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Synthesis of androstane derivatives fused with polyheterocycles at the D ring

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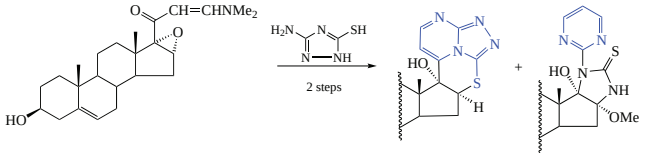
An unusual reaction of 16α,17α-epoxypregn-5-en-20-one with 3-amino-5-mercapto-1,2,4-triazole is accompanied by the heterocyclization involving epoxy ring opening and results in a mixture of new androstane derivatives fused with polyheterocycles at the D ring. Such polyheterocycles belong to 3-thia-1,2,8,8b-tetraazaacenaphthylene and 1,2a,7,7b-tetraazacyclopenta[*cd*]indene-2-thione families incorporating isomeric [1,2,4]triazolopyrimidine systems.



Keywords: 16α,17α-epoxypregn-5-en-20-one, fused heterocycles, androstane D ring, 3-thia-1,2,8,8b-tetraazaacenaphthylene, 1,2a,7,7b-tetraazacyclopenta[*cd*]indene-2-thione, [1,2,4]triazolopyrimidines, heterocyclization.

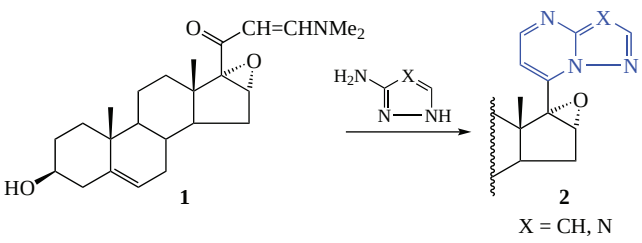
Dedicated to the Memory of Academician Oleg M. Nefedov.

Incorporation of heterocycles into the steroid nucleus provides its modification and broadens the physiological activity spectrum of these compounds.[1–8] Therefore, the development of methods for the synthesis of hetaryl-substituted steroids is of high importance. Previously,[9,10] we developed a convenient method for incorporating a heterocyclic substituent at position 17 of the steroid nucleus. In particular, the reaction of steroid amino enone **1** with binucleophiles, namely 3-aminopyrazole and 3-amino-1,2,4-triazole, results in 17-pyrazolo and 17-triazolopyrimidine derivatives of androstane **2** (Scheme 1).[10]

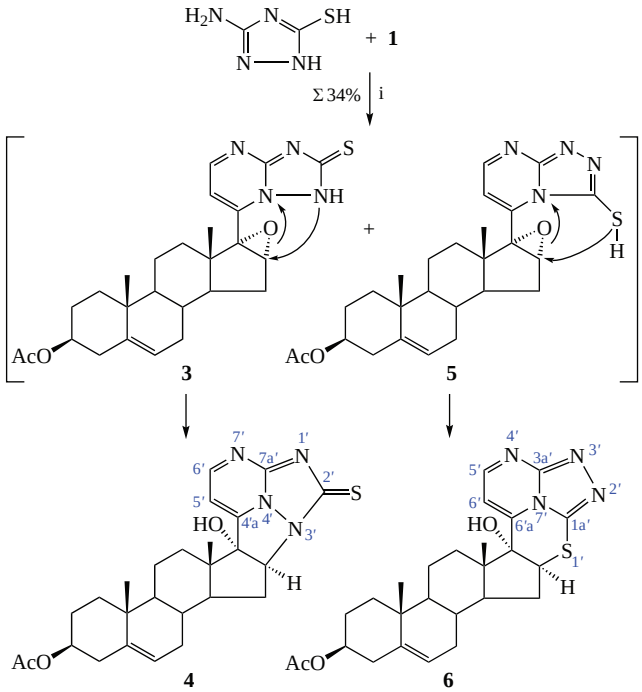
However, in an attempt to expand the range of the starting binucleophiles, it was unexpectedly found that the reaction of amino enone **1** with 3-amino-5-mercapto-1,2,4-triazole results in fused steroid **4** that is apparently formed upon intramolecular cyclization of intermediate **3** accompanied by epoxy ring opening (Scheme 2). In addition, the product of further cyclization of isomeric steroid **5**, *i.e.* compound **6**, is formed as a minor product. The ratio of products **4** and **6** is 4 : 1 (^{1}H NMR). Compounds **4** and **6** have equal chromatographic mobility, so we failed to separate them.

The ^{1}H NMR spectra of heterocyclic steroids **4** and **6**, unlike those of epoxy steroids **2** exhibiting the singlets, contain doublets of doublets for the 16-CH proton at δ 4.75 ($J_1 = J_2 = 7.8$ Hz) and δ 3.72 ($J_1 = 5.8$ Hz, $J_2 = 8.5$ Hz), respectively, and singlets from the 17-OH group at δ 6.76 and δ 6.22, respectively. In the two-dimensional ^{1}H–^{13}C HMBC NMR spectrum, correlations with the 13-C and 17-C carbon atoms are observed for the 17-OH proton. In the ^{13}C NMR spectrum of compound **4**, there is a significant downfield shift for the 17-C atom at δ 102.3 (it is δ 79.0 in compound **6**); the values of chemical shifts for the 16-CH atom are δ 74.3 and δ 42.5, respectively.

To remove the OAc group, a mixture of compounds **4** and **6** was treated with K_2CO_3 in MeOH under conditions usually employed for steroids. However, under these conditions steroid **4** underwent, along with removal of the OAc-group, an unusual



Scheme 1



Scheme 2 *Reagents and conditions*: i, AcOH, Δ, 11 h.

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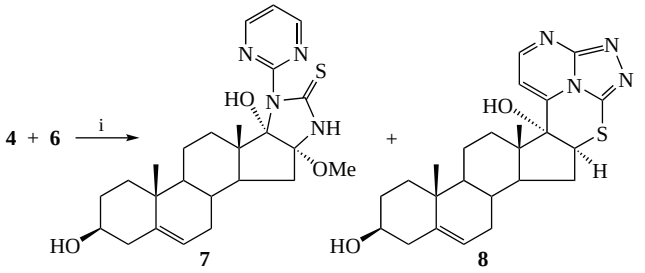


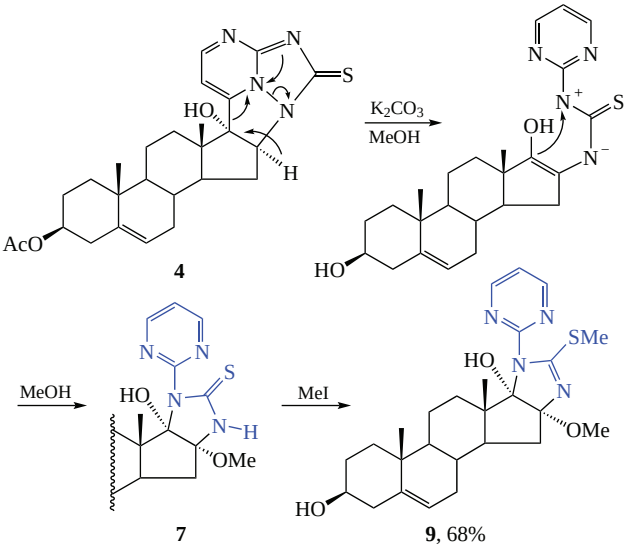
Scheme 3 *Reagents and conditions*: i, K_2CO_3, MeOH, room temperature, 27 h.

recyclization to furnish 3β,17α-dihydroxy-16α-methoxy-1′-(pyrimidin-2-yl)-2′,3′,16,17-tetrahydro-1′*H*-2′-thioxoandrost-5-eno[16,17-*d*]imidazole **7** (yield 57%), whereas steroid **6** underwent only the expected OAc removal to give compound **8** in 95% yield (Scheme 3). Compounds **7** and **8** differ significantly in chromatographic mobility and can be easily separated.

In the ^{1}H NMR spectrum of compound **7**, in contrast to the starting compound **4**, the doublet of doublets from the 16-CH proton is missing, but an additional signal for the pyrimidine proton appears instead (there are a triplet at δ 7.36, J = 4.8 Hz with 1H intensity and a doublet at δ 8.80, J = 4.8 Hz, with 2 H intensity, from the pyrimidine ring) as well as a singlet from NH at δ 9.98 and a singlet from the OCH_3 group at δ 3.28. In the ^{13}C NMR spectrum of compound **7**, the signals at δ 95.2 (16-C) and δ 103.7 (17-C) should be noted. In the two-dimensional ^{1}H–^{13}C NMR spectrum, correlations of the 17-OH proton at δ 5.85 with the 13-C, 16-C and 17-C carbon atoms, the CH_3O group protons with the 16-C atom and the NH proton at δ 9.98 with the 16-C, 17-C and C=S carbon atoms are observed. Upon pre-irradiation of the OCH_3 group protons at δ 3.28, a positive NOE effect with 17-OH protons at δ 5.85 and with NH at δ 9.98 is detected in the one-dimensional ROESY spectrum, and a positive NOE with the OCH_3 group protons at δ 3.28 is observed upon pre-irradiation of 17-OH protons at δ 5.85.

Compound **7** is apparently formed upon simultaneous opening of both the 1,2,4-triazole and pyrazole rings followed by MeOH addition (Scheme 4). The resulting compound **7** can be methylated at the sulfur atom on treatment with MeI to afford compound **9**. At the same time, compound **8** does not react under these conditions and remains unchanged.

To conclude, incorporation of a mercapto group into 3-amino-1,2,4-triazole dramatically changes the direction of its reaction with 16α,17α-epoxypregn-5-en-20-one derivatives and is accompanied by unusual cyclization to give derivatives fused with polycyclic heterocycles at the D ring through the C^{16}–C^{17} bond of the steroid. Compounds **6** and **8** herein obtained incorporate unique 3-thia-1,2,8,8b-tetraazaacenaphthylene heterocyclic system while product **4** includes no less unusual 1,2a,7,7b-tetraazacyclopenta[*cd*]indene-2-thione one. Both of them relate to fused [1,2,4]triazolopyrimidines of different fusion pattern and seem promising for multipurpose usage.



Scheme 4

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.10.014.

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