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SYNTHESIS OF AMINO DERIVATIVES OF CARANOL BY THE ADDITION OF CYCLIC AMINES TO 3-CARENE OXIDES

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Addition reactions of cyclic amines (morpholine, piperidine) to oxides of 3-carene in the presence of water have been studied. The reactions take place regio- and stereoselectively with the formation of amino derivatives of the carane series.

The promising nature of investigations in the field of the synthesis of amino derivatives of the terpene series is due to their valuable practical properties – they possess antiviral [1], antifeedant [2], and pesticidal [3] activities, with low toxicity for warm-blooded animals. The recent literature includes reports devoted to the development of synthetic approaches to amino derivatives of the bornane, pinane, and methane series [4, 5], while information on methods of obtaining amino derivatives with a carane structure are sparse and relate to traditional multistage syntheses [6].

In order to broaden the methods of synthesis in the field of amino derivatives of the carane series and also to obtain representatives of this group of substances with potential biological activity, we have studied the reactions of β-3,4- and α-3,4-epoxycaranes (I and II) with morpholine (III) and piperidine (IV) under catalytic conditions, since it is known that the performance of such reactions in the absence of catalysts is problematical [7].

When the reaction was performed in the presence of bases (EtONa; t-BuOK in DMSO), the initial epoxycaranes isomerized into (−)-car-4-en-3β-ol, the physicochemical constants and spectral characteristics of which agreed with those given in the literature [8]. While the use of dilute mineral acids (for example, from 1 to 0.1% H_2SO_4) favored a rapid reaction, it led to a very complex mixture of products, which was due to isomerization of the carane skeleton of the molecule [9].

The products of the addition of (III) and (IV) to the epoxycaranes (I and II) were obtained in fairly good yields on the prolonged heating of the reactants in the presence of water.

The product of the reaction of β-3,4-epoxycarane (I) with morpholine (III) consisted of an individual compound (V) the structure of which was determined from the results of IR and PMR spectroscopy and x-ray structural analysis. The PMR spectrum of compound (V) contained the signals of the protons of a cyclopropane ring (0.5-0.7 ppm), of a gem-dimethyl fragment (0.97 ppm), of a methyl group at C^3 (1.07 ppm), of a morpholine ring (2.37, 3.57 ppm), and of a hydroxy group at C^3 (3.1 ppm). The IR spectrum of the compound had the bands of the characteristic vibrations of the hydroxy group ($\nu_{(OH)}$ 3430 cm^{-1}) and also of hydrocarbon fragments, including a cyclopropane fragment ($\nu_{(CH)}$ 2995 cm^{-1}).

The structure of compound (V) in the crystalline state was studied by the method of x-ray structural analysis (Fig. 1 and Tables 1-3). It was established that the bicyclic skeleton of the (V) molecule had a conformation of the sofa type. The $C^2C^1C^6C^5C^4$ fragment was practically planar, and the hydroxy group at C^3 was oriented pseudoaxially and the morpholino

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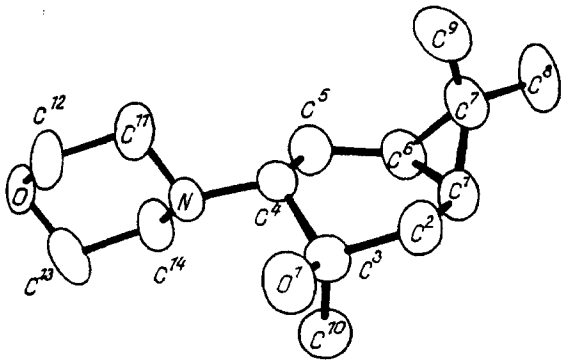


Fig. 1. Geometry of the molecule of the morpholinocaranol (V). The hydrogen atoms are not shown.

TABLE 1. Valence Angles (ω, degrees) of the Molecule (V)

Angle	ω	Angle	ω
C12OC13	110,0	C3C4C5	113,0
C4NC11	112,8	C4C5C6	114,7
C4NC14	116,3	C1C6C5	121,5
C11NC14	109,4	C1C6C7	60,6
C2C1C6	117,5	C5C6C7	126,9
C2C1C7	121,4	C1C7C6	60,0
C6C1C7	59,4	NC11C12	109,2
C1C2C3	112,6	OC12C11	111,4
C2C3C4	107,3	OC13C14	109,7
NC4C3	109,5	NC14C13	108.9
NC4C5	115,0		

group pseudoequatorially. Thus, the product obtained had the structure of 4α-morpholinocaran-3β-ol (V).

The interaction of β-3,4-epoxycarane (I) with piperidine (IV) took place in a similar way to the reaction of this oxide (I) with morpholine (III) and led to the formation, as the main product, of 4α-piperidinocaran-3β-ol (VI). The PMR spectrum of compound (VI) contained signals from the protons of a cyclopropane ring (0.5-0.7 ppm), of a gem-dimethyl fragment (0.97 ppm), of a methyl group at C^3 (1.07 ppm), of a piperidine ring (1.33-2.66 ppm), and of a hydroxy group at C^3 (3.2 ppm). In the IR spectrum of the product there was a characteristic band in the 3430 cm^{-1} region corresponding to the stretching vibrations of a hydroxy group, and the characteristic vibrations of the CH bonds of a cyclopropane fragment ($\nu_{(CH)}$ 2995 cm^{-1}). The fairly high yields of the desired products (V and VI) and the simplicity of their purification [recrystallization for (V) and submimation for (VI)] must be mentioned.

The interaction of α-3,4-epoxycarane with morpholine (III) and piperidine (IV) led to products (VII) and (VIII) under conditions identical with those for the reactions of β-3,4-epoxycarane (I) with compounds (III) and (IV) discussed above. The conclusion that 4β-morpholinocaran-3α-ol (VII) and 4β-piperidinocaran-3α-ol (VIII) had been formed in these reactions was based on the results of elementary analysis, IR spectroscopy, and PMR spectra. Each IR spectrum contained a band of the vibrations of a hydroxyl at C^3 ($\nu_{(OH)}$ 3400 cm^{-1}) and of the CH bonds of a three-membered ring ($\nu_{(CH)}$ 2995 cm^{-1}). In each PMR spectrum there were the signals of the protons of a gem-dimethyl group (0.86-1.03 ppm), of a methyl at C^3 (1.03-1.1 ppm), of a heterocyclic substituent (1.26-3.56 ppm), and of a cyclopropane fragment (0.5-0.8 ppm).

The similarity of the behaviors of the nitrogen bases (III) and (IV) as nucleophiles in their reactions with chloro derivatives of carane [10] and the absence of fundamental differences in the behaviors of 3-carene β- and α-oxides in reactions with sulfur-containing nucleophiles [11] permitted the fairly definite conclusion that the reactions of the epoxycaranes (I) and (II) with the nucleophiles (III) and (IV) would also take place by a common mechanical-structural scheme.

The conformational structures of compounds (VI-VIII) were shown on the basis of general information on the stereochemistry of 3β,4α- and 3α,4β-disubstituted caranes.

TABLE 2. Torsional Angles (φ, degrees) of the Rings in the Molecule (V)

Angle	φ	Angle	φ
C13OC12C11	59,2	C2C1C6C7	112,0
C12OC13C14	−61,5	C7C1C6C5	−117,5
C11NC4C3	134,0	C2C1C7C6	−105,6
C11NC4C5	−97,6	C1C2C3C4	−59,6
C14NC4C3	−98,4	C2C3C4N	−167,2
C14NC4C5	30,0	C2C3C4C5	63,2
C4NC11C12	−171,3	NC4C5C6	−164,0
C14NC11C12	57,5	C3C4C5C6	−37,4
C4NC14C13	171,3	C4C5C6C1	8,2
C11NC14C13	−59,5	C4C5C6C7	−66,8
C6C1C2C3	32,1	C5C6C7C1	109,1
C7C1C2C3	101,4	NC11C12O	57,3
C2C1C6C5	−5,6	OC13C14N	61,2

TABLE 3. Coordinates of the Nonhydrogen Atoms of the Molecule (V)

Atom	x	y	z
O	0,7720 (9)	0,2369 (3)	0,9193 (2)
O1	0,5715 (6)	0,5051 (3)	0,7145 (2)
N	0,7861 (7)	0,3508 (3)	0,7755 (2)
C1	1,0055 (9)	0,4952 (4)	0,5487 (3)
C2	0,787 (1)	0,5167 (4)	0,5916 (3)
C3	0,788 (1)	0,4901 (4)	0,6841 (3)
C4	0,8337 (8)	0,3844 (3)	0,6895 (3)
C5	1,0602 (9)	0,3576 (4)	0,6556 (3)
C6	1,1331 (9)	0,4127 (4)	0,5794 (3)
C7	1,033 (1)	0,4100 (4)	0,4947 (3)
C8	1,191 (1)	0,4208 (5)	0,4221 (3)
C9	0,847 (1)	0,3464 (4)	0,4747 (3)
C10	0,949 (1)	0,5492 (4)	0,7330 (4)
C11	0,657 (1)	0,2648 (4)	0,7765 (3)
C12	0,587 (1)	0,2440 (6)	0,8649 (4)
C13	0,892 (1)	0,3210 (5)	0,9187 (3)
C14	0,974 (1)	0,3410 (4)	0,8307 (3)

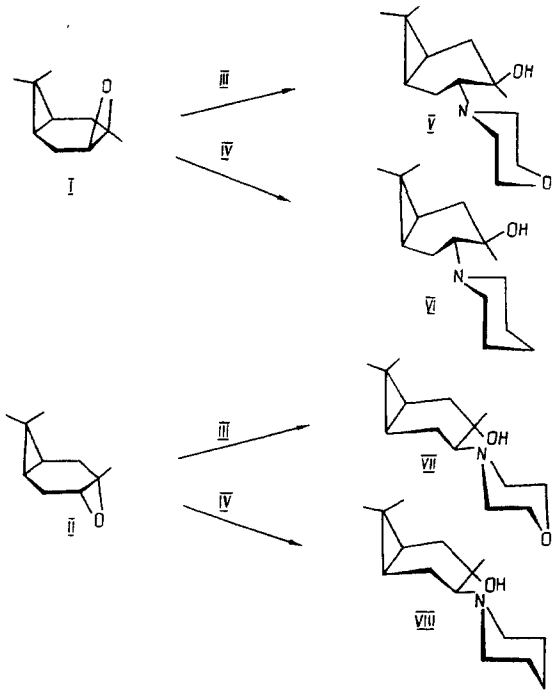
The catalytic effect of water at an elevated temperature in the reactions of the oxides (I) and (II) with the cyclic amines (III) and (IV) is obviously due to the protonation of the oxirane oxygen (in the manner of weak acids), which facilitates the attack of the nucleophilic reactants (III) and (IV).

In a study of the influence of catalysts of basic nature on the reaction of oxides of 3-carene with the nitrogen heterocycles (III) and (IV), we observed a considerably accelerating effect when thiourea was used. The reactions of the carene oxides (I) and (II) with morpholine and piperidine were complete in a comparatively short time under considerably milder conditions, which is obviously due to the high nucleophilicity of thiourea. The known ease of formation of oxathiolanes as intermediates in reactions of oxiranes with thiourea [12] promotes the subsequent addition of the amine, accompanied by the breakdown of this heterocycle and the splitting out of thiourea (see top of following page).

Thus, it has been established that the reactions of the β- and α-oxides of 3-carene with nitrogen-containing nucleophiles under catalytic conditions take place regio- and stereoselectively, forming individual 4-R derivatives of 3-caranols with the hydroxy group and the heterocyclic group in the trans relationship (R = morpholino, piperidino).

EXPERIMENTAL

The melting points of the substances were determined on a Kofler instrument. α_D Values were measured on a Polamat A polarimeter. The PMR spectra of compounds (V-VIII) were recorded in CCl_4 solutions on a Tesla BS-467 (60 MHz) instrument with HMDS as internal standard. The results of the analysis of compounds (V-VIII) corresponded to the calculated figures.



X-Ray Structural Analysis of Compound (V). The crystals of compound (V), $C_{14}H_{25}NO_2$ were rhombic, mp 64-65°C. At 20°C, a = 6.096(4), b = 14.366(3), c = 16.072(3) Å, Z = 4, d(calc.) = 1.13 g/cm^3, space group $P2_12_12_1$. The cell parameters and the intensities of 734 reflections with $F^2 \geq 3$ were measured on an Enraf-Nonius CAD-4 automatic K-diffractometer (λMoKα, graphite nonochromator, $\omega/2\Theta$ scanning, $\Theta \leq 25°$). The structure was interpreted by the direct method, using the MULTAN program and was refined in the anisotropic approximation. All the hydrogen atoms were revealed from a difference series and were not subsequently refined; their contribution to the structural amplitudes was taken into account in the concluding stage of refinement with fixed positional and isotropic temperature parameters (B_{iso} = 4 Å^2). The final values of the discrepancy indices were R = 0.52, R_w = 0.070. All the calculations were made on a PDP = 11/23 computer by the SPD program.

α-3,4-Epoxycarane was obtained by the method described in [13], bp 75-80°C (10 mm Hg), $[\alpha]_D^{20}$ +14.2°, n_D^{20} 1.4660.

β-3,4-Epoxycarane was obtained by the method of [14], bp 69-70°C (10 mm Hg), $[\alpha]_D^{20}$ −1.5°, n_D^{20} 1.4680.

4α-Morpholinocaran-3β-ol (V). A glass tube was charged with 1.52 g (0.01 mole) of β-3,4-epoxycarane, 1.74 g (0.02 mole) of morpholine, and 0.72 g (0.04 mole) of water. The tube was sealed and was heated at 140°C for 60 h. After the end of the reaction, the excess of morpholine and the water were distilled off under reduced pressure (p = 8 mm Hg). The product was purified by recrystallization from hexane. Yield 1.25 g (53%), mp 64-65°C, $[\alpha]_D^{26}$ −53.7° (c 20.8; EtOH). PMR spectrum (CCl_4, δ, ppm): 0.5-0.7 (m, 2H, H-1.6), 0.97 (s, 6H, $(CH_3)_2$-7), 1.07 (s, 3H, CH_3-3), 2.37 (m, 4H, $(CH_2)_2$—), 3.57 (t, 4H, $(CH_2)_2$—O) 3.10 (s, 1H, OH).

4α-Piperidinocaran-3β-ol (VI). A glass tube was charged with 1.52 (0.01 mole) of β-3,4-epoxycarane, 1.7 g (0.02 mole) of piperidine, and 0.72 g (0.04 mole) of water. The tube was sealed and was heated at 140°C for 60 h. After the end of the reaction, the excess of piperidine and the water were distilled off under reduced pressure (p = 8 mm Hg). The product was purified by sublimation. Yield 1.82 g (78%), mp 70-71°C, $[\alpha]_D^{26}$ −55.1° (c 12.09; EtOH). PMR spectrum (CCl_4, δ, ppm): 0.5-0.7 (m, 2H, H-1.6), 0.97 (s, 6H, $(CH_3)_2$-7), 1.07 (s, 3H, CH_3-3), 1.33-2.66 (m, 14H, $(CH_2)_7$), 3.20 (s, 1H, OH).

4β-Morpholinocaran-3α-ol (VII). A glass tube was charged with 3.04 g (0.02 mole) of α-3,4-epoxycarane, 3.48 g (0.04 mole) of morpholine, and 1.44 g (0.08 mole) of water. The tube was sealed and was heated at 140°C for 100 h. After the end of the reaction the residual α-3,4-epoxycarane and morpholine and the water were distilled off under reduced pressure (p = 8 mm Hg). The product was isolated by column chromatography on silica gel [R_f 0.1;

hexane ether (4:1)] and was additionally purified by recrystallization from hexane. Yield 0.52 g (11%), mp 42-43°C, $[\alpha]_D^6$ +36.6° (c 1.3; EtOH). PMR spectrum (CCl_4, δ, ppm): 0.6-0.8 (m, 2H, H-1.6), 0.93, 1.03 (s, 6H, $(CH_3)_2$-7), 1.10 (s, 3H, CH_3-3), 2.33-2.66 (m, 4H, $(CH_2)_2$–), 3.56 (t, 4H, $(CH_2)_2$–O), 2.13 (s, 1H, OH).

4β-Piperidinocaran-3α-ol (VIII). A glass tube was charged with 3.04 g (0.02 mole) of α-3,4-epoxycarane, 3.36 g (0.04 mole) of piperidine, and 1.44 g (0.08 mole) of water. The tube was sealed and was heated at 140°C for 55 h. After the end of the reaction, the residual α-3,4-epoxycarane and piperidine and the water were distilled off under reduced pressure (p = 8 mm Hg). The product was isolated by column chromatography on silica gel [R_f 0.1; hexane–ether (4:1)] and was additionally purified by sublimation. Yield 2.3 g (49%), mp 53-54°C, $[\alpha]_D^{26}$ +42.2° (c 2.51; EtOH). PMR spectrum (CCl_4, δ, ppm): 0.5-0.7 (m, 2H, H-1.6), 0.86, 0.93 (s, 6H, $(CH_3)_2$-7), 1.03 (s, 3H, CH_3-3), 1.26-2.26 (m, 14H, $(CH_2)_7$), 2.40 (s, 1H, OH).

Synthesis of (VI) in the Presence of Thiourea. A mixture of 1.0 g (0.0066 mole) of β-3,4-epoxycarane, 1.12 g (0.013 mole) of piperidine, and 0.5 g (0.0066 mole) of thiourea was heated at 100°C for 16 h. After the end of the reaction, the mixture was poured into 100 ml of water and was extracted with ether (4 × 50 ml). The extract was dried with $CaCl_2$. The product was isolated by column chromatography on silica gel [R_f 0.1; ether–hexane (4:1)] and was additionally purified by sublimation. Yield 0.86 g (55%). The spectral characteristics and physicochemical constants of the product obtained were identical with those of compound (VI).

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