SOME HETEROCYCLIC ANALOGS OF PSEUDOSOLASODINE

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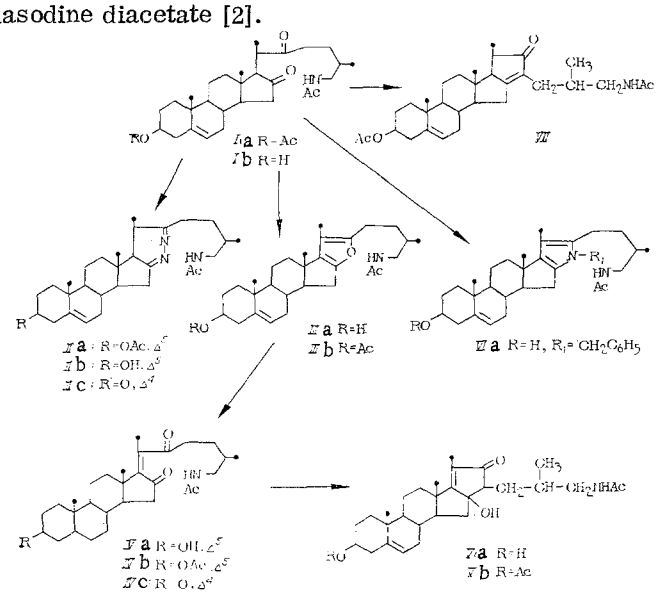
Solasodine is an aglycone of the Solanum type of steroidal alkaloids. It is a compound which possesses considerable physiological activity and is used as a starting material for the preparation of corticoid and sex hormones [1].

We have synthesized some heterocyclic analogs of pseudosolasodine and have studied their biological properties. The starting materials for the synthesis of these analogs was the 1,4-diketone (I), obtained from the oxidative cleavage of solasodine diacetate [2].



When Ia is heated with hydrazine hydrate in alcohol, the pyridazine-androstenol (IIa) is obtained; the structure of this compound was confirmed by IR, NMR, mass-spectral, and analytical data (Tables 1 and 2). The reaction mixture did not contain any aminopyrrole or saturated pyridazine analogs [3]. Hydrolysis of the acetyl group in IIa gave IIb which was oxidized by the Oppenauer method to the pyridazine (IIc).

Treatment of compound Ia with boiling acetic anyhdride containing p-toluenesulfonic acid followed by alkaline hydrolysis of the acetyl group gave the furanoandrostenol (IIIa), the structure of which was confirmed by spectral and analytical data (see Tables 1 and 2). The UV spectrum of IIIa has an absorption maximum at 228 nm, and the NMR spectrum a signal at 1.88 ppm from the methyl group on the furan ring in the absence of a proton at position 16 of the steroidal ring system. Acetylation of IIIa with acetic anhydride in pyridine gives IIIb which on oxidation with sodium dichromate in acetic acid in converted to the unsaturated analog of the diketone I (IVb).

The furanoandrostenolones (III) readily undergo autoxidation; solutions of IIIa and IIIb in organic solvents are found to contain IVa and IVb after standing in air at room temperature (TLC data). Compounds IVa and IVb were also isolated by preparative TLC. Failure to prepare the furanoandrostenol with a Δ^4-3-keto group can also be explained by its tendency to autoxidize. This compound, prepared by the Oppenauer oxida-

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TABLE 1. Proton Chemical Shifts for Compounds II-V (in ppm)

Compound	CH_3 (angular		CH_3		OAc	NHAc	H			2H at C_{26}
	at C_{19}	at C_{18}	at C_{20}	at C_{25}			at C_3	at C_4	at C_6	
IIa	1,01	1,04	2,24 s	0,94 d	1,98	2,02	4,56m	—	5,37 m	3,1 tr
IIb	1,13	1,13	2,39 s	0,94 d	—	2,02	3,5m	—	5,43 m	2,96 tr
IIc	1,10	1,29	2,34 s	0,98d	—	2,02	—	5,76s	—	3,05 tr
IIIa	0,9	1,06	1,88 s	0,95 d	—	1,96	3,5m	—	5,3 m	3,1 tr
IIIb	0,94	1,1	1,91 s	0,96d	1,98	2,04	4,6m	—	5,38 m	3,14 tr
IVa	1,06	1,1	1,98 s	0,92d	—	2,01	3,5m	—	5,4 m	3,08 tr
IVb	1,06	1,1	1,92 s	0,92d	1,98	2,02	4,5m	—	5,3 m	3,1 tr
IVc	1,12	1,21	1,91 s	0,9d	—	2,0	—	5,7s	—	3,08 tr
Va	1,07	1,31	1,74s	0,94d	—	1,96	3,5m	—	5,35 m	3,05 tr
Vb	1,08	1,3	1,72s	0,94d	1,96	2,02	4,6m	—	5,27 m	3,05 tr

Note. s, singlet; d, doublet; tr, triplet; m, multiplet.

TABLE 2. Mass-Spectra and Chromatographic Data for Compounds II-V

Compound	λ_{max}, nm	lg ε	M^+, m/l	R_f	ν, cm^{-1}
IIa	260	3,28	507	0,43	3390, 1715, 1670
IIb	260	3,29	465	0,31	3280, 3100, 1655
IIc	242	4,3	463	0,38	3250, 3060, 1660
IIIa	228	3,97	453	0,41	3360, 3260, 3080, 1660—1630
IIIb	228	3,97		0,57	3280, 3080, 1725, 1650—1630
IVa	250	3,86		0,18	3310, 3100, 1710, 1690, 1645
IVb	250	3,83	511	0,41	3280, 3100, 1735, 1710, 1690, 1650—1630
IVc	242	4,48	467	0,19	3300, 1710, 1665—1620
Va	238	4,05	469	0,14	3300, 1700, 1650
Vb	238	4,03	511	0,34	3300, 1730, 1700, 1650

tion of IVa and isolated from the reaction mixture by preparative chromatography, is oxidized by atmospheric oxygen to compound IVc.

The NMR spectra of both pairs of compounds (IIIa and IVa, and IIIb and IVb) are very similar, and only the signal due to the angular methyl group at C_{19} in IVb is displaced to the low-field region. Mass-spectra data shows that the molecular weights of IVb and IIIb differ by 16 units. Compounds III and IV exhibit considerably different UV absorption maxima, and the IR spectrum of IV has an absorption band at 1735 cm^{-1} due to the unsaturated 1,4-diketone (Tables 1 and 2).

The unsaturated diketones IV, in contrast to the saturated diketones I, react readily in alkaline medium, and in 2% KOH in methanol at room temperature undergo an internal aldol condensation with simultaneous hydrolysis of the acetyl group at position 3 to give compound Va. Acetylation of Va with acetic anhydride in pyridine gives Vb. On treatment of I with alkali, only the acetyl group at position 3 is hydrolyzed. The diketone I undergoes an internal croton condensation to give the ketone (VII) only after heating for many hours with strong base [2].

After heating I in alcoholic ammonia in an autoclave the reaction mixture was found to contain some pyrroleandrostenol (VIa), an extremely labile compound which could not be isolated. The benzylpyrrole (VIb) obtained by refluxing Ia in benzylamine solution, was more stable and was isolated by preparative chromatography on silica gel; however, the crystalline material, on standing in air or even in a vacuum desiccator, was unstable and therefore unsuitable for biological study.

Compounds Ia, IIa-c, IIIa and b, and IVc were tested; the study included an investigation of the androgenic, anabolic, thymolytic, antiinflammatory, and mineralocorticoid activities of the compounds. For all the compounds except IVc, the antimineralocorticoid action was studied, and for compounds Ia, IIb, and IIc, the gestagenic effect was investigated.

Activities were studied by methods described in [4 and 5]; all the substances were injected as solutions in oil.

Injection of IIb and IIc (50 mg/kg) into adrenalectomized rats together with DOC (0.5 mg/kg subcutaneously) increased the sodium-retaining action of DOC by approximately 60% and decreased its potassium-uretic activity by approximately 50%.

When orchidectomized rats were given weekly injections of IIIa, IIIb, and IVc (20 mg/kg) together with testosterone propionate (2 mg/kg), the androgenic action of the latter was increased by 60-70%; IIa and IIIb also increased its anabolic effect by 30-40%. Injection of IIIa (1 mg/kg), together with estrone (0.01 mg/kg), into infantile mice increased the uterotropic activity of the estrone by approximately 35%.

None of the compounds showed androgenic (20 mg/kg), anabolic (20 mg/kg), antiandrogenic (20 mg/kg), estrogenic (1 mg/kg), antiestrogenic (1 mg/kg), gestagenic (4 mg/kg), thymolytic (10 mg/kg), antiinflammatory (10 mg/kg), mineralocorticoid (50 mg/kg) or antimineralocorticoid (50 mg/kg) action.

Thus, this study of the hormonal activity of some heterocyclic analogs of pseudosolasidine shows that these compounds, although they do not show any hormonal action, do modify the effects of natural hormones (testosterone, estrone, deoxycorticosterone). Interestingly, this effect is selective: thus, the pyridazine–androstenols (group II) modify the activity of the mineralocorticoids, but do not alter the effect of the sex hormones; the furanoandrostenols, and derivatives of the unsaturated diketones (groups III and IV), on the contrary, while not altering the activity of deoxycorticosterone, increase the action of the sex hormones.

EXPERIMENTAL CHEMICAL PART

A Perkin–Elmer (England) spectrophotometer was used for IR spectra which were taken in mineral oil; NMR spectra were recorded on a Varian X-100-A-12 (USA) instrument with tetramethylsilane as internal standard; mass spectra were recorded on an MAT-112 (direct introduction of sample into source) at 70 eV.

Chromatography was carried out on thin layers of Silufol UV-254 in a cyclohexane–acetone (1 : 1) mixture for compounds I, III-V, and for compound II in a chloroform–methanol (9 : 1) mixture, and developed with a 1% solution of vanillin in 10% hydrochloric acid. Silica gel L40/100 Chemopol (Czechoslovakia) was used for preparative chromatography. Samples were compared with known compounds by mixed melting points, IR spectra, and chromatographic mobility.

[3-(γ-Methyl-δ-acetylaminobutyl)-4-methylpyridazino]-[6, 5k]-3β-acetoxyandrost-5-ene (IIa). To a solution of 10 g of Ic in 100 ml of ethyl alcohol is added 2 ml of hydrazine hydrate. The mixture is refluxed for 25 h and after cooling, poured into water, the product extracted with methylene chloride, and the solvent evaporated to dryness in vacuum. The oily residue is triturated with ether and precipitate filtered off. A yield of 8.9 g of IIa with mp 227.8°C (Mettler FP-5, 3 deg/min) is obtained. Found, %: C 73.59; H 8.95; N 8.18. $C_{31}H_{45}N_3O_2$. Calculated, %: C 73.33; H 8.93; N 8.27.

[3-(γ-Methyl-δ-acetylaminobutyl)-4-methylpyridazino]-[6, 5k]-3β-hydroxyandrost-5-ene (IIb). A solution of 8 g of IIa in 100 ml of 2% KOH in methanol is left at room temperature for 30 min. The solution is neutralized with acetic acid, poured into water, and the product extracted with methylene chloride. The extract is evaporated to dryness and the residue triturated with a mixture of ether and methanol to give 6.96 g of IIb, mp 189.5°C (from acetone and methanol, 9 : 1, Mettler FP-5, 3 deg/min). Found, %: C 72.68; H 9.55; N 8.66; H_2O 4.10. $C_{29}H_{43}N_3O_2 \cdot H_2O$. Calculated, %: C 72.3; H 9.35; N 8.7; H_2O 3.86.

[3-(γ-Methyl-δ-acetylaminobutyl)-4-methylpyridazino]-[6, 5k]-androst-4-en-3-one (IIc). To a solution of 1.8 g of IIb in 100 ml of dry toluene and 7 ml of distilled cyclohexanone is added, over a period of 10 min, a 5-ml of solution of aluminum isopropylate in toluene (29.6%). The reaction mixture refluxed for 1.5 h, and after the addition of sodium potassium tartrate, steam distilled. The residue is extracted with methylene chloride, the extract evaporated to dryness, and the oily residue chromatographed on silica gel. After washing with a mixture of ether and 40% methanol, the oil (1.56 g) is triturated with a mixture of ether and acetone to give 1.36 g of IIc, mp 210.2°C (from aqueous methanol, Mettler FP-5, 3 deg/min). C 74.70; H 8.91; N 8.98. $C_{29}H_{41}N_3O_2$. Calculated, %: C 75.12; H 8.91; N 9.06.

[2-(γ-Methyl-δ-acetylaminobutyl)-3-methylfurano]-[5, 4k]-3β-hydroxyandrost-5-ene (IIIa). A mixture of 10 g of I, 100 ml of acetic anhydride, and 0.1 g of p-toluenesulfonic acid is refluxed for 1 h, poured into water, and extracted with ethyl acetate. The extract is washed with water, dried, and evaporated to dryness. The oily residue is dissolved in 125 ml of 2% KOH in methanol and the solution allowed to stand at room temperature for 30 min. The precipitate is filtered off, washed with water, and dried to give 4.3 g of IIIa, mp 193-194°C (from acetone). Found, %:C 76.37; H 9.52; N 2.91. $C_{29}H_{43}NO_3$. Calculated, %: C 76.77; H 9.55; N 3.08.

[2-(γ-Methyl-δ-acetylaminobutyl)-3-methylfurano]-[5, 4k]-3β-acetoxyandrost-5-ene (IIIb). Compound IIIa (0.45 g) is acetylated with 0.5 ml of acetic anhydride and 6 ml of pyridine at room temperature for 18 h. The solution is poured into water, the residue filtered off, washed with water, and the damp material recrystallized from methanol with the addition of charcoal. A yield of 0.3 g of IIIb, mp 127-130°C is obtained. Found, %: C 75.12; H 8.82; N 2.57. $C_{31}H_{45}NO_4$. Calculated, %: C 75.11, H 9.15; N 2.82.

26-Acetylamino-3β-hydroxy-16,22-secofurosta-5,17(20)-dien-16,22-dione (IVa). A solution of 1.3 g of IIIa in 20 ml of chloroform is allowed to stand in air at room temperature for 10 days. Examination by TLC shows IVa is the predominant product in the reaction mixture. The chloroform solution is chromatographed on a silica gel column and eluted with chloroform and a mixture of chloroform and ethyl acetate (1 : 1) to give 1.07 g of an oily residue which on recrystallization from acetone gives 0.38 g of IVa, mp 182-184°C. Found, %: C 73.99; H 9.10; N 2.77. $C_{29}H_{43}NO_4$. Calculated, %: C 74.16; H 9.22; N 2.98.

26-Acetylamino-3-β-acetoxy-16,22-secofurosta-5,17(20)-dien-16,22-dione (IVb). A. To a solution of 3.0 g of IIIb in 30 ml of acetic acid at room temperature is added a solution of 0.9 g of sodium dichromate in 6 ml of acetic acid. The temperature rises to 27°C. The reaction mixture is maintained at room temperature for 2 h, poured into water and the precipitate extracted with chloroform. The solvent is evaporated and the residue, on trituration with ether, gives 1.6 g of IVb, mp 130-133°C. Found, %: C 72.48; H 8.91; N 2.59. $C_{31}H_{45}NO_5$. Calculated, %: C 72.76; H 8.86; N 2.73.

B. The methanol mother liquor from the recrystallization of IIIb was evaporated to dryness to give 1.2 g of an oily residue which, after two recrystallizations from acetone, yielded 0.2 g of IVb identical to that described above.

26-Acetylamino-16,22-secofurosta-4,17(20)-dien-3,16,22-trione (IVc). Compound IIIa (1 g) is oxidized by the method given for IIb. After extraction of the residue with methylene chloride, the extract is washed with water, dried, and the solvent evaporated. The residue is purified by chromatography on silica gel, using a chloroform–acetone solvent mixture, to give 0.47 g of an oil which, on recrystallization from petroleum ether and acetone (95 : 5), yields 0.25 g of IVc with mp 126-128°C. Found, %: C 74.34; H 8.74; N 2.73. $C_{29}H_{41}NO_4$. Calculated, %: C 74.48; H 8.84; N 2.99.

[1-Keto-2-(β-methyl-γ-acetylaminopropyl)-methylcyclopentan-3-ol]-[3,4k]-androst-5-en-3β-ol (Va). A solution of 0.62 g of IVb in 5 ml of 2% methanolic potassium hydroxide is allowed to stand at room temperature for 1 h, and then decanted into water. The precipitate which forms is filtered off, dried, and triturated with hexane to give 0.11 g of VA, mp 150-155°C (decomp.). Found, %: C 74.18; H 9.51; N 2.43. $C_{29}H_{13}NO_4$. Calculated, %: C 74.16; H 9.22; N 2.98.

3β-Acetoxy-[1-keto-2-(β-methyl-γ-acetylaminopropyl)-5-methylcyclopentane]-[3,4k]-androst-5-ene (Vb). Compound VA (0.8 g) is acetylated with 2 ml of acetic anhydride in 10 ml of pyridine, as described above. After pouring into water, the product is extracted with benzene, the extract washed with dilute hydrochloric acid and water, and the solvent evaporated to dryness. The residue is recrystallized from methanol with the addition of charcoal to give 0.37 g of Vb, mp 179-181°C. Found, %: C 72.21; H 9.07; N 2.40. $C_{31}H_{45}NO_5$. Calculated, %: C 72.76; H 8.86; N 2.73.

[1-Benzyl-2-(γ-methyl-δ-acetylaminobutyl)-3-methylpyrrolo]-[5, 4k]-3β-hydroxyandrost-5-ene (VIa). A mixture of 5 g of I and 25 ml of benzylamine is refluxed for 2 h. When cool, the solution is poured into water, the precipitated material filtered off, washed with water, and dried, (5.65 g). This is then hydrolyzed with 50 ml of 2% methanolic KOH at room temperature for 30 min. The solution is poured into water, VIa filtered off, washed with water, and dried. Purification of 1 g of VIa by chromatography on aluminum oxide using ether–acetone (95 : 5) as eluent gives 0.4 g of VIa which, on trituration with acetone, yields 0.22 g of VIa, mp 123-126°C. Found, %: C 79.68; H 9.28; N 4.78. $C_{36}H_{50}N_2O_2$. Calculated, %: C 79.65; H 9.28; N 5.16.

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