65.* SYNTHESIS OF 1-BENZYL-4-METHYL-5-CYANO-6-HYDROXY-7-AZAINDOLINE

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UDC 547.754:543.051

Treatment of the ammonium (I) or benzylammonium salt of 2,6-dihydroxy-3-((β-hydroxyethyl)-4-methyl-5-cyanopyridine (II) \(^t\) with a mixture of benzylamine and phosphorus pentoxide yielded 2-benzylamino-3-((β-hydroxyethyl)-4-methyl-5-cyano-6-hydroxypyridine (III), which, when heated with phosphorus oxychloride, is converted to 1-benzyl-4-methyl-5-cyano-6-hydroxy-7-azaindoline (IV). The products of thermal fragmentation of II with benzylamine were studied by the method of chromatography-mass spectrometry. In addition to compound III, N,N'-dibenzylurea (V) and the dibenzylamide of malonic acid (VI) were preparatively isolated from the reaction products. The cyclization of I and II to 4-methyl-6-hydroxy-2,3-dihydro-7-azabenzo furan (VII) and 4-methyl-5-cyano-6-hydroxy-2,3-dihydro-7-azabenzofuran (VIII) was carried out. Heating VIII with benzylamine at 200-210°C led to compound III.

In recent years data have appeared \([3, 4]\) on the intensification of the β-adrenoblocking activity and the appearance of vasodilative, as well as hypotensive properties when cyano-substituents are introduced into pyridine or indole molecules together with the 3-isopropylamino-2-hydroxypropoxy group. These compounds evoked interest in the synthesis and study of new cyano-containing β-adrenoblockers of the N-heteroaromatic series. According to the data of \([1]\), 1-benzyl-6-(3-isopropyl-amino-2-hydroxypropoxy)-7-cyano-5-azaindoline is 10 times as active as the known drug preparations propranolol and pindolol (visken) in β-adrenoblocking activity in experiments \textit{in vitro}. To obtain the 7-azaindolinyl analog of this compound, 1-benzyl-4-methyl-5-cyano-6-hydroxy-7-azaindoline (I) can be used as the starting material. The production of compound I, undescribed in the literature, is a nontrivial problem. General methods of synthesis of 7-azaindolines developed earlier on the basis of the reactions of amines with 2-chloro-3-((β-chloroethyl)pyridines \([5]\) or 2,3-dihydro-7-azabenzo furans \([6]\) do not give positive results in this case: the first since the corresponding 2-chloro-3-((β-chloroethyl)pyridine cannot be obtained from the ammonium salt of 2,6-dihydroxy-3-((β-hydroxyethyl)-4-methyl-5-cyano-6-hydroxy-7-azaindoline (II) without elimination of the cyano group, and the second since 4-methyl-5-cyano-6-hydroxy-2,3-dihydro-7-azabenzo furan (III) undergoes thermal fragmentation at the temperatures necessary for conversion of the dihydrofuran ring to a pyrroline ring.

We developed the synthesis of 1-benzyl-4-methyl-5-cyano-6-hydroxy-7-azaindoline (I) according to the scheme cited on the following page.

The ammonium salt of II, produced by the reaction of cyanoacetamide with α-acetobutyrolactone according to the method of Stevens et al. \([7]\), modified by M. V. Rubtsov \([8]\), in the case of treatment with sufficiently strong basic and relatively nonvolatile amines, is converted to new ammonium salts and, in particular, forms the benzylammonium salt IV with a yield of 92% when it is heated with benzylamine (4 h at 150-160°C). Interaction of the salt II with stronger bases — aromatic amines — does not permit the production of analogous arylammonium salts: Even after prolonged boiling with aniline, compound II is recovered virtually entirely unchanged.

\*For communication 64, see \([1]\).

\(^t\)Here and henceforth the names of the compounds will be cited without consideration of the state of the lactam–lactim tautomeric equilibrium, which, according to the data of \([2]\), usually is greatly shifted in the direction of the 2-hydroxy-6-oxo-tautomers for 2,6-dihydroxypyridine compounds. The structural formulas of the compounds reflect the predominant tautomeric forms.


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Heating the benzylammonium salt IV with 65% sulfuric acid, analogously to that described for compound II [8], leads to a loss of the cyano group, closing of the dihydrofuran ring, and the formation of 4-methyl-6-hydroxy-2,3-dihydro-7-azabenzofuran (III). The use of phosphorus oxychloride in this reaction instead of sulfuric acid permitted us to carry out the cyclization without elimination of the cyano group and to obtain 4-methyl-5-cyano-6-hydroxy-2,3-dihydro-7-azabenzofuran (V) with a yield of 97%. In contrast to the previously described [6] recylization of 2,3-dihydro-5-azabenzofurans in the case of heating to 200°C with benzylamines to the corresponding substituted 5-azaindolines, compound V under the same conditions does not form a bicyclic 7-azaindoline derivative I but is converted with a 79% yield to monocyclic 2-benzylamino-3-(β-hydroxyethyl)-4-methyl-5-cyano-6-hydroxypyridine (VI). Conducting the reaction at 245°C leads to the appearance of negligible amounts of the 7-azaindoline compound I, detected in the reaction products by the method of thin-layer chromatography. However, the process of fragmentation of the pyridine molecule chiefly occurs; one of its products — N,N'-dibenzylurea (VII) — could be preparatively isolated with a 30% yield. Fragmentation of the pyridine ring and thermal conversions of benzylamine also occur when benzylammonium (IV) or ammonium (II) salts of 2,6-dihydroxy-3-(β-hydroxyethyl)-4-methyl-5-cyanoypyridine are heated with benzylamine to 200-210°C (10 h). The yield of the 2-benzylamino derivative VI in the first case is 44-50%, in the second 38%. Products of fragmentation of the pyridine ring — N,N'-dibenzylurea (VII) and the dibenzylamide of malonic acid (VIII), identified according to mixed melting points and according to the IR spectra with known samples produced by counter-synthesis according to the methods of [9, 10] — were preparatively isolated. Chromatographic analysis of the complex mixture remaining suggested possible structures (yield) for the other fragmentation products: 5-hydroxy-3-pentyn-2-one (6%), 2-pentan-4-one-1-al (22%), 3-(α-methyl-β-formylvinyl)-4,5-dihydrofuran (13%), dibenzylamine (9%), 1-benzyl-3-acetyl-2,3-dihydropropyrrolidine (2%), 1,6-dihydroxy-3-vinyl-4-methylpyridine (2.8%), and 2-acetylbenzylamine (2%). More than 10 additional minor unidentified substances were detected in this mixture.

The benzylammonium salt of IV is converted most smoothly to 2-benzylamino-3-(β-hydroxyethyl)-4-methyl-5-cyano-6-hydroxypyridine (VI) in treatment with a mixture of benzylamine and phosphorus pentoxide for 12 h at 150-170°C, i.e., under the conditions recommended earlier [11] for one-step conversion of hydroxy(oxo)-N-heteroaromatic compounds to the corresponding amino derivatives. The yield of compound VI according to the method of [11] is 73%.

Closing of the pyrroline ring in compound VII is accomplished by heating with phosphorus oxychloride in the presence of dimethylamine. The cyclization process is not accompanied by replacement of the hydroxy group by chlorine in the 6-position, although under analogous conditions [12], 6-hydroxy-7-cyano-5-azaindolines are smoothly converted to the corresponding 6-chloro-7-cyano-5-azaindoline derivatives.

The unambiguous conversion of the salts II and IV through 2-benzylamino derivative VI to the 7-azaindoline I convincingly shows that in 2,6-dihydroxy-3-(β-hydroxyethyl)-4-methyl-5-cyanoypyridine, the most acid is the hydroxyl in the 2-position, and salt formation of the indicated compound with ammonia and amines proceeds, if not entirely than largely at this hydroxyl. All the aforementioned permits us to give up the previously accepted image of such salts as dihydroxypyridine derivatives bonded to amines through a point [7, 8] and change to the writing of structural formulas of the type of II and IV.