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FIRST EXAMPLE OF CONSTRUCTION OF A PYRROLE RING BONDED TO A STEROID SYSTEM BY THE TROFIMOV REACTION*

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The oxime of Δ^5-pregnen-3β-ol-20-one reacts with acetylene in the KOH–DMSO system to form a mixture of products containing 3β-vinyloxy-17β-(1-vinyl-2-pyrrolyl)-Δ^5-androstene as the major product (63% yield) and also the O-vinyloxime of 3β-vinyloxy-Δ^5-pregnen-20-one (10%), 3β-vinyloxy-17α- and 3β-vinyloxy-17β-Δ^5-pregnen-20-one (25%, 1:4 ratio).

Keywords: acetylene, pregnenolone oxime, pyrroles, steroids.

Two-step construction of a pyrrole ring from acetylene and ketones (through ketoximes) in the KOH–DMSO system (the Trofimov reaction) [1-5] is an effective tool in the chemistry of heterocyclic compounds [2, 3, 5]. But before our study, it remained unclear whether it was possible to extend this reaction to ketosteroids, where the pyrrole ring formed may be either added to the steroid skeleton or introduced to a substituent and both these variants may be realized simultaneously. The solution to this problem opens up a new universal approach to modification of ketosteroids.

Our pyrrolization of Δ^5-pregnen-3β-ol-20-one (**1**), selected as a typical representative of ketosteroids, made it possible to estimate the stability of the Δ bond in the presence of a superbasic catalyst (KOH–DMSO) and the relative rates of formation of the pyrrole ring and vinylation of the alcohol, oxime, and pyrrole functional groups.

A few examples are known of combination of pyrrole and steroid moieties in molecules of both synthetic and natural compounds [6-8], which sometimes have extremely high biological activity (for example, batrachotoxin from skin sectretion of the Colombian frog *Phyllobates aurotaenia*) [8]. So application of the Trofimov reaction to ketosteroids may be of interest both for the chemistry of steroids and for the chemistry of pyrrole, and also for a targeted search for biologically active substances.

In order to cut down on the number of possible products, we determined the conditions (100°C, 5 h, initial acetylene pressure 14 atm, autoclave) in which exhaustive vinylation of the 3-OH group and the NH pyrrole functional group occurs:

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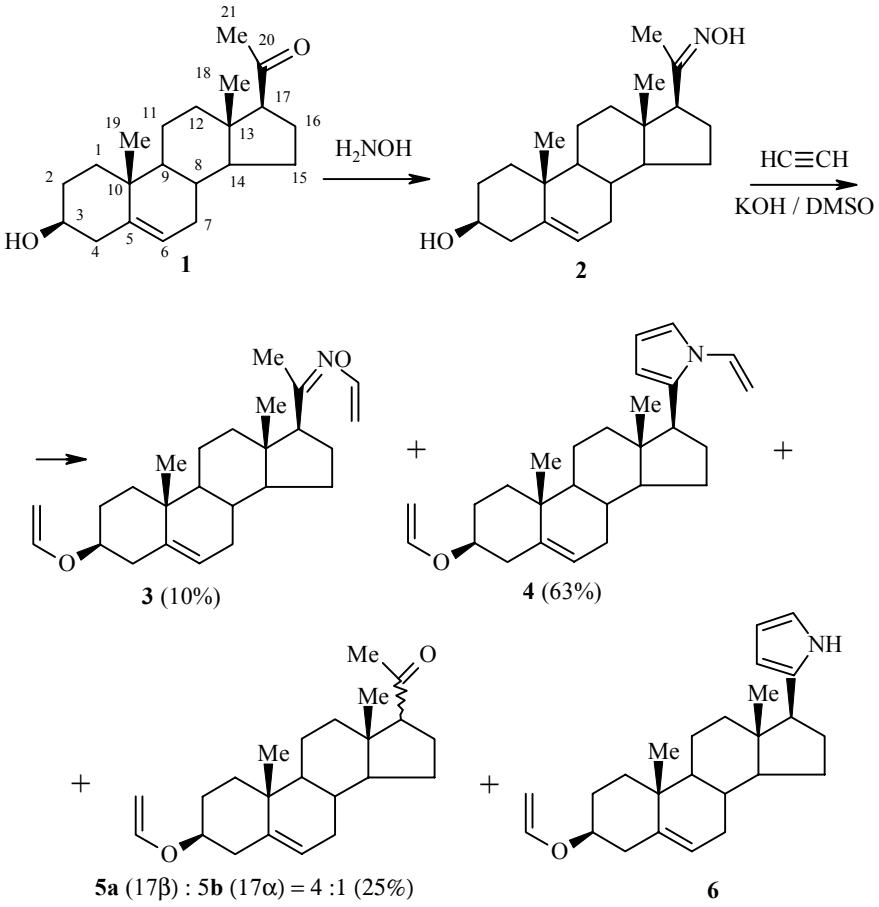


Under these conditions, the reaction of ketoxime **2** with acetylene occurs quantitatively, yielding the products **3-5**, the first representatives of the previously unknown class of functionalized steroids, in the ratio 1:5:2 (^{1}H NMR).

The expected migration of the endocyclic double bond or change in the initial configuration of the steroid portion (in the case of **3** and **4**) is not observed. The major product is compound **4** (63% yield), combining in one molecule fragments of the steroid, the vinyl ether, and 1-vinylpyrrole, which ensures that different types of chemical modification are possible, including addition and polymerization reactions.

When the reaction is carried out under milder conditions (75°C, 5 min), along with vinylpyrrole **4,** we also observe formation of its precursor: 3β-vinyloxy-17β-(2-pyrrolyl)-Δ^5-androstene (**6**). The ratio of the products suggests that vinylation of the alcohol and oxime groups is the process that occurs most easily.

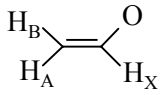
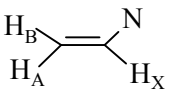
The rates of formation and vinylation of the pyrrole moiety are comparable and approximately two times slower than the rates of vinylation of the alcohol and oxime functional groups. Obviously the yield of 1H-pyrrole **6** may be increased since we know that when KOH is substituted by NaOH or LiOH, or when the reaction is conducted in aqueous DMSO, pyrrole vinylation processes are suppressed [1, 2].

In the ^{1}H NMR spectra of products **2-6** (Table 1), the most characteristic signals are those corresponding to H-3, H-6, H-17 and the methyl groups in the 18, 19, and 21 positions. Introduction of an O-vinyl group in the 3 position is accompanied by a downfield shift of the H-3 signal (by 0.14 ppm compared with the spectrum of the starting compound **1**). In ketoxime **2** and O-vinylketoxime **3**, we observe upfield shifts for the signals from H-17 (0.28 ppm) and the methyl group in the 21 position (0.21 ppm). Formation of a pyrrole ring in 3β-vinyloxy-17β-(2-pyrrolyl)androstenes **4** and **6** leads to disappearance of the signals from the methyl groups (Table 1). All the protons of the vinyl and pyrrolyl substituents have the typical chemical shifts and spin–spin

TABLE 1. ^{1}H NMR Spectra of Compounds **1-6**

Com-pound	Chemical shifts (δ, ppm) and spin-spin coupling constants (*J*, Hz)						
	H-3, m	H-6, m	H-17, m	18-Me, s	19-Me, s	21-Me, s	other signals
1*	3.49	5.30	2.48	0.59	0.96	2.07	—
2	3.51	5.34	2.20	0.63	1.00	1.86	—
3	3.62	5.34	2.19	0.64	1.00	1.89	OCH=CH$_2$*^{2}: 3.99 (1H, dd, H$_A$, $^{2}J_{AB}$ = 1.3, $^{3}J_{AX}$ = 6.7); 4.28 (1H, dd, H$_B$, $^{3}J_{BX}$ = 13.7); 6.33 H$_X$ (1H, dd) =NOCH=CH$_2$*^{2}: 4.03 (1H, dd, H$_A$, $^{2}J_{AB}$ = 1.8, $^{3}J_{AX}$ = 6.9); 4.52 (1H, dd, H$_B$, $^{3}J_{BX}$ = 14.3); 6.90 (1H, dd, H$_X$)
4	3.63	5.38	2.74	0.55	0.99		OCH=CH$_2$*^{2}: 3.99 (1H, dd, H$_A$, $^{2}J_{AB}$ = 1.3, $^{3}J_{AX}$ = 6.7); 4.28 (1H, dd, H$_B$, $^{3}J_{BX}$ = 13.7); 6.30 H$_X$ (1H, dd) NCH=CH$_2$*^{2}: 4.58 (1H, dd, $^{2}J_{AB}$ = 1.0, $^{3}J_{AX}$ = 8.8); 5.05 (1H, dd, H$_B$, $^{3}J_{BX}$ = 15.7); 6.99 H$_X$ (1H, dd); pyrrole ring: 6.01 (1H, dd, H-3', $^{3}J_{3'-4'}$ = 3.7, $^{4}J_{3'-5'}$ = 1.7); 6.16 (1H, dd, H-4', $^{3}J_{4'-5'}$ = 3.0); 6.94 (1H, dd, H-5')
5a	3.63	5.37	2.51	0.62	1.01	2.11	OCH=CH$_2$*^{2}: 3.99 (1H, dd, H$_A$, $^{2}J_{AB}$ = 1.3, $^{3}J_{AX}$ = 6.7); 4.28 (1H, dd, H$_B$, $^{3}J_{BX}$ = 13.7); 6.33 H$_X$ (1H, dd)
5b	3.63	5.37	2.80	0.91	0.99	2.12	OCH=CH$_2$*^{2}: 3.98 (1H, dd, H$_A$, $^{2}J_{AB}$ = 1.3, $^{3}J_{AX}$ = 6.7); 4.28 (1H, dd, H$_B$, $^{3}J_{BX}$ = 13.7); 6.32 H$_X$ (1H, dd)
6	3.63	5.37	2.74	0.55	0.99		OCH=CH$_2$*^{2}: 3.99 (1H, dd, H$_A$, $^{2}J_{AB}$ = 1.3, $^{3}J_{AX}$ = 6.7); 4.28 (1H, dd, H$_B$, $^{3}J_{BX}$ = 13.7); 6.33 H$_X$ (1H, dd) pyrrole ring: 5.93 (1H, m, H-3'); 6.13 (1H, m, H-4'); 6.66 (1H, m, H-5'); 8.00 (1H, br. s, NH)

* Assignment made using data in [9].

*^{2} Protons in the vinyl groups are labeled as follows:  and  .

coupling constants [1-3]. The deoximation product, the ketone **5**, is a mixture of 17-β- (**5a**) and 17-α-isomers (**5b**) (4:1). Predominance of the isomer **5a** is the result of steric hindrances which occur in the case of the α-isomer **5b** with pseudoaxial orientation of the acetyl group. Such isomerization was observed earlier when pregnenolone **1** was treated with a methanol KOH solution [10].

Due to the presence of C-17 epimers, in the ^{1}H NMR spectrum of ketone **5** we observe two sets of signals corresponding to the vinyl group, the methyl radicals in the 18, 19, 21 positions, and the H-17 proton. The greatest difference between the chemical shifts in isomers **5a** and **5b** is characteristic for the signals from the 18-Me and H-17 protons. In the spectra of O-vinylketoxime **3** and N-vinylpyrrole **4**, the above-mentioned signals are singlets. For the compounds **1**, **2** and **3**, **4** we do not observe a significant difference between the chemical shifts of the protons of the 18-Me groups, which suggests absence of epimerization.

Thus under the conditions suggested here, the Trofimov reaction is applicable to ketosteroids and, when using modern separation technology, can be used to create combinatorial libraries for exotically functionalized steroid compounds.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker-400 DPX (400.13 MHz) in $CDCl_3$; HMDS was used as an internal standard. The IR spectra were recorded on a Bruker ISF 25. The UV spectrum was obtained on a Milikhrom A-02 with UV detection in the 200-360 nm range.

Oxime **2** is obtained in quantitative yield by reaction of $NH_2OH{\cdot}HCl$ (1.05 equiv.) with 1.00 equiv. of commercial Δ^5-pregnen-3β-ol-20-one (ICN Biochemical, Inc.) in pyridine.

Reaction of Δ^5-Pregnen-3β-ol-20-one Oxime with Acetylene. A mixture of ketoxime **2** (3.32 g, 10 mmol) and KOH (1.68 g, 30 mmol) in DMSO (50 ml) was saturated with acetylene (14 atm) in an autoclave, heated (100°C, 5 h), cooled, diluted with water and extracted with diethyl ether. The extract was washed with water and dried over $MgSO_4$. After evaporation of ether, the mixture of products obtained was separated using preparative TLC (Al_2O_3, diethyl ether–pentane, 1:3). After the separation, very viscous products **3-5** were obtained, ~90% pure, in yields (according to ^{1}H NMR spectra): **3**, 10%; **4**, 63%; **5a,b**, 25%. We could not obtain purer substances, since we were unable to determine crystallization conditions for the isolated samples, and selecting different supports and eluents and using column chromatography were also unsuccessful.

The spectrum of pyrrole **6** was obtained in a mixture with compounds **1-5**, which form under milder conditions: KOH–DMSO, 75°C, 5 min, initial acetylene pressure 14 atm. Yield of product **6** was 5% (^{1}H NMR).

The UV spectrum of pyrrole **4** has an absorption band (λ 245 nm, ε 4.1) which is typical of 1-vinylpyrroles [1, 3].

In the IR spectra of compounds **3, 4, 5a,b**, the 3β-vinyloxy group has the following typical absorption bands: (film, cm^{-1}) [11]: 3114, 3018, 3060, 1634-1637, 1378, 1324, 1196, 1174, 1129, 961, 817; the pyrrole ring (**4**) is represented by the characteristic [1, 2] bands: 1476, 1292, 709; the N-vinyl group (**4**) is observed at the familiar [1, 3] frequencies: 1392 (C–N), 817 (=CH_2); the presence of a carbonyl group in **5a,b** is confirmed by the strong absorption at 1702-1704 cm^{-1}, and the NH group in **6** gives a broad band at 3390 cm^{-1}.

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