Effect of ω-substituents in the hydrazones of conjugated pregnane 20-ketosteroids on their ability to cyclize to pyrazolines*

A. V. Kamernitskii, E. I. Chernoburova, V. V. Chertkova, V. N. Yarovenko, I. V. Zavarzin, and M. M. Krayushkin*

N. D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences, 47 Leninskii prosp., 119991 Moscow, Russian Federation
Fax: +7 (495) 135 5328. E-mail: zavi@mail.ioc.ac.ru

The reactions of 3β-acetoxy-5-pregnan-20-one with thiooxamic acid hydrazides were studied. Depending on the nature of substituents in the thiohydrazide, the reactions give the corresponding hydrazones or pyrazolines resulting from hydrazone cyclization.

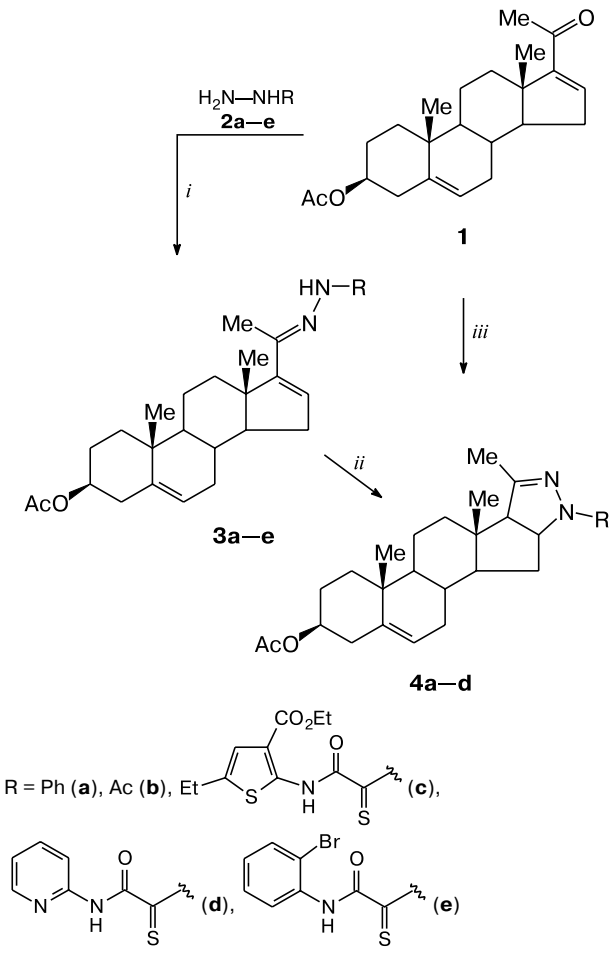
Key words: steroids, thiooxamic acid hydrazides, hydrazones, pyrazolines, heterocyclization.

The condensation of dehydropregnenolone acetate (**1**) with phenylhydrazine (**2a**) in acetic acid is known[1] to afford 20-phenylhydrazone (**3a**), which readily cyclizes on heating to pyrazoline derivative **4a** (Scheme 1). The *N*-acetylhydrazone of the same ketosteroid **3b** does not cyclize but is stabilized in the *E*-form incapable of cyclization under the reaction conditions.

The corresponding *N*-acetylpyrazoline **4b** can be obtained by heating compound **1** with hydrazine hydrate in acetic acid.[1] The mechanism of this reaction has not been studied, and it remained unclear what compound is formed first, either 20-acetylhydrazone, which subsequently cyclizes, or pyrazoline, which is then acetylated under the reaction conditions.

We found that the influence of the substituent at the amine nitrogen atom of the hydrazone fragment is not limited to the positions nearest to the hydrazone group. A study of the reaction of 20-ketosteroid **1** with thiooxamic acid hydrazides **2c—e** has revealed that the reaction pathway depends also on the nature of the distant ω-substituent in the thiohydrazide. In the case of derivatives **2c,d**, intermediate hydrazones **3c,d** cyclize to give pyrazolines **4c,d**, whereas in the case of **2e**, the reaction stops after the formation of hydrazone **3e**.

Scheme 1



Conditions: *i*. AcOH; *ii*. AcOH or Py/AcOH, Δ (for **3a,c,d** → **4a,c,d**); *iii*. $N_2H_4 \cdot H_2O$, AcOH (for **1** → **4b**).

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker AC-300 instrument (operating at 300 MHz). Mass spectra were recorded on a Kratos instrument with direct inlet, an ionization energy of 70 eV, and a control voltage of 1.75 kV. Commercially available

* Dedicated to Academician O. M. Nefedov on the occasion of his 75th birthday.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 11, pp. 2038—2039, November, 2006.

1066-5285/06/5511-2117

chemicals (Acros) were used. Thiooxamic acid hydrazides **2c—e** were prepared by a known method.[2]

Ethyl {5-ethyl-2-[2-hydrazino-2-thioxoacetylamino]thiophene-3-carboxylate} (2c), yield 57%, m.p. 152—154 °C. Found (%): C, 43.90; H, 5.97; N, 13.90; S, 21.37. $C_{11}H_{15}N_3O_3S_2$. Calculated (%): C, 43.84; H, 5.02; N, 13.94; S, 21.28. ^{1}H NMR (DMSO-d_6), δ*: 1.20, 1.40 (both t, 3 H each, Me); 2.80, 4.30 (both m, 2 H each, CH_2); 7.10 (s, 1 H, thiophene); 12.40 (s, 1 H, NH). MS, *m/z*: 301 $[M]^+$.

***N*-(2-Pyridyl)-2-hydrazino-2-thioxoacetamide (2d)**, yield 67%, m.p. 141—143 °C. Found (%): C, 42.90; H, 4.07; N, 28.47; S, 16.40. $C_7H_8N_4OS$. Calculated (%): C, 42.85; H, 4.11; N, 28.55; S, 16.34. ^{1}H NMR (DMSO-d_6), δ: 7.14, 7.82 (both m, 1 H each, Py); 8.08 (d, 1 H, Py, J = 7.9 Hz); 8.40 (m, 1 H, Py); 10.35 (s, 1 H, NH). MS, *m/z*: 196 $[M]^+$.

***N*-(2-Bromophenyl)-2-hydrazino-2-thioxoacetamide (2e)**, yield 65%, m.p. 161—163 °C. Found (%): C, 34.93; H, 2.88; Br, 29.26; N, 15.47; S, 11.81. $C_8H_8BrN_3OS$. Calculated (%): C, 35.05; H, 2.94; Br, 29.15; N, 15.33; S, 11.70. ^{1}H NMR (DMSO-d_6), δ: 7.15, 7.45 (both m, 1 H arom. each); 7.72, 8.31 (both d, 1 H arom. each, J = 8.0 Hz); 10.51 (s, 1 H, NH). MS, *m/z*: 274 $[M]^+$.

Reactions of ketosteroid 1 with thiooxamic acid hydrazides (general procedure). Method *A*. A solution of compound **1** (0.356 g, 1 mmol) and the corresponding thiohydrazide (**2c—e**) (1.1 mmol) in glacial acetic acid (7 mL) was refluxed for 4 h. The reaction mixture was then cooled, water (10 mL) was added, and the mixture was left for 16 h. The precipitate that formed was filtered off, washed successively with water and heptane, and dried *in vacuo*. The target products **4c,d** and **3e** were purified by thin layer chromatography (SILPEARL, ethyl acetate—hexane, 1 : 1).

Method *B*. A solution of compound **1** (0.356 g, 1 mmol) and thiohydrazide **2d** (0.215 mg, 1.1 mmol) was refluxed for 4 h in pyridine (7 mL) in the presence of catalytic amounts of AcOH (~1 drop). After cooling, water (10 mL) was added to the reaction mixture and the product was extracted with ethyl acetate (3×7mL). The organic extracts were combined, washed with 2% HCl and water, dried with $MgSO_4$, concentrated, and kept *in vacuo*. The residue was purified by thin layer chromatography (SILPEARL, ethyl acetate—hexane, 1 : 1) to give compound **4d**.

3β-Acetoxy-3´-methyl-1´-[2-oxo-2-(3-ethoxycarbonyl-5-ethyl-2-thienylamino)ethanethioyl]androst-5-ene-[17,16-*d*]pyrazoline-2 (4c). Yield 56%, m.p. 135—137 °C. Found (%): C, 63.95; H, 7.20; N, 6.39. $C_{34}H_{45}N_3O_5S_2$. Calculated (%): C, 63.82; H, 7.09; N, 6.57. ^{1}H NMR (DMSO-d_6), δ: 0.99 (s, 3 H, 18 Me); 1.05 (s, 3 H, 19 Me); 1.20, 1.40 (both t, 3 H each, Me); 2.05 (s, 3 H, 21 Me); 2.13 (s, 3 H, OAc); 2.80 (s, 2 H, CH_2); 3.40 (d, 1 H, 17 CH, $J_{17,16}$ = 8.0 Hz); 4.30 (m, 2 H, CH_2); 4.46 (m, 1 H, 3 CH); 5.05 (t, 1 H, 16 H, J = 8.0 Hz); 5.40 (s, 1 H, 6 CH); 7.05 (s, 1 H from thiophene); 11.32 (s, 1 H, NH). MS, *m/z*: 639 $[M]^+$.

3β-Acetoxy-3´-methyl-1´-[2-oxo-2-(pyridine-2-ylamino)ethanethioyl]androst-5-ene-[17,16-*d*]pyrazoline-2 (4d). Yield 50% (method *A*) and 53% (method *B*), m.p. 130—132 °C (benzene). Found (%): C, 67.50; H, 7.27; N, 10.38. $C_{30}H_{38}N_4O_3S$. Calculated (%): C, 67.39; H, 7.16; N, 10.48. ^{1}H NMR (DMSO-d_6), δ: 0.99 (s, 3 H, 18 Me); 1.05 (s, 3 H, 19 Me); 2.05 (s, 3 H, 21 Me); 2.13 (s, 3 H OAc); 3.40 (d, 1 H, 17 CH, $J_{17,16}$ = 8.1 Hz); 4.41 (m, 1 H, 3 CH); 5.05 (t, 1 H, 16 CH, J = 8.1 Hz); 5.40 (s, 1 H, 6 CH); 7.14, 7.82 (both m, 1 H each, Py); 8.05 (d, 1 H, Py, J = 7.9 Hz); 8.38 (m, 1 H, Py); 10.95 (s, 1 H, NH). ^{13}C NMR, δ: 183.0 (C=S); 169.7 ($C{=}O_{OAc}$); 166.1 ($C{=}O_{O=CNH}$); 164.6 ($C_{\alpha'\text{-Py}}$); 151.7 (CH_{Py}); 138.3 (CH_{Py}); 121.8 (CH_{Py}); 119.7 (CH_{Py}). MS, *m/z*: 534 $[M]^+$.

20-[2´-(2-Bromoanilino)-2-oxoethanethioylhydrazono]-3β-acetoxypregna-5,16-dien-20-one (3e). Yield 41%, m.p. 185—186 °C. Found (%): C, 60.55; H, 6.31; N, 6.79. $C_{31}H_{38}BrN_3O_3S$. Calculated (%): C, 60.78; H, 6.25; N, 6.86. ^{1}H NMR (DMSO-d_6), δ: 0.98 (s, 3 H, 18 Me); 1.05 (s, 3 H, 19 Me); 2.05 (s, 3 H, 21 Me); 2.13 (s, 3 H, OAc); 4.41 (m, 1 H, 3 CH); 5.40 (s, 1 H, 6 CH); 6.62 (m, 1 H, 16 CH); 7.15, 7.45 (both m, 1 H arom. each); 7.72, 8.30 (both d, 1 H arom. each, J = 8.0 Hz); 10.72, 11.75 (both s, 1 H each, NH). MS, *m/z*: 612 $[M]^+$.

References

1. A. V. Kamernitskii, N. S. Pavlova-Grishina, and A. V. Skorova, *Izv. Akad. Nauk SSSR. Ser. Khim.*, 1980, 1136 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1980, **28**, 843 (Engl. Transl.)].
2. V. N. Yarovenko, A. V. Shirokov, O. N. Krupinova, I. V. Zavarzin, and M. M. Krayushkin, *Zh. Org. Khim.*, 2003, **39**, 1204 [*Russ. J. Org. Chem.*, 2003, **39** (Engl. Transl.)].

* In the spectra of compounds **2c—e**, the signals of the $NH{-}NH_2$ group are faint.

Received July 7, 2006;
in revised form September 22, 2006