THE SYNTHESIS OF PREGNANE DERIVATIVES WITH AN AROMATIC B-RING*

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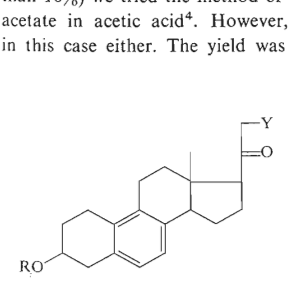
Received July 13th, 1976

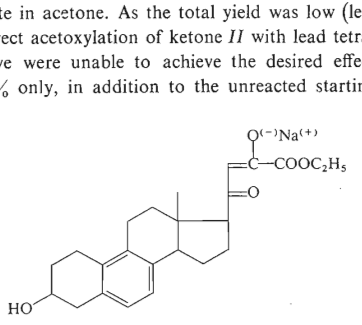
The syntheses of some analogues of steroid hormones of pregnane type with an aromatic B-ring are described, among them the analogue of cortexolone (Reichstein's substance S).

In the preceding paper[1] we described the synthesis of analogues of androgens with an aromatic B-ring. Here the preparation of analogues of pregnane type is described.

For the preparation of 21-acetate *V* or *VI* we used Ruschig's method[2-4]. Condensation of ketone[1] *I* with diethyl oxalate under catalysis with sodium methoxide gave the sodium salt of the enol form *III* which on addition of iodine and decomposition with sodium methoxide afforded ketone *IV*. The latter was converted to 21-acetate *V* with potassium acetate in acetone. As the total yield was low (less than 10%) we tried the method of direct acetoxylation of ketone *II* with lead tetraacetate in acetic acid[4]. However, we were unable to achieve the desired effect in this case either. The yield was 5% only, in addition to the unreacted starting



I, R = H, Y = H
II, R = Ac, Y = H
IV, R = H, Y = I
V, R = H, Y = OAc
VI, R = Ac, Y = OAc

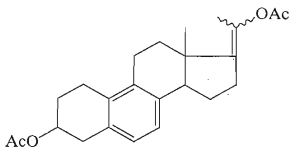


III

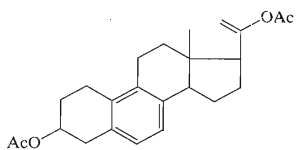
* Part CXCI in the series On Steroids; Part CXC: This Journal *42*, 353 (1977).

material. Only when applying a modification of this method[5-7], *i.e.* reaction with lead tetraacetate in benzene in the presence of boron trifluoride etherate and methanol were we able to achieve yields up to 90% from substances *I* and *II*. Alcohol *V* was then converted by acetylation to 3-acetate *VI* which was identical with the substance obtained by direct acetoxylation of ketone *II*.

We used ketone *II* as starting material for the synthesis of compound *XIII*. On reaction with acetic anhydride in the presence of *p*-toluenesulfonic acid[1] a 2 : 1 mixture of *E*- and *Z*-isomers of the enol acetate *VII* was formed, as evident from the comparison of the intensities of the signals due to 18-H in the ^{1}H-NMR spectrum (Table I). Reaction of ketone *II* with isopropenyl acetate in the presence of sulfuric acid gave in addition to a mixture of *VII* also enol acetate *VIII* in an approximately 1 : 2



VII



VIII

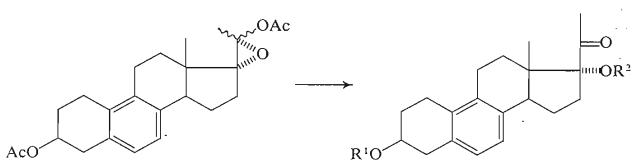
ratio (Table I). The mixture of isomeric enol acetates *VII* gave a mixture of isomeric epoxides *IX* on reaction with monoperphthalic acid[1] while the mutual ratio (2 : 1) remained unchanged as evident from the comparison of the intensities of the signals of 18-H in the ^{1}H-NMR spectrum. In the preceding paper[1] we have described the conversion of these isomeric epoxides to 17α-hydroxy ketones *X* and *XI*.

TABLE I

Shifts of 18-H and Relative Heights of Integration Curves of Compounds *VII*—*IX*

Compound	*VII* (E or Z)		*VIII*	*IX* (20 R or 20s)	
Shift 18-H	0·71	0·78	0·59	0·77	0·84
Relative height of the integration curve	7[a]	3[a]	0[a]	7[a]	3[a]
	5[b]	2[b]	15[b]		

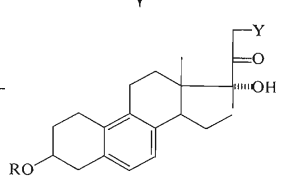
[a] After acetylation with acetic anhydride and *p*-toluenesulfonic acid; [b] after acetylation with isopropenyl acetate and sulfuric acid.



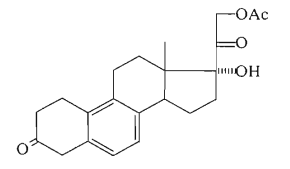
IX

X, R^1 = H, R^2 = H
XI, R^1 = Ac, R^2 = H
XII, R^1 = Ac, R^2 = Ac
XIII, R^1 = H, R^2 = Ac

VII



XIV, R = Ac, Y = Br
XV, R = H, Y = Br
XVI, R = Ac, Y = OAc
XVII, R = H, Y = OAc



XVIII

Both hydroxy ketones *X* and *XI* when acetylated with acetic anhydride in the presence of *p*-toluenesulfonic acid afforded diacetate *XII* which gave 17-monoacetate *XIII* in good yield by selective hydrolysis with hydrochloric acid in methanol. When saponifying compounds *XII* and *XIII* with potassium hydroxide in methanol, dihydroxy ketone *X* was obtained.

For the construction of the corticoid side chain we made use of a known method (*cf.*[4]). 17α-Hydroxy-20-ketone *X* and its 3-acetate *XI* were very resistent to bromination with bromine in acetic acid, but with Jacques reagent they afforded the corresponding bromo ketones *XIV* or *XV* rather smoothly. These were converted by boiling with potassium acetate in acetone to 21-acetoxy derivatives *XVI* and *XVII* respectively. Finally, when oxidizing alcohol *XVII* the labile 3-ketone *XVIII* was formed, representing an analogue of the 21-acetate of Reichstein's substance S.

EXPERIMENTAL

The melting points were determined on a Kofler block. Analytical samples were dried at 25°C/0·2 Torr. Optical rotations were measured in chloroform with a ±3° error. The infrared spectra

were measured with a Zeiss UR 10 spectrophotometer in chloroform, the mass spectral measurements were carried out on an AEI MS 902 spectrometer. The ^{1}H-NMR spectra were recorded on a Varian HA-100 instrument in deuteriochloroform with tetramethylsilane as internal reference. The CD curves were recorded on a Jouan-Roussel Dichrographe II in methanol. The identity of the samples prepared by different routes was checked by mixture melting point determinations, by thin-layer chromatography, and by IR spectra. Neutral alumina of activity II was supplied by Reanal (Budapest), silica gel according to Pitra and Štěrba was prepared in the Service Laboratories of our Institute.

3β-Hydroxy-21-acetoxy-19-norpregna-5,7,9(10)-trien-20-one (*V*)

A) Benzene (10 ml) was added to a solution of sodium (350 mg) in methanol (4·5 ml) and 2 ml of solvents were distilled off. The suspension was cooled to room temperature and diethyl oxalate (0·45 ml) and a solution of ketone *I* (300 mg) in a mixture of ether (2 ml) and benzene (11 ml) were added to it dropwise under stirring. The mixture was stirred for 4 hours, diluted with ether (20 ml) and allowed to stand in a refrigerator overnight. The separated sodium salt *III* was filtered off under suction, then washed with absolute ether and suspended in methanol (8 ml). A solution of iodine (400 mg) in methanol (11 ml) was added dropwise to the suspension at −10°C and the mixture was stirred at room temperature for one hour. It was then cooled to −10°C and a solution of 47 mg of sodium in 2·5 ml of methanol was added to it dropwise. After two hours' stirring at room temperature the mixture was diluted with water (70 ml), the product was extracted with ether, the extract washed with water, 5% aqueous sodium thiosulfate solution and water, then dried and the solvent evaporated. The residue was dissolved in acetone (40 ml) and refluxed for 6 hours in the presence of potassium acetate (1 g) acetic acid (0·55 ml) and water (9·5. ml). Acetone was distilled off in a vacuum, the residue diluted with water, the product extracted with ethyl acetate, the extract washed with water, then dried and the solvent evaporated. The residue was chromatographed on a column of silica gel (50 g) with a mixture of benzene and ether (90 : 10). Corresponding fractions were combined and evaporated. The residue weighed 48 mg, m.p. 132—135°C (ether), $[\alpha]_D^{20}$ +43° (*c* 1·9). For $C_{22}H_{28}O_4$ (356·4) calculated: 74·13% C, 7·92% H; found: 74·28% C, 7·74% H.

B) Lead tetraacetate (910 mg) was added to a stirred solution of ketone *I* (500 mg) in benzene (25 ml) and methanol (1·37 ml), and boron trifluoride etherate (3·41 ml) was added to the mixture which was then stirred at room temperature for 5 h. After dilution with chloroform it was washed with water, 5% aqueous sodium hydrogen carbonate and water, dried and the solvent evaporated. The residue was chromatographed on a column of silica gel (100 g) with a benzene–ether mixture 90 : 10. Corresponding fractions were combined and evaporated. The residue weighed 340 mg; m.p. 134—136°C (ether) $[\alpha]_D^{20}$ +45° (*c* 1·8), identical with those of the compound obtained under *A*.

3β,21-Diacetoxy-19-norpregna-5,7,9(10)-trien-20-one (*VI*)

A) Ketone *II* (240 mg) was heated with a mixture of acetic acid (7 ml), acetic anhydride (0·25 ml) and lead tetraacetate (400 mg) at 70°C for 14 h. The mixture was diluted with water, the product extracted with dichloromethane and the extract washed with water, 5% aqueous sodium hydrogen carbonate and water. After drying the extract was evaporated and the residue chromatographed on four preparative thin-layer plates with silica gel (20 × 20 cm) in benzene and ether (95 : 5) (double development). The more polar substance was acetoxy ketone *VI* (14 mg) while the less polar substance was the unreacted ketone *II* (210 mg). Ketone *VI* had m.p. 145—147°C (chloro-

form–methanol) and $[\alpha]_D^{20}$ +62° (*c* 2·0). For $C_{24}H_{30}O_5$ (398·5) calculated: 72·33% C, 7·59% H found: 72·20% C, 7·43% H.

B) Lead tetraacetate (270 mg) was added to a solution of ketone *II* (170 mg) in benzene (7·4 ml) and methanol (0·4 ml) and boron trifluoride etherate (1·0 ml) was added dropwise to the mixture which was then stirred at room temperature for 6 h. After working up as in the case of substance *V* (B) the residue was crystallized from a mixture of chloroform and methanol. The obtained acetoxy ketone *VI* (95 mg) had m.p. 148–149°C, $[\alpha]_D^{20}$ +66° (*c* 1·9). ^{1}H-NMR spectrum: 0·59 s (3 H, 18-H), 4·58 d and 4·83 d (2 H, 21-H, J = 17 Hz), 2·04 s (3 H, CH_3COO), 2·17 s (3 H, CH_3COO).

C) Alcohol *V* (50 mg) was acetylated with acetic anhydride (0·3 ml) in pyridine (0·5 ml) at room temperature for 5 h. The mixture was worked up and the product crystallized from a mixture of chloroform and methanol. The acetate *VI* obtained (21 mg) had m.p. 148–149°C, $[\alpha]_D^{20}$ +68° (*c* 2·0).

Enol Acetate of 3β-Acetoxy-19-norpregna-5,7,9-(10)-trien-20-one (*VII* and *VIII*)

From a mixture of ketone *II* (2·5 g), isopropenyl acetate (22 ml) and sulfuric acid (0·015ml) 10 ml of solvent were evaporated over 1·5 h. A mixture of isopropenyl acetate (20 ml) and sulfuric acid (0·015 ml) was then added and 20 ml of solvent were distilled off from the mixture over 2 h. The remaining mixture was diluted with light petroleum and filtered through a column of alumina (50 g). The column was washed with a mixture of light petroleum and ether (9 : 1). According to ^{1}H-NMR spectrum the residue represents a mixture of three substances. ^{1}H-NMR spectrum: 0·585 s (18-H in *VIII*), 0·710 s, 0·775 s (18-H in VII), in a 15 : 5 : 2 ratio.

3β,17α-Dihydroxy-19-norpregna-5,7,9(10)-trien-20-one (*X*)

a) Diacetate *XII* (60 mg) was refluxed under nitrogen with potassium hydroxide (100 mg) in methanol (10 ml) for 1·5 h. The mixture was concentrated to half its volume, diluted with ethyl acetate, the organic layer washed with water, dried and evaporated. After two-fold crystallization from a mixture of acetone and light petroleum dihydroxy ketone *X* (19 mg) was obtained, m.p. 191–193°C, $[\alpha]_D^{20}$ +57° (*c* 2·0), in agreement with the literature data[1].

b) Acetate *XIII* 100 mg was saponified in the same manner as diacetate *XII*. M.p. 189–192°C.

3β,17α-Diacetoxy-19-norpregna-5,7,9(10)-trien-20-one (*XII*)

a) Diol *X* (700 mg) was acetylated with acetic anhydride (10 ml) in acetic acid (30 ml) under catalysis with *p*-toluenesulfonic acid (700 mg) at room temperature for 2 h. Pyridine (15 ml) was then added and the mixture decomposed with ice and worked up. Crystallization from a mixture of chloroform and methanol gave diacetate *XII* (595 mg), m.p. 237–238°C, $[\alpha]_D^{20}$ −46° (*c* 1·8). IR spectrum: 1244, 1720, 1738 cm^{-1}. CD spectrum: $\Delta\varepsilon$ +2·49, 287 nm. For $C_{24}H_{30}O_5$ (398·5) calculated: 72·33% C, 7·59% H; found: 72·40% C, 7·61% H.

b) Hydroxy ketone *XI* (100 mg) was acetylated with acetic anhydride (1·0 ml) in acetic acid (5·0 ml) in the presence of *p*-toluenesulfonic acid (100 mg) in the same manner as in the preceding case. M.p. 237–238°C.

3β-Hydroxy-17α-acetoxy-19-norpregna-5,7,9(10)-trien-20-one (*XIII*)

A mixture of diacetate *XII* (600 mg), methanol (75 ml) and hydrochloric acid (0·5 ml) was refluxed for 1·5 h. The solution obtained was diluted with ethyl acetate, the organic layer washed

with water, 5% aqueous sodium hydrogen carbonate and water, then dried and the solvents evaporated. Crystallization of the residue from a mixture of acetone and light petroleum gave monoacetate *XIII* (360 mg), m.p. 188–190°C, $[\alpha]_D^{20}$ −48° (*c* 1·4). IR spectrum: 1259, 1715·1731, 3614 cm^{-1}. For $C_{22}H_{28}O_4$ (356·4) calculated: 74·13% C, 7·92% H; found: 73·08% C, 7·96% H.

21-Bromo-3β-acetoxy-17α-hydroxy-19-norpregna-5,7,9(10)-trien-20-one (*XIV*)

Jacques reagent (trimethyl-phenylammonium bromide perbromide; 130 mg) was added to a stirred solution of ketone *XI* (120 mg) in tetrahydrofuran (2·0 ml) and the mixture was exposed to the effect of solar radiation (without irradiation the reaction does not take place). After 20 minutes the mixture was diluted with ether and water, organic layer was washed with water, 5% aqueous sodium hydrogen carbonate, 5% sodium thiosulfate and water, then dried and evaporated. The residue was chromatographed on two silica gel plates (20 × 20 cm) with benzene and ether mixture (95 : 5; double development). The unreacted ketone *XI* (32 mg) was more polar, while the less polar product was bromoketone *XIV* (64 mg) of m.p. 156–157°C (methanol), $[\alpha]_D^{22}$ +5·3° (*c* 2·0). For $C_{22}H_{27}BrO_4$ (435·4) calculated: 60·69% C, 6·25% H, 18·36 Br; found: 60·68% C, 6·15% H, 18·54% Br.

21-Bromo-3β,17α-dihydroxy-19-norpregna-5,7,9(10)-trien-20-one (*XV*)

Jacques reagent (750 mg) was added to a stirred solution of ketone *X* (700 mg) in tetrahydrofuran (10 ml) and the mixture was exposed to the effect of solar radiation. After one hour, when the solution became colourless, it was worked up as in the case of bromoketone *XIV*. The crude product was chromatographed on three silica gel plates (40 × 20 cm) with a mixture of benzene and ether 9 : 1 (double development). The more polar substance was unreacted ketone *X* (160 mg) and the less polar substance was bromoketone *XV* (510 mg), m.p. 179–181°C (ether), $[\alpha]_D^{20}$ +2·4° (*c* 1·6). For $C_{20}H_{25}BrO_3$ (393·3) calculated: 61·12% C, 6·41% H, 20·32% Br; found: 61·12% C, 6·44% H, 20·17% Br.

3β,21-Diacetoxy-17α-hydroxy-19-norpregna-5,7,9(10)-trien-20-one (*XVI*)

A solution of bromoketone *XIV* (54 mg) and potassium acetate (160 mg) in acetone (4·5 ml) was refluxed for 5 h under nitrogen. The mixture was diluted with ethyl acetate and water, the organic layer washed several times with water, dried and evaporated. Crystallization from a mixture of acetone and light petroleum gave 21-acetoxyketone *XVI* (25 mg), m.p. 204–206°C, $[\alpha]_D^{20}$ +27° (*c* 2·1). IR spectrum: 1730, 1750, 3618 cm^{-1}. ^{1}H-NMR spectrum: 0·60 s (3 H, 18H), 4·90 d + + 5·16 d (2 H, 21-H, J = 18 Hz). For $C_{24}H_{30}O_6$ (414·5) calculated: 69·54% C, 7·30% H; found 69·58% C, 7·37% H.

3β,17α-Dihydroxy-21-acetoxy-19-norpregna-5,7,9(10)-trien-20-one (*XVII*)

A solution of bromoketone *XV* (500 mg) and potassium acetate (2·8 g) in acetone (10 ml) was refluxed under stirring for 2 h in a nitrogen atmosphere. The mixture was worked up as in the preceding case. Crystallization from acetone–light petroleum gave 21-acetoxy derivative *XVII* (430 mg), m.p. 176–177°C, $[\alpha]_D^{20}$ +28° (*c* 1·3). ^{1}H-NMR spectrum: 0·59 s (3 H, 18-H), 4·87 d + + 5·18 d (2 H, 21-H, J = 18 Hz). For $C_{22}H_{28}O_5$ (372·4) calculated: 70·94% C, 7·58% H; found: 71·03% C, 7·60% H.

17α-Hydroxy-21-acetoxy-19-norpregna-5,7,9(10)-triene-3,20-dione (*XVIII*)

Alcohol *XVII* (200 mg) was dissolved in acetone (10 ml) and oxidized with excess CrO_3 (Jones' reagent) at 0°C under nitrogen for 10 minutes. Excess reagent was decomposed with oxalic acid, the mixture was diluted with ether and water, the organic layer washed with water, 5% aqueous sodium hydrogen carbonate and water, dried and evaporated. The residue was chromatographed on two thin-layer silica gel plates (40 × 20 cm) with benzene–ether mixture 95 : 5 (double development). Crystallization of the product from ether gave ketone *XVIII* (98 mg), m.p. 73—76°C (decomp.), $[\alpha]_D^{20}$ +49° (*c* 1·9). IR spectrum: 1693, 1730, 1738 sh, 3616 cm^{-1}. For $C_{22}H_{26}O_5$ (370·4) calculated: 71·33% C, 7·08% H; found: 71·45% C, 7·00% H.

The authors thank Drs V. Černý and V. Pouzar for their constant interest and valuable advice. Technical assistance was provided by Miss T. Stichová and Mrs M. Bárová. The analyses were carried out in the Analytical Laboratory of this Institute by Mrs E. Šípová and Mrs V. Rusová under the direction of Dr J. Horáček. The infrared and circular dichroism spectra were recorded and interpreted by Dr S. Vašíčková and the ^{1}H-NMR *spectra by Dr M. Buděšínský.*

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Translated by the author (Ž. P.).