried on sodium carbonate, filtered and evaporated. The crude reaction product (7 g), m.p. 166°, was dissolved in boiling methanol (75 ml), the solution was kept for a few hours. at 10°, whilst crystals precipitated. The collected product (2.6 g), m.p. 171°, was identified with (II), one spot predominated on t.l.c. (6.5. cm:15 cm). Recrystallization of this crop afforded 2 g (28,6%), m.p. 171-173°, αD −65.6 (c 1.4). Lit. (3) : 172-174°, αD −69.2; lit. (7): 177° (sublimate), αD −61.5.

After evaporation of the methanol of the mother liquors, the dried crystallization residue was dissolved in benzene and the solution brought on a silica gel column (Merck 7734). Benzene used for the preparation of the column and for elution was treated as follows: one-liter fractions of benzene were shaken with 50-ml fractions of concentrated aqueous ammonia. The organic layer was carefully decanted and filtered on filter paper. Silica gel (25 g) was shaken with 200 ml of benzene saturated with aqueous ammonia before filling the column. A gradient elution was run with following solutions: initial eluent was benzene saturated with ammonia (1750 ml), final eluent was benzene saturated with ammonia-ether, 1/9, v/v (2000 ml). No separate fractions of the eluate were taken until the first products reached the bottom of the column; this was visible from the colouring of the silica gel suspension. Successive 20-ml fractions of the eluate were then analysed by the t.l.c. technique; analogous fractions were combined to give what follows: after evaporation, the first 800 ml yielded 150 mg (2.14%) of the least polar products, the next 2000 ml, 3155 mg (42.21%) of the subsequently identified 20β-epimer (III), the next 340 ml, 170 mg (2.42%) of a mixture of (III) and (II) in the ratio 2/3, the last 560 ml and 200 ml of methanol finally yielded the total amount of the 20α-epimer (II), 1770 mg (25.29%).

Crystallization from benzene or methanol of the second crop gave analytically pure samples of 20β-amino-5-pregnen-3β-ol (III), m.p. 218.6-219.2° αD −76.2 (c 0.8). Infrared spectrum, see figure 2. Lit. (3): 170-172°, αD −60.4.

Anal. $C_{21}H_{35}ON$ (317.5)	% calcd.	C 79.44	H 11.11	N 4.41
	% found	79.50	11.10	4.30

A 1:1 mixture of epimers (II and III) melts at 164.8-167.8°.

Following derivatives allowed further identification of the two epimers:

20β-p-nitrobenzylideneamino-5-pregnen-3β-ol, m.p. 210-211°, αD −210

Anal. $C_{28}H_{38}O_3N_2$ (450.6)	% calcd.	C 74.63	H 8.50	N 6.22
	% found	74.42	8.30	6.18

20α-p-nitrobenzylideneamino-5-pregnen-3β-ol, m.p. 240°, αD +32; lit. (7): 242°:

20β-benzylideneamino-5-pregnen-3β-ol, m.p. 192.6-193°, αD −165; lit. (3). 192-194°.

Anal. $C_{28}H_{39}ON$ (405.6)	% calcd.	C 82.91	H 9.69	N 3.45
	% found	82.50	9.96	3.40

20α-benzylideneamino-5-pregnen-3β-ol, m.p. 193.2-196°, αD +11; lit. (20): 191°.

20β-acetamido-3β-acetoxy-5-pregnene (IIIa), m.p. 249°.

Anal. $C_{25}H_{39}O_3N$ (401.6)	% calcd.	C 74.77	H 9.79	N 3.49
	% found	74.87	9.87	3.38

20β-acetamido-5-pregnen-3β-ol (IIIb), m.p. 248-248.5, αD −25.4.

Anal. $C_{23}H_{37}O_2N$ (359.5)	% calcd.	C 76.83	H 10.37
	% found	77.00	10.48

20β-trifluoroacetamido-3β-trifluoroacetoxy-5-pregnene (IIIc), m.p. 194-195°.

Anal. $C_{25}H_{33}F_6O_3N$ (509.6)	% calcd.	C 58.93	H 6.53	N.2.75
	% found	58.73	6.61	2.93

20α-trifluoroacetamido-3β-trifluoroacetoxy-5-pregnene (IIc), m.p. 195.5-196°.

	% found	59.26	6.75

([20]) P.L. JULIAN, E.W. MEYER, and H.C. PRINTY, *J. Am. Chem. Soc.*, **70**, 887 (1948).

20β-dimethylamino-5-pregnen-3β-ol (VI) and its O-acetyl derivative (VIe)

Dimethylation of 20β-amino-5-pregnen-3β-ol (III) (178 mg) was carried out with a mixture of formic acid-35% aqueous formaldehyde. The isolated oily residue was submitted to alkaline hydrolysis. After extraction, the crude material was dissolved in ether and the solution filtered on a silica gel column, a product was obtained which after a few recrystallizations from methanol had m.p. 180.4-181.6°, αD −63 (*c* 0.9 $CHCl_3$) and could be identified with the literature (12) 20β-dimethylamino-5-pregnen-3β-ol, m.p.; 175-177°, αD −62.5.

The acetic ester of our product showed m.p. 207-207.5, αD −60.

Anal. $C_{25}H_{41}O_2N$	% calcd.	C 77.47	H 10.66	
	% found	77.50	10.59	

20β-amino-5α-pregnan-3β-ol (V) by catalytic hydrogenation of (III)

20β-amino-5-pregnen-3β-ol (III) (105 mg) dissolved in 3 ml of absolute acetic acid was hydrogenated in the presence of 20.4 mg of Adams' catalyst. The crude reaction product (106 mg) melted at 174°; after four recrystallizations from methanol, the m.p. was 176.2-177.4°, αD +2.

Anal. $C_{21}H_{37}ON$ (319.5)	% calcd.	C 78.94	H 11.67	N 4.38
	% found	78.65	11.76	4.65

Molecular weight determined by mass spectrometry: 319. No depression of m.p. was observed upon mixing with (*V*) obtained as described below.

20β-dimethylamino-5α-pregnan-3β-ol (VII) and its O-acetyl derivative (VIIe).

This product (VII) was prepared in the same way as (VI); however, a pure product was isolated in a 80% yield without filtration on silica gel. It crystallized from methanol, m.p. 181.6-182°, αD +12.5 (c 1 $CHCl_3$): lit. (2): 178.5-179°, αD +12.5.

Anal. $C_{23}H_{41}ON$ (347.6)	% calcd.	C 79.47	H 11.89	N 4.03
	% found	79.78	12.23	3.95

This compound showed a very high crystalline character and crystallized with variable amounts of solvent, which resulted in a few unsuccessful analyses. The known O-acetyl derivative was found to have m.p. 161.8-163°, αD0 after recrystallization from petroleum ether; lit. (4): 161.5-162.5, αD1.

20α-amino-*5α*-pregnan-*3β*-ol (IV) and *20β-amino-5α-pregnan-3β-ol (V)*

A solution of 1.9 g of 3β-hydroxy-5-pregnen-20-one oxime (I) in 60 ml of absolute acetic acid to which 80 mg of Adams' platinum oxide was added, was stirred for 12 hrs. in a hydrogen atmosphere at 20°/one atm. (hydrogen uptake: 400 ml). After removal of the greatest amount of the solvent under reduced pressure at 80°, the residue was basified by addition of a 4 *M* sodium hydroxide solution and extracted with methylene chloride. The dried extracts yielded 1.9 g of a cristalline material (m.p. 165°) consisting of two predominant products (t.l.c.), which were separated by column chromatography, the method described under 1) was applied: gradient elution from a silica gel column with benzene saturated with aqueous ammonia-ether, 9/1, 1000 ml, as initial eluent, and benzene saturated with aqueous ammonia-ether, 5/5, 3000 ml, as final eluent, gave: 80 mg of an oximated product, 580 mg of the 20β-epimer (V) (30%) and 1250 mg of the 20α-epimer (IV) (66%). Recrystallisation from methanol or benzene gave analytically pure compounds: 20α-amine (IV) showed m.p. 173-175°, αD +13.6, lit. (4): 173°, αD +13; 20β-amine (V) showed m.p. 176.8-177.4°, αD +3, lit. (3): 174-176°. A 1:1 mixture of the two epimers melted at 169-174°.

Following derivatives were prepared in order to characterize the two epimers:

20β-p-nitrobenzylideneamino-5α-pregnan-3β-ol, m.p. 137° (ether), αD −122,

20α-p-nitrobenzylideneamino-5α-pregnan-3β-ol, m.p. 225-228°, αD +84.

20β-benzylideneamino-5α-pregnan-3β-ol was not obtained as a crystalline product.

20α-benzylideneamino-5α-pregnan-3β-ol, m.p. 189.6-190.4°, αD +65, lit (4): 184°, αD +78.

20β-acetamido-3β-acetoxy-5α-pregnane (Va), m.p. 207-207.5°.

Anal. $C_{25}H_{41}O_3N$ (403.6)	% calcd.	C 74.40	H 10.24
	% found	73.97	9.97

20β-acetamido-5α-pregnan-3β-ol (Vb), m.p. 256-257°.

Anal. $C_{23}H_{39}O_2N$ (361.6)	% calcd.	C 76.40	H 10.87
	% found	76.34	10.72

20β-trifluoroacetamido-3β-trifluoroacetoxy-5α-pregnane (IVc), m.p. 192-192.5°.

Anal. $C_{25}H_{35}F_6O_3N$ (511.5)	% calcd.	C 58.70	H 6.89
	% found	59.24	7.13

20α-trifluoroacetamido-3β-trifluoroacetoxy-5α-pregnane (Vc), m.p. 199-200°.

	% found	59.25	6.94

20β-trifluoroacetamido-5α-pregnan-3β-ol (IVd), m.p. 226-226.5°, lit. (3): 219-221°.

3 β-acetoxy-20 α-amino-5 α-pregnane (IVe) and 3 β-acetoxy-20 β-amino-5 α-pregnane (Ve)

The epimer mixture (m.p. 112°) from the catalytic reduction of 3β-acetoxy-5- pregnen-20-one oxime (Ie) (2.54 g) has following composition: 750 mg of 20β-epimer (Ve) (30.49%) and 1625 mg of 20α-epimer (IVe) (65.09%). A few recrystallizations from methanol gave analytically pure samples : 20β-epimer (Ve), m.p. 146-147°, αD —16.7,

Anal. $C_{23}H_{39}O_2N$ (361.6)	% calcd.	C 76.40	H 10.87	N 3.87
	% found	76.05	10.64	3.70

20 α-epimer (Ve), m.p. 117-118°, αD −10.5,

	% found	76.17	10.58	3.69

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