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Pharmacochemistry

Synthesis of some 5α-Androstano[17,16-d]pyrazoles from Tigogenin

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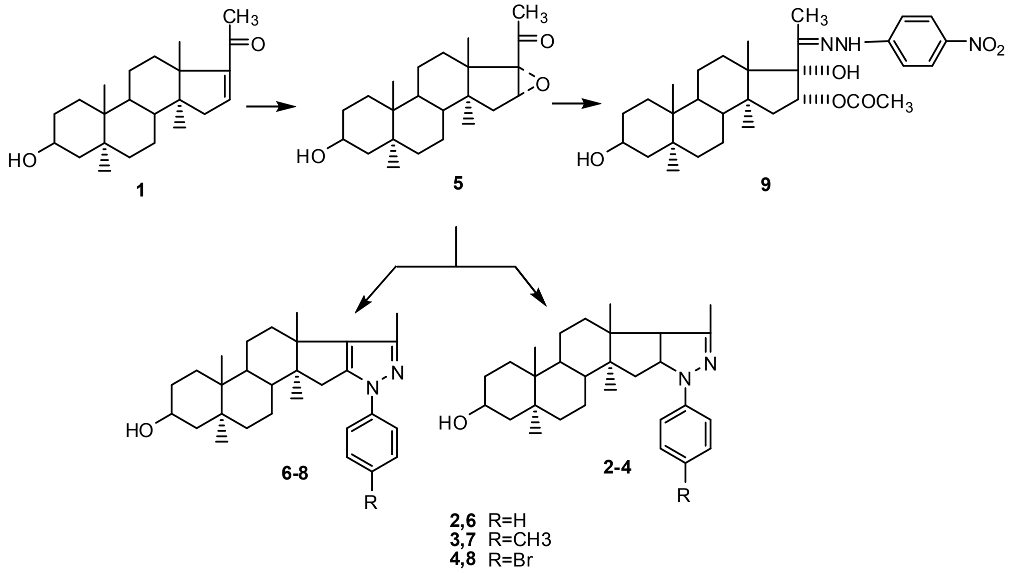
(Presented by Academy Member Eter Kemertelidze)

ABSTRACT. Condensation reaction of several arylhydrazines with 16α, 17α-epoxy-5α-pregnan-3β-ol-20-one synthesized from 5α-pregn-16-en-3β-ol-20-one–intermediate product of tigogenin transformation – were studied for the purpose of synthesizing potentially bioactive 5α-androstano [17,16-d] pyrazoles. Despite various conditions (different temperature, in protic and aprotic solvents) of the reaction, a complex mixture was obtained and then separated by column chromatography (eluent-hexane-ethylacetate). Two main products of intermolecular cyclization: 5α-androstano [17,16-d] pyrazole and its hydrogenated analogue – 5α-androstano [17,16-d]pyrazolines were isolated by substitution of electron-donating group (phenylhydrazine, p-methyl-, p-bromophenylhydrazine) at the hydrazine amine atom. In the presence of electron-withdrawing group (p-nitrophenylhydrazine) at the hydrazine amine atom cis-opening product of epoxygroup – 16α-acetoxy-5α-pregnan-3β, 17α-diol-20-one hydrazine – was obtained. The structures of synthesized compounds were established by NMR ^{1}H, ^{13}C and mass-spectral data. Structures of 3β-hydroxy-1′-phenyl-3′-methyl-5α-androstano [17,16-d] pyrazoles were confirmed by IR, NMR ^{1}H, ^{13}C, DEPT-135, HMBC and mass-spectral data. Synthesis of 5α-androstano [17,16-d] pyrazolines with 5α-androstano [17,16-d] pyrazoles by condensation reactions in the mentioned conditions was not described previously. *© 2018 Bull. Georg. Natl. Acad. Sci.*

Key words: pyrazoles, pyrazolines, epoxypregnanolone, hydrazine, hydrazone, 5α-steroides, cyclocondensation

Steroidal pyrazoles and pyrazolines are important classes of heterocyclic compounds as their representatives often exhibit hypotensive, antimicrobial, antiparasitic, antitumor, anti-inflammatory activity [1-6]. Steroidal compounds condensed with nitrogen-containing heterocycles in 16,17-position are of great interest, despite insufficient knowledge about similar analogues of saturated 5α-steroids.

Previously we have studied acid-catalyzed cyclocondensation reaction of some arylhydrazines (phenylhydrazine, p-methyl-, p-bromo- and p-nitrophenylhydrazine) with tigogenin transformation product - 5α-pregn-16-en-3β-ol-20-one **1**, and 3β-hydroxy-1′-aryl-3′-methyl-5α-androstano [17,16-d]pyrazolines **2-4** were isolated and characterized [7]. Later, the synthesis of



Scheme 1. The transformation of ketone **5** to the corresponding [17,16-d] pyrazoles

biologically active 5α-steroids [8] by condensation reaction of aforesaid hydrazines with 16α, 17α-epoxy-5α-pregnan-3β-ol-20-one **5** obtained from ketone **1** as described in [9], was studied.

It is known that 20-hydrazones of oxide can be obtained on the first stage of the reaction of 16α, 17α-epoxypregn-5-en-3β-ol-20-one with acetic acid at 20°C in the presence of hydrazine derivatives [10,11]. After the *cis*-opening of the oxide ring an acetic acid residue is introduced, giving 20-hydrazone of 16α-acetoxypregn-5-en-3β, 17α-diol. In turn, the reaction with hydrazine hydrate in boiling alcohol or ethylene glycol leads to the formation of a cyclization product – 3β-hydroxyandrost-5-eno[17,16-d]-3′-methylpyrazole.

According to the method [12] the 13-hour long reaction of 16α,17α-epoxypregn-5-en-3β-ol-20-one with phenylhydrazines in glacial acetic acid under nitrogen atmosphere at 25°C analogous cis-opening of oxide ring yields 20-phenylhydrazone of 16α-acetoxypregn-5-en-3β,17α-diol.

We investigated the interaction of 16α, 17α-epoxy-5α-pregnanolone **5** with phenylhydrazine in both aprotic (DMF) and protic (glacial acetic acid, ethylene glycol, ethanol) solvents and discovered that in all cases the reaction product represented a hard-to-separate mixture. From the latter the main products of intramolecular cyclocondensation – pyrazole **6** and its hydrogenated analogue – pyrazoline **2** were isolated by column chromatography. The reaction with p-methyl- and p-bromophenylhydrazines proceeds in a similar way giving pyrazolines **3, 4** and pyrazoles **7, 8**. On the other hand, when ketone **5** interacts with p-nitrophenylhydrazine in glacial acetic acid, cis-opening of the oxide ring results in the formation of hydrazone **9**.

Apparently, during the condensation reaction of 16α, 17α-epoxypregn-5-en-3β-ol-20-one with hydrazines at 20°C [10,11] on the first stage an intermediate hydrazone of oxide formed, which then is cyclized to pyrazole upon heating. We failed to isolate such intermediate hydrazones for compounds **6-8**. It can be concluded that in this case, similarly to previously described synthesis of pyrazolines [7], cyclocondensation takes place at the moment of the formation of hydrazones and goes to completion upon refluxing the reaction mixture. As expected [13], the presence of electron-donating substituents in hydrazine amine facilitated the cyclization reaction (steroids **2-4**, **6-8**), whereas an electron-withdrawing substituent interfered with this process (hydrazone **9**).

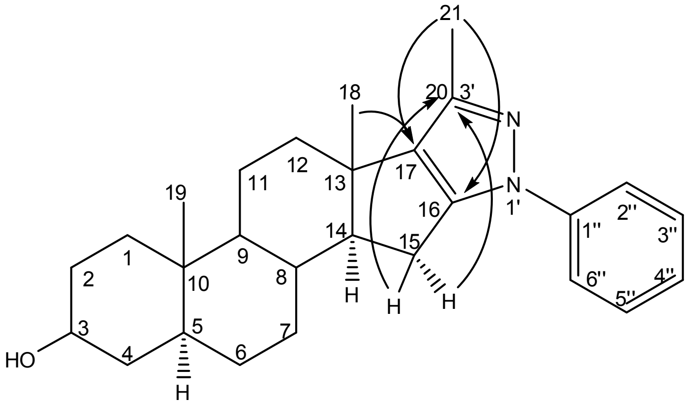


Fig.1. HMBC couplings in pyrazole **6**

The structure of pyrazole **6** was confirmed using IR, NMR and mass spectral data. In IR spectrum characteristic frequencies of OH group at 3227 cm^{-1}; C=N bond – 1599 cm^{-1}; C=C bond – 1545 cm^{-1} and aromatic bond – 1509 cm^{-1} were observed. Analysis of NMR ^{1}H, ^{13}C and DEPT-135 spectra proved the existence of four C-17, 1$^{//}$, 16, 20 aromatic (δ_c 138.3, 141.3, 144.1, 148.0) and two C-10,13 aliphatic (δ_c 36.5, 41.8) quaternary carbon atoms, and also five C-2$^{//}$, 6$^{//}$, 4$^{//}$, 3$^{//}$, 5$^{//}$ sp^2 (δ_c 120.7 - 2C, 127.0, 130.5 - 2C) and five C-8, 5, 9, 14, 3 sp^3 methine (δc 35.6, 46.4, 56.3, 64.0, 71.8), eight C-11, 15, 6, 2, 7, 1, 4, 12 methylene (δc 22.0, 28.7, 29.8, 32.2, 33.0, 38.0, 38.9, 37.0) and three C-19, 21, 18 methyl (δc 12.4, 12.8, 19.2) carbon atoms.

HMBC spectrum of pyrazole **6** exhibited correlations between the signals of methyl protons 21-CH_3 (δ_H 2.22 ppm) and 18-CH_3 (δ_H 1.01 ppm) with quaternary carbon C-17 (δc 138.3), also 21-CH_3 with C-16 (δc 144.1) and cross-peaks between H-15α (δ_H 2.62 ppm) and H-15β (δ_H 2.82 ppm) protons with C-20 (δc 148.0) (Fig. 1 and Table 1).

In the ^{1}H NMR spectra of steroids **6-8** singlet signal of angular 18-CH_3 group appeared at 0.96-1.04 ppm, 19-CH_3 group at 0.85-0.88 ppm, and 21-CH_3 group at 2.22-2.26 ppm. Multiple 3α-protons exhibited at δ 3.52-3.61 ppm, signals of aromatic protons at 7.16-7.56 ppm. In the ^{1}H NMR spectra of steroids **6-8,** as expected, there were no signals of hydrogens of pyrazoline **2-4** from C-16 and C-17 at δ 4.40 and 3.16 ppm, respectively.

In NMR ^{13}C spectra of pyrazoles **6-8** aromatic carbons of the benzene ring appear at 118.9-141.3 ppm, C-20 heterocycle in the 147.5-148.0 ppm region. The peaks from C-16 and C-17, (characteristic for pyrazolines around δ 64.8 and 66.3 ppm, respectively), shifted to weaker fields and appeared in δ 140.5-144.1 and 135.0-138.0 ppm interval.

The structure of hydrazine **9** was proved by IR, NMR and mass spectra. In the IR spectrum of compound **9** characteristic frequencies of OH and NH groups are at 3593-3470 and 3219 cm^{-1}, C=O ester group at 1726 cm^{-1}, C=N bonds at 1693cm^{-1}, aromatic bonds at 1597 cm^{-1}. The characteristic bands of stretching vibrations of Ar-NO_2 were observed at 1527 and 1321 cm^{-1}. In ^{1}H NMR spectra of the angular 18-CH_3, 19-CH_3 and 21-CH_3 groups were noted at 0.70, 0.85 and 2.00 ppm, the 16α-acetyl group at 2.11ppm, 3α- and 16β-protons at 3.64 and 4.16 ppm, respectively, aromatic protons - 7.07, 8.20 ppm and the proton of the NH group - 7.54 ppm. The molecular ions m/z $[M+H]^+$ corresponded to the brutto formulas of steroids **6-9**.

Experimental part

^{1}H and ^{13}C NMR spectra were registered in CD_3OD and $CDCl_3$ on a spectrometer Avance 400 Bruker (400.13 MHz for ^{1}H and 100.61 MHz for ^{13}C) with $SiMe_4$ as an internal standard. IR spectra were recorded from KBr discs on a spectrometer FT-IR Varian 660, mass spectra – on Agilent 1100 series HPLC-APCI MS (positive-ion mode) using an Inertsil prep-ODS column (6.0 - 250 mm) and H_2O-MeCN, 20:80 eluent. Melting points were determined on a NAGEMA apparatus. The course of reactions and purity of products were controlled by TLC on Silufol UV-254 plates using benzene-aceton, 5:1 and benzene-methanol, 10:1. Silikagel L100/250 (Chemapol, Czech Rep.), elution with

Table 1. **NMR Spectra of pyrazole 6 (CD_3OD,δ,ppm, J/Hz)**

Atom C	δ_c	DEPT	δ_H	HMBC
1	38.0	CH_2	1.06 (1H, m) 1.71 (1H,dt, J = 13.3, 3.8)	
2	32.2	CH_2	1.33-1.30 (1H, m) 1.82-1.78 (1H, m)	
3	71.8	CH	α3.52 (1H,m)	
4	38.9	CH_2	1.30(1H, m) 1.60 (1H, m)	
5	46.4	CH	α1.20 (1H, m)	
6	29.8	CH_2	1.28 (2H, m)	
7	33.0	CH_2	1.05 (1H, m) 1.72 (1H, m)	
8	35.6	CH	β1.68-1.66 (1H, m)	
9	56.3	CH	α0.83(1H,td,J=11.5, 3.9)	
10	36.5	C	-	
11	22.0	CH_2	1.51 (1H, m) 1.70(1H, m)	
12	37.0	CH_2	1.60 (1H, m) 2.11 (1H, m)	
13	41.8	C	-	
14	64.0	CH	α2.07(1H,,td,J=11.3, 6.8)	8, 13, 18
15	28.7	CH_2	α 2.62 (1H,dd, J = 14.3, 6.8) β 2.82 (1H,dd, J = 14.3, 11.8)	14,20 13,14, 17,20
16	144.1	C	-	
17	138.3	C	-	
18	19.2	Me	1.01(s)	12,13,14,17
19	12.4	Me	0.88(s)	1,5,9,10
20	148.0	C	-	
21	12.8	Me	2.22(s)	16, 17
1''	141.3	C	-	
2'',6''	120.7	CH	7.54 (2H,d, J = 7.6)	1'', 4'', 6'' 1'', 2'', 4''
3'',5''	130.5	CH	7.44 (2H,t, J = 8.0)	1'',5'' 1'', 3''
4''	127.0	CH	7.25 (1H,t, J = 7.4)	2'', 6''

mixtures hexane-ethylacetate 30:1, 20:1, 10:1, 5:1 was used for column chromatography. Chromatograms were processed by phosphomolybdic acid solution (10%) in EtOH followed by heating.

General method for the synthesis of 3β-hydroxy-1'-aryl-3'-methyl-5α-androstano[17,16-d]pyrazoles 6-8 and 3β-hydroxy-1'-aryl-3'-methyl-5α-androstano[17,16-d]pyrazolines 2-4. The mixture of ketone **5** was reacted with an equal weight of steroid with an amount of the corresponding hydrazine hydrochloride under the following conditions: 1) 6 hours boiling in ethanol, in the presence of a catalytic amount of acetic acid; 2) 24 hours in glacial acetic acid under nitrogen atmosphere at 25°C; 3) 2 hours in DMF at 110°C; 4) 4 hours in ethylene glycol at 80°C. The reaction mixture was cooled to room temperature, poured into icy water. The precipitate was filtered, washed with water, then with n-heptane, dried, and separated by column chromatography. Pyrazoles **6-8** and pyrazolines **2-4** were identified as the main products.

3β-Hydroxy-1/-phenyl-3/-methyl-5α-androstano[17,16-d]pyrazole (6), 3β-hydroxy-1/-phenyl-3/-methyl-5α-androstano[17,16-d]pyrazoline (2). Yields: 6 - 27% and 2 - 24%. M.p. of 6 160-162oC. IR-spectrum (KBr, □, cm-1): 3227(OH), 1599 (C=N), 1545(C=C), 1509(C=C arom.). The NMR spectral data given in Table 1. LC-MS m/z [M+H]+ 405.3. C27H36N2O. M.m. 404.3.

3β-Hydroxy-1/-p-methylphenyl-3/-methyl-5α-androstano[17,16-d]pyrazole (7), 3β-hydroxy-1/-p-methylphenyl-3/-methyl-5α-androstano[17,16-

d]pyrazoline (3). Yields: 7 - 25% and 3 - 21%. M. p. of 7 143-145oC. 1H NMR (CDCl3, δ, ppm., J/Hz): 0.85(3H, s, 19-CH3), 0.96(3H, s, 18-CH3), 2.24(3H, s, 21-CH3), 2.32(3H, s, 4//-CH3), 3.59 (1H, m, H-3), 7.16(2H, d, J=8.5, 2//,6//-H), 7.42(2H, d, J=8.5, 3//,5//-H).13CNMR (CDCl3, δ, ppm.): 12.2, 12.4, 18.7, 20.8, 26.2, 27.8, 28.4, 31.3, 31.7, 34.1, 35.1, 35.7, 36.6, 38.0, 40.2, 44.8, 54.7, 62.4, 71.1(C-3), 118.9(C-2//,6//), 129.6(C-3//,5//), 135.0(C-17), 136.7(C-4//), 137.5(C-1//), 142.1(C-16), 147.5(C-20). LC-MS m/z [M+H]+ 419.3. C28H38N2O. M.m. 418.3.

3β-Hydroxy-1′-p-bromophenyl-3′-methyl-5α-androstano[17,16-d]pyrazole (8), 3β-hydroxy-1′-p-bromophenyl-3′-methyl-5α-androstano[17,16-d]pyrazoline (4). Yields: 8 - 21% and 4 - 20%. M.p. of 8 270-272oC. 1H NMR (CDCl3, δ, ppm., J/Hz): 0.88(3H, s, 19-CH3), 1.04(3H, s, 18-CH3), 2.26(3H, s, 21-CH3), 3.61(1H, m, H-3), 7.3 (2H, d, J=8.3, 2//,6//-H), 7.56(2H, d, J=8.3, 3//,5//-H).13C NMR (CDCl3, δ, ppm.): 12.4, 18.9, 20.8, 28.0, 28.5, 29.7, 31.5, 31.9, 34.2, 35.1, 35.8, 36.7, 38.1, 40.4, 45.0, 54.8, 62.6, 71.2(C-3), 120.9(C-4//), 126.0 (C-2//,6//), 132.2(C-3//,5//),135.0(C-17), 138.1(C-1//), 140.5(C-16), 147.9(C-20). LC-MS m/z [M+H]+ 483.2. C27H35BrN2O. M.m. 482.2.

M.p., IR and NMR spectral data of compounds **2-4** are identical to the pyrazolines, which we described previously [7].

16α-Acetoxy-5α-pregnan-3β,17α-diol-20-one p-nitrophenylhydrazone (9). The solution of ketone **5** 0.07g (0.21 mmol) and a steroid-equivalent amount of p-nitrophenylhydrazine in 5 ml of glacial acetic acid was stirred at 20°C for 10 hours, left for the night and then the reaction mixture was poured into ice water. The precipitate was filtered, washed with water, air-dried, and purified by column chromatography eluting with corresponding mixture hexane-ethylacetate, 30:1 20:1, 15:1. Yield 0.072g (65%) hydrazine **9**. M.p. 181-183oC. IR-spectrum (KBr, ν, cm-1): 3593-3470(OH), 3219(NH), 1726(C=O), 1693(C=N), 1597(C=C arom.), 1527, 1321(C-NO2). 1H NMR (CDCl3, δ, ppm., J/Hz): 0.70(3H, s, 18-CH3), 0.85(3H, s, 19-CH3), 2.00(3H, s, 21-CH3), 2.11(3H, s, CH3COO), 3.64(1H, m, H-3), 6.26(1H, m, H-16), 7.07(2H, d,J=8.90, H-Ar), 7.54(1H, s, NH), 8.20(2H, d,J=8.96, H-Ar). LC-MS m/z [M+H]+ 528.3. C29H41N3O6. M.m. 527.3.

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ფარმაკოქიმია

ზოგიერთი 5α-ანდროსტანო [17,16-დ] პირაზოლის სინთეზი ტიგოგენინიდან

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პოტენციური ბიოლოგიურად აქტიური 5α-ანდროსტანო[17,16-დ]პირაზოლების სინთეზის მიზნით, შესწავლილია ზოგიერთი არილჰიდრაზინის კონდენსაციის რეაქცია 16α,17α-ეპოქსი-5α-პრეგნან-3β-ოლ-20-ონთან, რომელიც სინთეზირებულია ტიგოგენინის გარდაქმნის შუალედური პროდუქტის-5α-პრეგნ-16-ენ-3β-ოლ-20-ონისგან. რეაქციის ჩატარებისას სხვადასხვა ტემპერატურაზე, როგორც აპროტონულ, ისე პროტონულ გამხსნელებში წარმოიქმნება რთული ნარევი, რომელიც გასუფთავებულია სვეტის ქრომატოგრაფირებით (ელუენტი ჰექსან-ეთილაცეტატის ნარევი). ჰიდრაზინის ამინის ატომთან ელექტრონ-დონორული ჯგუფის (ფენილჰიდრაზინი, პ-მეთილ-, პ-ბრომფენილჰიდრაზინი) ჩანაცვლების შემთხვევაში გამოყოფილია შიდამოლეკულური ციკლიზაციის ორი ძირითადი პროდუქტი: 5α-ანდროსტანო [17,16-d] პირაზოლები და მათი ჰიდრირებული ანალოგები – 5α-ანდროსტანო [17,16-d] პირაზოლინები. ჰიდრაზინის ამინის ატომთან ელექტრონ-აქცეპტორული ჯგუფის (პ-ნიტროფენილჰიდრაზინი) არსებობისას კი წარმოიქმნება ეპოქსიჯგუფის ცის-გახსნის პროდუქტი –16α-აცეტოქსი-5α-პრეგნან-3β,17α-დიოლ-20-ონის ჰიდრაზონი. მიღებული ნაერთების აღნაგობა დადასტურებულია ^{1}H,^{13}C ბმრ- და მას-სპექტრებით. 3β-ჰიდროქსი-1$'$-ფენილ-3$'$-მეთილ-5α-ანდროსტანო, [17,16-დ], პირაზოლის სტრუქტურა დამტკიცებულია ი.წ.-, ^{1}H, ^{13}C ბმრ-, DEPT-135, HMBC და მას-სპექტრების მონაცემებით. აღნიშნულ პირობებში კონდენსაციის რეაქციის ჩატარებისას 5α-ანდროსტანო [17,16-d] პირაზოლებთან ერთად 5α-ანდროსტანო [17,16-d] პირაზოლინების წარმოქმნა ადრე არ არის აღწერილი.

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