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SYNTHESIS OF 2,7-NAPHTHYRIDINES BY THE RECYCLIZATION OF TRIMETHYLFORMYLPIPERIDONE

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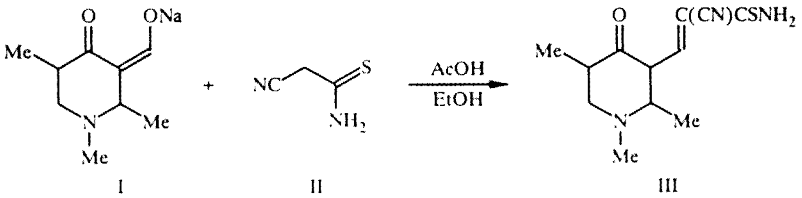
The structure of the product of interaction of the sodium salt of 1,2,5-trimethyl-3-formylpiperid-4-one with cyanothioacetamide was specified. It was shown that the Knoevenagel adduct formed at the first stage in basic conditions undergoes recyclization with the formation of 1,2,3,5,6,7,8,8a-octahydro-1-oxo-6,7,8a-trimethyl-4-cyano-2,7-naphthyridine-3-thione, the structure of which was confirmed by the data of physicochemical methods of analysis and chemical conversions.

Substituted 3-cyanopyridine-2(1H)-thiones are utilized widely in the synthesis of condensed pyridines which are not readily accessible [1]. The main method for the synthesis of the former is by the reactions of 1,3-dicarbonyl compounds with cyanothioacetamide.

It was shown previously that the reaction of the sodium salt of 1,2,5-trimethyl-3-formylpiperid-4-one (I) with cyanothioacetamide (II) gives a compound to which, on the basis of data of x-ray structural analysis, was assigned the structure 1-(1,5-dimethylpyrid-4-on-3-yl)ethylcyanothioacetamide [2]. However, in the study of the chemical properties of this compound and the structure of products of its conversion, we encountered the impossibility of interpreting the results obtained on the basis of the proposed structure. In this connection, we carried out repeated investigation of the reaction of the salt (I) with cyanothioacetamide (II).



When the method presented in the work [2] was carefully observed, we obtained the compound possessing the same melting temperature and PMR and IR spectra as previously described. Analysis of the high-resolution PMR spectrum allows the conclusion that it is the substituted piperidone (III), which is formed by the Knoevenagel condensation between the ketoaldehyde, obtained by the acidification of the salt (I), and cyanothioacetamide (II). It is known [3] that the 1,2,5-trimethylpiperid-4-one utilized for the synthesis of the salt (I) exists in the form of a mixture of two geometrical isomers differing in the axial or equatorial orientation of the methyl group at the position 5, whereby the 2-CH_3 group occupies the axial position. As can be seen from the PMR spectrum (see the Experimental section), compound (III) is also the mixture of four isomers, the approximate ratio of which comprises 1.8:1.8:1:1. The methyl group at the position 2 and the methylenecyanothioacetamide group at the position 3 are axial for all isomers, which is indicated by the SSCCs between the 2-H and 3-H protons (2.5 Hz for one and 1.5 Hz for the other pair of isomers), corresponding to their equatorial–equatorial disposition. The singlet signal of the protons of the N–CH_3 group occurs at 2,98 ppm for one and at 3.03 ppm for the other pair of isomers. Such a low-field shift can be explained by the contact of the nitrogen atom of the piperidone ring with the electron-deficient centers of the cyanothioacetamide group. That proposal agrees with the presence of the proton at the position

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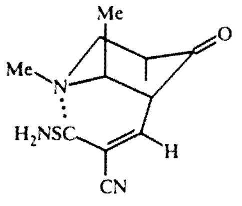
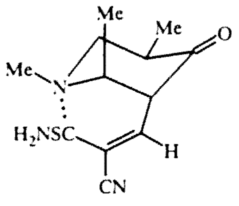
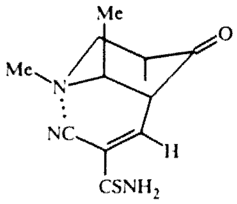
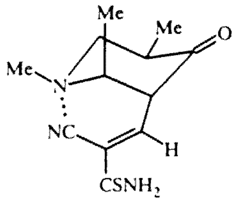
3 (in the opposed case, the compound would exist in the form of the zwitterion). Therefore, on the basis of the analysis of the PMR spectrum, the following structure can be assigned to isomers of compound (III):


IIIa


IIIb

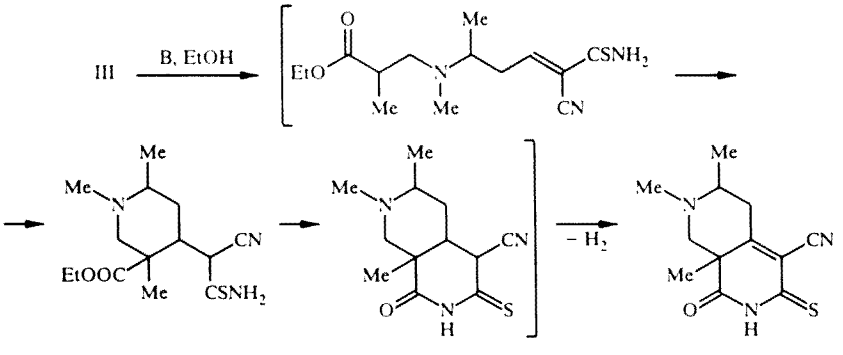

IIIc


IIId

The proposed structures are confirmed by the presence of two absorption bands of the nitrile group in the IR spectrum of the piperidone (III) at 2242 and 2234 cm^{-1}, as well as the sharply visible molecular ion with the *m/e* 251 in its mass spectrum.

The structure presented for the isomers of compound (III) conforms with its chemical behavior. Evidently, due to the steric remoteness of the keto and cyanothioacetamide groups in this piperidone, the further ring closure of neither the thiopyran nor the pyridinethione rings occurs in its synthesis, as takes place in the case of adducts obtained from other ketoaldehydes [4].

Ring closure also does not proceed when compound (III) is heated with triethylamine in benzene or tetrahydrofuran: the initial compound is isolated from the reaction medium, whereby the ratio of the isomers remains approximately as previous. However, when the piperidone (III) is boiled in alcohol containing a catalytic amount of piperidine, the recyclization reaction proceeds with the formation of the 2,7-naphthyridine (IV):

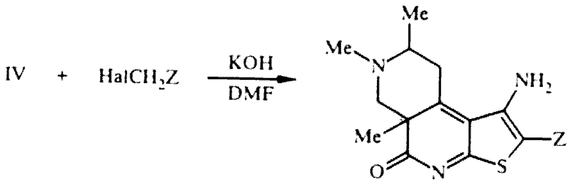


IV

B = piperidine

Such a conversion can be explained by the sequential reactions of acid cleavage according to Claisen, intramolecular addition according to Michael, the interaction of the thioamide and ester groups, and dehydrogenation. The methyl group at the position 7 of compound (IV) occurs in the axial position, which is indicated by the SSCCs of the 7-H proton with the 8-CH_2 group (4 and 2.5 Hz).

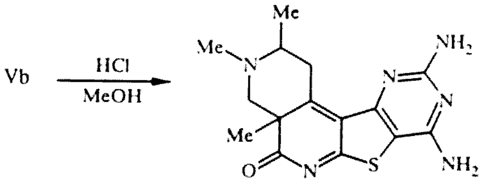
Compound (IV) enters into the hetero-ring closure reaction, characteristic of 3-cyanopyridinethiones [4, 5], with phenacyl bromide and N-cyanochloracetamidine with the formation of the thienonaphthyridines (Va,b):



Va, b

Va Z = COC_6H_4Br-4, b Z = $C(NH_2)NCN$

We converted the compound (Vb) into the corresponding condensed diaminopyrimidine (VI) according to the method of the work [5]:



VI

Therefore, spectral data and chemical conversions of compound (III) presented above confirm the structure proposed.

EXPERIMENTAL

The melting temperatures were determined on a Kofler stage. The IR spectra were taken on the Specord M-80 instrument using tablets of KBr. The PMR spectra were taken on the Bruker WM-250 instrument in solutions of DMSO-D_6, and the mass spectra were taken on the Varian MAT CH-6 (70 eV) instrument.

(1,2,5-Trimethyl-4-oxopiperid-3-yl)methylenecyanothioacetamide (III). Compound (III) is obtained by the method described in the work [2]. The yield is 64%. The mp is 171-175°C. The IR spectrum is as follows: 3384, 3304, 3136 (NH), 2980, 2916 (CH), 2242, 2234 (CN), 1644, 1628 (CO), 1576, 1472, 1436, and 1423 cm^{-1}. The PMR spectrum is as follows: 0.94, 0.95, 0.97, 0.99 (3H, 4d, J = 7 Hz, 5-Me), 1.03, 1.04 (1.95H, 2d, J = 7 Hz, 2-Me), 1.27 (1.05H, d, J = 7 Hz, 2-Me), 2.15-2.37 (1H, m, 5-CH), 2.89-3.07 (2H, m, 2-CH and 6-CH_e), 2.98 (1.05H, s, 1-Me), 3.03 (1.95H, s, 1-Me), 3.28-3.45 (m, overlaps with the signal of H_2O, 6-CH_a), 4.31 (0.17H, d, J = 1.5 Hz, 3-CH), 4.35 (0.17H, d, J = 1.5 Hz, 3-CH), 4.42 (0.33H, d, J = 2.5 Hz, 3-CH), 4.46 (0.33H, d, J = 2.5 Hz, 3-CH), 7.10 (0.35H, 2s, CH side chain), 7.30 (0.65H, s, CH side chain), 9.22 and 9.77 (2 × 0.7H, 2 broad s, NH_2), and 9.72 and 9.90 ppm (2 × 1.3H, 2 broad s, NH_2). The mass spectrum, given as *m/z* (%), is as follows: 253 (1), 252 (3), 251 (24, M^+), and 152 (100). Found, %: C 57.13, H 6.91, and N 16.67. $C_{12}H_{17}N_3OS$. Calculated, %: C 57.34, H 6.82, and N 16.72.

1,2,3,5,6,7,8,8*a*-Octahydro-1-oxo-6,7,8a-trimethyl-4-cyano-2,7-naphthyridine-3-thione (IV). To the solution of 5 mmole of compound (III) in alcohol is added 0.5 ml of piperidine, and the reaction mixture is heated to boiling and is stirred for 0.5 h. The precipitated product (IV) is filtered off, washed with alcohol, and dried in air. The yield is 74%. The mp is 222-224°C. The IR spectrum is as follows: 3424, 3176 (NH), 2908, 2848 (CH), 2224 (CN), 1752 (CO), 1600, 1582, 1472, 1446, and 1440 cm^{-1}. The PMR spectrum is as follows: 1.28 (3H, d, J = 7 Hz, 6-Me), 2.27 and 2.34 (2 × 3H, 2s, 8a-Me and 7-Me), 2.44 and 2.53 (2H, ABX, J_{AB} = 12, J_{AX} = 4, J_{BX} = 2.5 Hz, 5-CH_2), 2.86-2.94 (1H, m, 7-CH), 2.94 and 3.57 (2 × 1H, 2d, J = 15 Hz, 8-CH_2), and 13.7 ppm (1H, broad s, NH). The mass spectrum, given as *m/z* (%), is as follows: 235 (14), 234 (41, M^+-Me), 233 (87, M^+-CH_4), 232 (84, M^+-CH_4−H), and 189 (100). Found, %: C 57.68, H 5.93, and N 16.76. $C_{12}H_{15}N_3OS$. Calculated, %: C 57.81, H 6.06, and N 16.85.

3-Amino-2-(4-bromophenacyl)-4,5,6,7-tetrahydro-5,6,7*a*-trimethylthieno[2,3-c]-2,7-naphthyridine-8(7*a*H)-one (Va). To the solution of 3 mmole of compound (IV) in 10 ml of DMF are added 3 mmole of KOH (the 10% aqueous solution), and the mixture is stirred for 5 min prior to the addition of 3.1 mmole of 4-bromophenacyl bromide. After 5 min of stirring, 3 mmole more of KOH are added to the reaction mixture, which is left for 2 h at room temperature. The product (Va) is precipitated with water, washed with alcohol, and dried in air. The yield is 92%. The mp is 198-200°C. The IR spectrum is as follows: 3472, 3284 (NH_2), 2932, 2792 (CH), 1605, 1578 (CO), 1558, 1456, 1430, and 1400 cm^{-1}). The PMR spectrum is as follows: 1.29 (3H, d, J = 7 Hz, 5-Me), 2.37 (1H, dd, J_1 = 11.5, J_2 = 6 Hz, 4-CH_a), 2.41 (3H, s, 6-Me), 2.60 (3H, s, 7a-Me), 2.78 (1H, dd, J_1 = 11.5, J_2 = 5 Hz, 4-CH_e), 3.07 (1H, m, 5-CH), 3.57 (2H, s, 7-CH_2), 7.69 and 7.03 (4H, AA'BB', Ar), and 6.22 ppm (2H, broad s, NH_2). The mass spectrum, given as *m/z* (%), is as follows: 432 (29, M^+-Me), 431 (98, M^+-CH_4), 430 (84, M^+-Me, M^+-CH_4−H), 429 (98, M^+-CH_4), 428 (47, M^+-CH_4−H), 388 (87), 387 (100), 386 (88), and 395 (99). Found, %: C 53.76, H 4.60, and N 9.38. $C_{20}H_{20}BrN_3O_2S$. Calculated, %: C 53.82, H 4.52, and N 9.41.

3-Amino-2-aminocyaniminomethyl-4,5,6,7-tetrahydro-5,6,7*a*-trimethylthieno[2,3-c]-2,7-naphthyridine-8(7*a*H)-one (Vb). To the solution of 3 mmole of the naphthyridinethione (IV) in 20 ml of DMF are added 3 mmole of KOH (the 10% aqueous solution), and the mixture is stirred for 5 min at room temperature prior to the addition of 3 mmole of N-cyanochloracetamidine with stirring for 5 min more. Further, 6 mmole more of KOH (the 10% aqueous solution) are added, and the mixture is stirred for 0.5 h. The product (Vb) is precipitated with water, filtered off, washed with cold alcohol, and recrystallized from acetonitrile. The yield is 85%. The mp is 198-200°C. The IR spectrum is as follows: 3472, 3284 (NH_2), 2185, 2135 (CN), and 1578 cm^{-1} (CO). The PMR spectrum is as follows: 1.31 (3H, d, J = 7 Hz, 5-Me), 2.42 (1H, dd, J_1 = 11.5, J_2 = 6 Hz, 4-CH_a), 2.45 (3H, s, 6-Me), 2.67 (3H, s, 7a-Me), 2.82 (1H, dd, J_1 = 11.5, J_2 = 5 Hz, 4-CH_e), 3.09 (1H, m, 5-CH), 3.61 (2H, s, 7-CH_2), 6.71 (2H, s, 3-NH_2), and 7.32 ppm (2H, broad s, amidine NH_2). Found, %: C 54.81, H 5.23, and N 25.47. $C_{15}H_{18}N_6OS$. Calculated, %: C 54.69, H 5.20, and N 25.51.

2,4-Diamino-8,9,10,11-tetrahydro-7*a*,9,10-trimethylpyrimido[4′,5′:4,5]thieno[2,3-c]-2,7-naphthyridine-7(7*a*H)-one (VI). The mixture of 1 mmole of the thienonaphthyridine (Vb) is suspended in 20 ml of methanol containing 1 ml of 35.5% HCl, and the mixture is boiled for 1 h. The cooled reaction mixture is then poured into water and neutralized with Na_2CO_3. The precipitated residue of the product (VI) is filtered off, washed with cold alcohol and hexane, and dried in air. The yield is 73%. The mp is 245-247°C. The IR spectrum is as follows: 3452, 3374, 3145 (NH_2), and 1596 cm^{-1} (CO). The PMR spectrum is as follows: 1.30 (3H, d, J = 7 Hz, 10-Me), 2.42 (3H, s, 9-Me), 2.60 (3H, s, 7a-Me), 2.90 (1H, dd, J_1 = 11, J_2 = 6 Hz, 11-CH_a), 3.10 (1H, m, 10-CH), 3.25 (1H, dd, J_1 = 11, J_2 = 5 Hz, 11-CH_e), 3.57 (2H, s, 8-CH_2), 6.05 (2H, broad s, 2-NH_2), and 6.72 ppm (2H, broad s, 4-NH_2). Found, %: C 54.76, H 5.12, and N 25.48. $C_{15}H_{18}N_6OS$. Calculated, %: C 54.69, H 5.20, and N 25.51.

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