SYNTHESIS OF SPIRO ANALOGS OF LILOLIDINE ALKALOIDS

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The Friedel–Krafts intramolecular cyclization of N-chloroacetyl- and N-o-bromopropionyl-4-methylspiro[tetrahydroquinoline-2-cyclohexanes] was used to obtain 2-oxo-1,2,5,6-tetrahydro-4H-spiro[pyrrolo(3,2,1-i,j)quinoline-4,1'-cyclohexanes] — spiro analogs of lilolidine alkaloids.

The 1,2,5,6-tetrahydropyrrolo[3,2,1-i,j]quinoline tricyclic condensed system is the main fragment of lilolidine alkaloids [1, 2]. Compounds containing such a fragment are effective psychotropic preparations and herbicides. The most common method of synthesizing tetrahydropyrrolo[3,2,1-i,j]quinolines is based on the intramolecular cyclization of N-(β-haloalkyl)- or N-(α-haloacyl)-substituted tetrahydroquinolines in the presence of aluminum chloride [3, 4]. We used this method in syntheses of analogs of lilolidine alkaloids spiroannelated at the 4 position with the cyclohexane ring.

The initial N-chloroacetyl- and N-o-bromopropionyl-1,2,3,4-tetrahydro-4-methylspiro[quinoline-2-cyclohexanes] I, II were obtained by acylation of 1,2,3,4-tetrahydro-4-methylspiro[tetrahydroquinolinecyclohexane] with halides of the corresponding acids [5].

The cyclization of compounds I and II was carried out in the presence of aluminum chloride without a solvent, and also in boiling Freon-113 and heptane. 2-Oxo-6-methyl- and 2-oxo-6,6-dimethyl-1,2,5,6-tetrahydro-4H-spiro[pyrrolo(3,2,1-i,j)quinoline-4,1'-cyclohexanes] III and IV were obtained in 23-75% yield.

The cyclization of compound I in boiling heptane follows a single path with the formation of only the spiro compound III. In all other cases, in addition to cyclization products III and IV, the reaction mixture also yielded the recyclization products of compounds I and II: 3-methyl-4-chloroacetylamino- and 4-α-bromopropionylaminospiro[indane-1-cyclohexanes] (V and VI), the synthesis of which has been described previously [5], as well as 1,2,3,4-tetrahydro-4-methylspiro[quinoline-2-cyclohexane].

The latter compound is evidently formed as a result of splitting of the initial compounds.

The structure of compounds III and IV was confirmed by spectroscopic data. In the IR spectra, the absorption band of the C=O bond shifts by 30 cm⁻¹ and 22 cm⁻¹ in comparison to compounds I and II and is observed at 1710 cm⁻¹, confirming the formation of a pyrrolidine ring.
The aromatic part of the PMR spectrum of compounds III and IV (Table 1) is characterized by the presence of signals of three interacting protons, 7-, 8-, and 9-H. In contrast to recyclization products V and VI [5], where in the PMR spectra, because of the anisotropy of the acylamine substituent in the C(4) position, the signal of the 5-H proton is shifted to the region 7.78-7.83 ppm, in the PMR spectra of compounds III and IV the aromatic protons are observed in the 0.2 ppm interval, and the triplet signal from the 8-H proton is the one with the strongest polarity. In the PMR spectrum of compound IV, the presence of two doublets of group 1-CH₃ protons and two quartets of 1-H protons indicates the presence of two geometrical isomers with respect to the relative arrangement of the methyl group at C(1) and the unshared electron pair of the nitrogen atom. In the cis arrangement of the unshared pair of the nitrogen atom and of the substituent at C(1), the signal of the latter shifts to the weak field [6]. This causes the nonequivalency of the 1-H protons in compound III.

A characteristic feature of the PMR spectra of compounds III and IV is a pronounced weakly polar signal of the two protons of the cyclohexane ring (this was demonstrated by double resonance) as a result of their location in the descreening cone of the C=O group. Dreiding’s molecular models show that the protons in the C(2) and C(6) positions of the cyclohexane ring are not equivalent with respect to the carbonyl group; apparently, the 2'-H protons are subjected to the influence of the C=O group.

The mass spectra of compounds III and IV are characterized by the presence of maximum-intensity peaks of molecular ions with m/z of 255 and 269, which correspond to their empirical formulas. The principal direction of fragmentation of the M⁺ ions of these compounds is due to the splitting of the cyclohexane ring; this gives rise to the fragmented ions [M−CH₃]⁺, [M−C₂H₅]⁺, [M−C₃H₇]⁺, [M−C₄H₉]⁺. The other direction of fragmentation of M⁺ ions is due to the elimination of the C₇H₁₁ molecule as a result of benzyl cleavage and to the formation of characteristic ions with m/z equal to 160 and 174, which evidently have the structure of pyrrolidinotropylium cations.

In the second stage of fragmentation, the [M−C₃H₇]⁺ and [M−C₄H₉]⁺ ions eliminate the ketene molecule RCH=C=O, forming ions with m/z equal to 170 and 184, respectively. The last ion then eliminates the ethylene molecule to form a low-intensity fragment ion with m/z equal to 156.

We have thus shown the feasibility of a preparative synthesis of spiro analogs of lilolidine alkaloids from N-α-halogenated spiro[tetrahydroquinoline-2-cyclohexanes].