Chemistry of Heterocyclic Compounds, Vol. 38, No. 1, 2002

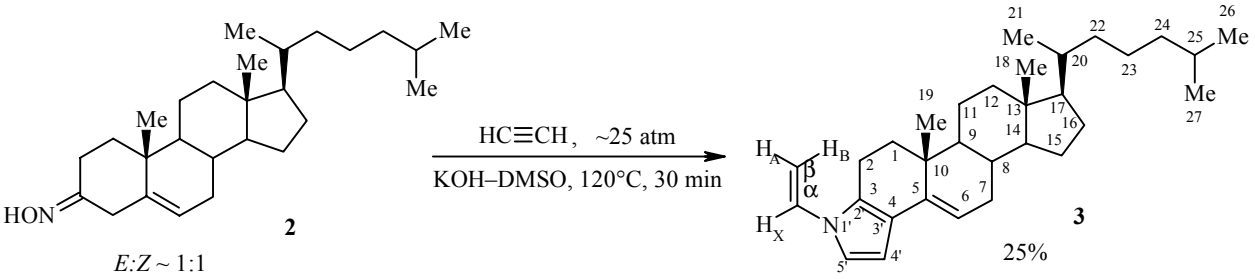
ANNELATION OF THE PYRROLE TO THE STEROID SKELETON USING THE TROFIMOV REACTION*

A. M. Vasil'tsov, A. B. Zaitsev, A. I. Mikhaleva, E. Yu. Shmidt, and A.V.Afonin

The product of annelation of the N-vinyl pyrrole ring with steroid skeleton of 5-cholestene was obtained in a single regioselective step by the reaction of 5-cholesten-3-one oxime with acetylene in KOH-DMSO by the Trofimov reaction.

Keywords: acetylene, N-vinylpyrroles, ketosteroids, Trofimov reaction, KOH–DMSO system.

The reaction of ketoximes, containing a methylene group in the α-position to the oxime function, with acetylene in strongly basic conditions (the Trofimov reaction [1-7]) is an effective and universal method for the construction of 1H- and N-vinylpyrrole systems. The expected interest in the biological properties of the desired products led us to investigate the use of this reaction for modification of ketosteroids, using 5-cholesten-3-one (**1**) as an example, particularly since pyrrole rings had been introduced into other isopropenoids by this reaction [8]. Including in a single molecule the steroid skeleton and the pyrrole structure, units which are connected with biological activity in many natural and synthetic compounds, has great potential for the creation of new medicinals, among them polymers (*via* polymerization of the N-vinyl group) with prolonged activity.



In this paper we report the first successful attempt at annelation of the steroid skeleton with the N-vinylpyrrole unit by the interaction 5-cholesten-3-one oxime (**2**) with acetylene in the strongly basic KOH–DMSO system. The reaction occurs regioselectively with the formation of a single product of pyrrolisation of the methylene group at position 4 (compound **3**) in a preparative yield of 25%.

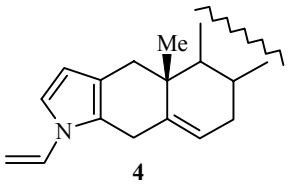
* Presented to Academician of the Russian Academy of Sciences M. G. Voronkov on his 80th birthday.

A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch, Russian Academy of Sciences, Irkutsk 664033, Russia; e-mail: mikh@irioch.irk.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, 66-70, January 2002. Original paper submitted April 27, 2001.

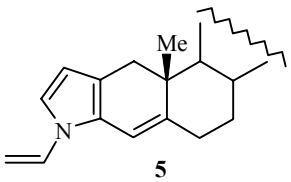
 0009-3122/02/3801-0060$27.00

The oxime **2** was prepared from ketone **1** as a mixture of the *E*- and *Z*-configurational isomers. This is most clearly apparent from the presence of two signals for each of atoms $C_{(2)}$ and $C_{(4)}$ differing by 5-7 ppm (Table 1) in the ^{13}C NMR spectrum of oxime **2**, caused by the different spatial orientation of the OH groups relative to these carbon atoms [9]. The purity of compound **3** is indicated by the presence of a single set of signals for the vinyl group and the pyrrole ring in the ^{1}H and ^{13}C NMR spectra (Tables 1 and 2), although hypothetically the two isomers **4** and **5** could have been formed.

A correlation between protons H-6 and H-4' was observed in the 2D NOESY spectrum of **3** which shows the structure unambiguously (similar correlations in the structures of **4** and **5** are not possible because of the long distance between proton H-4' and H-6 and H-5 respectively).



4



5

Apart from the resonances of $C_{(3)}$ and $C_{(4)}$, which form part of the pyrrole ring, the signals of the carbon atoms of the steroid residue are changed little on formation of the pyrrole ring. The strong field shift of the signal for $C_{(6)}$ (~7 ppm) in the vinylpyrrolocholestene **3** (in comparison with the ketone **1** and the oxime **2**) is explained by conjugation of the Δ^5 bond with the pyrrole unit.

TABLE 1. Chemical Shifts in the ^{13}C NMR Spectra of Compounds **1-3***

Carbon atom	δ, ppm			Carbon atom	δ, ppm		
	1	**2**	**3**		**1**	**2**	**3**
$C_{(1)}$	36.19	36.38	34.69	$C_{(17)}$	56.68	56.87	57.04
$C_{(2)}$	36.74	20.95 (*E*) 27.91 (*Z*)	19.13	$C_{(18)}$	11.92	12.09	12.05
$C_{(3)}$	208.70	159.97 160.39	126.67	$C_{(19)}$	19.17	19.14 19.24	18.81
$C_{(4)}$	49.21	32.08 (*Z*) 37.10 (*E*)	120.45	$C_{(20)}$	35.74	35.98	35.90
$C_{(5)}$	138.61	138.62 139.73	137.32	$C_{(21)}$	18.74	18.91	18.50
$C_{(6)}$	122.71	122.13 122.78	115.30	$C_{(22)}$	36.92	37.99 38.08	36.15
$C_{(7)}$	31.78	31.26	31.75	$C_{(23)}$	23.84	24.02	23.94
$C_{(8)}$	31.98	31.98	31.83	$C_{(24)}$	39.74	39.92	39.97
$C_{(9)}$	48.13	49.70	48.24	$C_{(25)}$	27.96	28.21	28.09
$C_{(10)}$	37.43	37.69	36.29	$C_{(26)}$	22.76	23.01	22.90
$C_{(11)}$	21.36	21.31 21.38	21.63	$C_{(27)}$	22.55	22.75	22.65
$C_{(12)}$	39.52	39.71	39.61	$C_{(3')}$			105.57
$C_{(13)}$	42.42	42.53	42.45	$C_{(4')}$			116.65
$C_{(14)}$	56.23	56.33	56.30	C_{α}			130.33
$C_{(15)}$	24.25	24.46	24.36	C_{β}			96.38
$C_{(16)}$	28.17	28.42	28.35				

* Data from [10] were partially used to assign the signals.

TABLE 2. Chemical Shifts (δ, ppm) and Coupling Constants (*J*, Hz) in the ^{1}H NMR Spectra of Compounds **1-3**

Compound	H-6	H-4'	H-5'	H_A	H_B	H_X
1	5.33 (1H, m)					
2	5.42 (1H, m) 5.37 (1H, m)					
3	5.69 (1H, m)	6.25 (1H, d, $^3J_{4',5'}$ = 3.1)	6.86 (1H, d)	4.58 (1H, dd, $^2J_{AB}$ = 1.3, $^3J_{AX}$ = 6.7)	5.01 (1H, dd, $^3J_{BX}$ = 13.7)	6.77 (1H, dd)

Compound	Me(18)	Me(19)	Me(21)	Me(26*)	Me(27*)
1	0.70 (3H, s)	1.18 (3H, s)	0.92 (3H, s)	0.87 (3H, d)	0.86 (3H, d)
2	0.69 (3H, s)	1.10 (3H, s)	0.90 (3H, s)	0.86 (3H, d)	0.85 (3H, d)
3	0.71 (3H, s)	0.98 (3H, s)	0.92 (3H, s)	0.86 (3H, d)	0.85 (3H, d)

* ^3J = 1.8 Hz.

According to the mechanism of the Trofimov reaction [2, 3], which includes the initial formation of the O-vinylketoxime **A** with subsequent [3,3] sigmatropic rearrangement of its N-vinylhydroxylamine tautomer **B**, the such nature of this process may be explained by the greater stabilization of intermediates **A** and **B** by conjugation (in comparison with the possible isomeric structures). Decreasing the reaction temperature from 120° to 100°C and lower led to a considerable deceleration of pyrrolisation in comparison with the rates of side processes, the most probable of which there are prototropic isomerization of the bond $\Delta^5 \rightarrow \Delta^4$ in the ketoxime **2** and followed partial deoximation. It was shown by HPLC that only 50% of the initial oxime **2** remained after 1h in KOH–DMSO at 90°C in the absence of acetylene. Only traces of N-vinylpyrrolocholestene **3** were detected in the reaction mixture by ^{1}H NMR spectroscopy along with 4-cholestene-3-one oxime (an isomer of 5-cholesten-3-one oxime) after carrying out the reaction for 5 h at 100°C. One of the most likely reasons for the low rate of reaction under the given conditions may be the liquid crystalline state of the starting oxime, which specifically interacts with DMSO. We have previously observed unusual behavior of steroids in the KOH–DMSO system during the vinylation of cholestene with acetylene [11] when a remarkably narrow range of temperature for successful completion of the reaction was noted. When the temperature was raised above 120°C a considerable amount of oily impurity was produced which made isolation of the required products difficult. How many difficulties may have the alternative step-wise annelation of steroids with a pyrrole units is illustrated by the synthesis of N-phenylpyrrolo[2,3-*b*]cholestanes from derivatives of cholestan-2,3-dione [12]. Our synthesis of N-vinylpyrrolocholestene **3**, despite its moderate yield of the required product, in view of the simplicity of the process and the availability of the reagents may serve as a method for obtaining the basic structural unit for preparing a library of promising candidates for medicinal use by combinatorial chemical methods.

EXPERIMENTAL

^{1}H (400.13 MHz) and ^{13}C (101.61 MHz) NMR spectra were recorded on a Bruker 400-DPX spectrometer in $CDCl_3$ with HMDS as internal standard. Infrared spectra of KBr disks were recorded with a Bruker ISF 25 machine. Molecular masses and elemental compositions were determined from the exact mass of molecular ions on a Finnigan MAT-8200 mass spectrometer. Chromatographic experiments were carried out

with a Milikhrom A-02 (ZAO "EkoNova", Novosibirsk, Russia) microcolumn liquid chromatograph with a column (2 × 75 mm) filled with Nucleosil 100-5 C18 AB (Machery-Nagel, Germany) with an efficiency of 5000-6000 plates according to the chrysene peak in acetonitrile.

The cholesterol starting material is a commercial product from ICN Pharmaceuticals, Inc. Pyridinium chlorochromate, used as an oxidizing agent was synthesized by a known method [13].

5-Cholesten-3-one (1) was obtained by oxidation of the cholesterol with pyridinium chlorochromate in CH_2Cl_2 by a known method [14]. The product was purified by recrystallisation from aqueous acetone.

5-Cholesten-3-one oxime (2). A suspension of NaOAc (0.56 g, 6.8 mmol) and $NH_2OH·HCl$ (0.47 g, 6.8 mmol) in ethanol (40 ml) was added over 20 min with stirring to a mixture of ketone **1** (1.74 g, 4.5 mmol) and pyridine (25 ml). After stirring for 25 min the reaction mixture was poured into cold water (100 ml), the precipitate was filtered off, washed with water, and dried in air to give the oxime **2**. Yield 1.67 g (4.2 mmol, 93%).

N-Vinylcholesteno[3,4-*b*]pyrrole (3). A mixture of oxime **2** (0.82 g, 2.1 mmol), $KOH·0.5H_2O$ (0.7 g, 10.8 mmol) and DMSO (50 ml) was placed in a half liter steel rotating autoclave, charged with acetylene (initial pressure 14 atm, maximum pressure during the reaction 25 atm). The temperature was raised to 120°C with stirring and the mixture was stirred at this temperature for 30 min. After cooling, water (50 ml) was added to the reaction mixture which was then extracted with ether (4 × 40 ml). The extract was washed with water (4 × 30 ml) and dried over calcined potassium carbonate. After removal of the ether the residue was placed on a column (deactivated basic aluminum oxide, hexane). Vinylpyrrole **3** (0.23 g, 25%) was obtained as colorless transparent needles after recrystallisation from acetone. At 136°C the crystals became brown and at 146°C they melted to give a clear liquid. IR spectrum: ν, cm^{-1}: 1639 (vs) ($CH=CH_2$), 1570 (s) (C=CH), 1546 (sh) (pyrrole ring), 1491 (s) (pyrrole ring), 1465 (pyrrole ring), 1442, 1381 (s) (pyrrole skeleton), 1323 (m) (C-N), 1301 (m) (C–N), 1230 (s), 1168 (m), 1101, 1074, 1030 (m) (CH, planar def. pyrrole), 957 (m) (HC=CH rotation), 917 (m), 860 (s) ($=CH_2$ twist), 831 (m), 799 (m), 742 (m), 717 (s) (CH, out of plane def.), 677 (m), 614, 581 (m) (HC=CH twist). Mass spectrum, *m/z* (rel. intensity, %): 433 (100, M), 418 (9, M-CH_3), 320 (1, M-C_8H_{17}), 305 (1, M-CH_3-C_8H_{17}), 279 (2, M-CH_3-HC≡CH-C_8H_{17}), 278 (2, M-H-CH_3-HC≡CH-C_8H_{17}), 264 (1, M-2CH_3-HC≡CH-C_8H_{17}), 224 (6), 210 (6). Found: *m/z* = 433.7234. $C_{31}H_{47}N$. Calculated 433.7237. Found, %: C 85.11; H 11.56; N 3.48. $C_{31}H_{47}N$. Calculated, %: C 85.85; H 10.92; N 3.23.

REFERENCES

1. B. A. Trofimov, *Heteroatomic Derivatives of Acetylene: New Polyfunctional Monomers, Reagents, and Intermediates* [in Russian], Nauka, Moscow (1981).
2. B. A. Trofimov and N. Mikhaleva, *N-Vinylpyrroles* [in Russian], Nauka, Novosibirsk (1984).
3. B. A. Trofimov, in: A. R. Katritzky (ed.), *Adv. Heterocycl. Chem.,* Acad. Press, San Diego (1990), Vol. 51, 177.
4. B. A. Trofimov, in: R. A. Jones (ed.), *Pyrroles. The Synthesis, Reactivity, and Physical Properties of Substituted Pyrroles*, Intersci., Wiley, New York (1992), Pt. 2, 131.
5. A. F. Pozharskii, V. A. Anisimova, and E. B. Tsupak, *Prakticum on the Chemistry of Heterocycles* [in Russian], Rostov University Press, Rostov (1988), 9.
6. R. J. Tedeshci, in: *Encyclopedia of Physical Science and Technology*, Acad. Press, San Diego (1992), Vol. 1, 27.
7. G. P. Bean, in: R. A Jones (ed.), *Pyrroles. The Synthesis and the Chemical and Physical Properties of the Pyrrole Ring*, Intersci. Wiley, New York (1992), Pt. 1, 105.
8. B. A. Trofimov, A. M. Vasil'tsov, E. Yu. Shmidt, O. V. Petrova, and A. I. Mikhaleva, *Zh. Org. Khim.,* **30**, 576 (1994).

9. A. V. Afonin, I. A. Ushakov, O. A. Tarasova, E. Yu. Schmidt, A. I. Mikhaleva, and V. K. Voronov, *Zh. Org. Khim.,* **36**, 1831 (2000).
10. S. S. Korde, R. Katoch, R. A. Udasi, and G. K. Trivedi, *Magn. Res. Chem.,* **37**, 594 (1999).
11. B. A. Trofimov, A. M. Vasil'tsov, E. Yu. Schmidt, A. B. Zaitsev, A. I. Mikhaleva, and A. V. Afonin, *Synthesis*, 1521 (2000).
12. B. M. Trost and E. Keiman, *J.Org.Chem.,* **45**, 2741 (1980).
13. E. J. Corey and J. W. Suggs, *Tetrahedron Lett.,* 2647 (1975).
14. E. J. Parish and S. Chitrokorn, *Org. Prep. Proc. Int*., **15**, 365 (1983).