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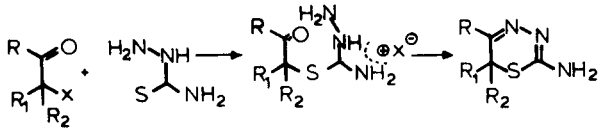
The reaction of 16α-bromoketosteroids, 2α-bromoketosteroids and 21-bromoketosteroids with thiosemicarbazide in 2-propanol produces the corresponding 2'-amino-1',3',4'-thidiazinosteroids. Acetylation of the 2'-aminothiadiazino-compounds led to the diacetamidothiadiazinosteroids. The title compounds prepared were substantiated by examination of infrared and nuclear magnetic resonance spectra.

J. Heterocyclic Chem., **17**, 1045 (1980).

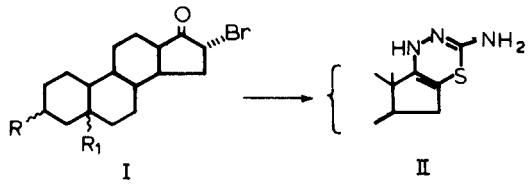
As a part of our study towards the development of new thiazosteroids with biological interest (2), we studied the reaction of steroidal α-bromoketones with thiosemicarbazide.

Compounds with a condensed thiadiazine ring in different positions on the steroid nucleus, are synthesized by a similar to Hantzsch's reaction (3), and are divided into



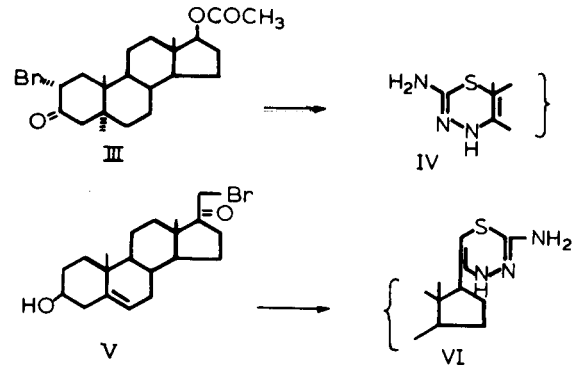
three clases:

A. 2'-Amino-1',3',4'-thiadiazino[6',5':20,21]steroids;
B. 2'-Amino-1',3',4'-thiadiazino[6',5':16,17]steroids;
C. 2'-Amino-1',3',4'-thiadiazino[6',5':2,3]steroids.



I II

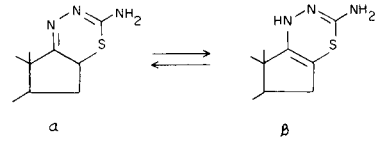
a, R = H, R_1 = 5α-H
b, R = 3β, CH_3COO, R_1 = 5α-H
c, R = 3α, CH_3COO, R_1 = 5α-H
d, R = 3β, CH_3COO, R_1 = Δ⁵



III IV V VI

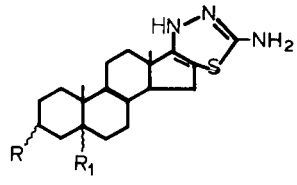
The compounds of class A prepared along with their respective yields are shown in Table 1.

The interaction of α-bromoketo-compounds with thiosemicarbazide yielded one or more of the following isomers:



α β

Table 1



Compound No.	R	R_1	M.p. °C	Formula	Yield %	Calcd. % C	H	N	Found% C	H	N
IIa	H	5α-H	240-242	$C_{20}H_{31}N_3S$	50	69.56	9.00	12.20	69.45	9.30	11.88
IIb	3β,CH_3COO	5α-H	211 dec.	$C_{22}H_{33}N_3O_2S$	29	65.50	8.18	10.42	65.44	8.20	10.22
IIc	3α,CH_3COO	5α-H	264-265	$C_{22}H_{33}N_3O_2S$	30	65.50	8.18	10.42	65.58	8.44	10.42
IId	3β,CH_3COO	Δ⁵	222-224 dec.	$C_{22}H_{31}N_3O_2S$	42	65.83	7.73	10.47	66.07	8.00	10.40

0022-152X/80/051045-03$02.25

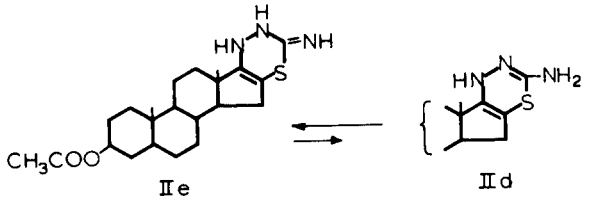
Table 2

Chemical Shifts, ppm in Deuteriochloroform

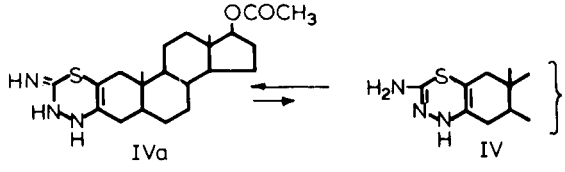
	Compound	Acetylated IIe	Compound IVa	Acetylated IVa
C=NH	8.29	8.53	8.50	8.76
NH	7.16	—	8.32	—
NH	6.24	—	6.20	—
C_5-H	5.38	5.34		
C_3-H	4.62	4.50		
C_{12}-H		4.50		
$>NCOCH_3$	—	2.18	—	2.15
C_{17}-H	—	—	3.83	4.58

According to recent reports (3) the chemical shift of the C-16 proton of structure α should be higher than δ 3. Such resonance was not detected for compound IId and the assigned structure corresponds to β or its tautomeric form.

Two tautomeric structures are considered for the condensed 2-amino-1,3,4-thiadiazine ring on the steroid nucleus (4).



IIe IId



IVa IV

The ^{1}H nmr data for the D and the A ring and their acetyl derivatives in deuteriochloform solution are given in Table 2. Compound IId shows three peaks at δ 8.29, 7.16 and 6.24 with intensities corresponding to one hydrogen each. It is shown by the addition of deuterium oxide that these peaks belong to exchangeable protons. Acetylation introduces two acetyl groups which are magnetically eqivalent and resonate at δ 2.18. In the acetylated D-ring only one exchangeable proton is observed. These data indicate that structure IIe predominates and the low field peaks are assigned as follows: C=NH, δ 8.29, NH, δ 7.16 and 6.24. Structure IId would give two resonances for the exchangeable protons, one for NH_2 and one for NH with the intensity ratio of 2:1. Similar considerations lead to the choice of structure IVa.

When solutions of D and A-ring are heated, the NH peaks are broadened; coalescence occurs at about 60°. Line shape changes are also observed upon cooling. Several conformation processes (5) may potentially occur in the thiadiazinic ring such as ring inversion, nitrogen inversion and Z-Y topomerization of the C=N bond the latter mediated through tautomerism. The problem will be further investigated.

In acetylated IIe one proton has detached itself from the methylene steroid region (δ 1 to 2) and appears together with proton C-3 at δ 4.5. The molecular model of the compound shows that the protons at position C-12 are subject to the magnetic anisotropy of the carbonyl of CH_3CO-N_4. Therefore, the new resonance at δ 4.5 was assigned to C_{12}-H.

EXPERIMENTAL

Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. Ir spectra were recorded with a Perkin-Elmer 521 spectrometer in solid phase potassium bromide. Nmr spectra were determined with a Varian Associates A-60 and with a Varian XL-100 instruments, using deuteriochloroform as a solvent and tetramethylsilane as the internal standard. Thin-layer chromatography was performed on silica gel plates using chloroform-methanol (95:5) as developer. Elemental analyses were performed by the Analytical Laboratory of the Chemistry Department, N.R.C. "DEMOKRITOS".

Procedures for the Preparation of 2'-Amino-1',3',4'-thiadiazinosteroids.

To a solution of 20 ml. of 2-propanol containing 1 mmole of the bromoketone (6-8), 1-2 mmoles thiosemicarbazide were added and the mixture was heated under reflux for 4-10 hours. The solution was poured into a saturated solution of sodium carbonate and the precipitate formed was collected by filtration, and washed several times with water. This solid was dissolved in the minimum amount of chloroform and purified by filtration over a silica gel column (eluant, chloroform). After removal of the solvent, the residue was crystallized from chloroform-methanol. The compounds prepared are reported in Table 1.

2'-Amino-1',3',4'-thiadiazino[6',5':2,3]-5α-androsten-16-3β-ol Acetate (IV).

This compound was prepared by the above general method in 44% yield after recrystallization from chloroform-methanol, m.p. 248-250°; ir: ν max 3400, 3220, 3130 cm^{-1} (NH), 1740, 1280 cm^{-1} (CO).

Anal. Calcd. for $C_{22}H_{33}N_3SO_2$: C, 65.50; H, 8.18; N, 10.42. Found: C, 65.36; H, 7.78; N, 10.25.

Diacetamido-1',3',4'-thiadiazino[6',5':2,3]-5α-androstan 17β-ol Acetate.

One hundred mg. of starting material with excess of pyridine and acetic anhydride was allowed to stand at room temperature for 24 hours. Then, it was worked up as usual and when recrystallized from methanol it gave a white substance, m.p. 259°.

Anal. Calcd. for $C_{26}H_{37}N_3O_4S$: C, 64.06; H, 7.59; N, 8.62. Found: C, 63.95; H, 7.79; N, 8.30.

Diacetamido-1′,3′,4′-thiadiazino[6′,5′:16,17]androstan-5,16-dien-3β-ol Acetate.

The diacetamido-compound (IId) was isolated in quantitative yield, using the above method, m.p. 243-245°, (methanol).

Anal. Calcd. for $C_{26}H_{35}N_3O_4S$: C, 64.32; H, 7.21; N, 8.66. Found: C, 64.05; H, 7.28; N, 8.90.

2′-Amino-1′,3′,4′-thiadiazino[6′,5′:20,21]pregna-5,20-dien-3β-ol (VI).

Following the above procedure of the general method the thiadiazino compound VI was obtained in 85% yield, m.p. 231-232°, (chloroform-methanol); ir: ν max 3420, 3450, 3265, 3150 cm^{-1} (OH, NH).

Anal. Calcd. for $C_{22}H_{32}N_3SO$: C, 68.21; H, 8.52; N, 10.85. Found: C, 68.41; H, 9.09; N, 10.85.

REFERENCES AND NOTES

(1) Taken in part from a thesis to be submitted by Dimitrios Kallias for the Ph.D. Degree at the University of Patras.

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