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SYNTHESIS OF SPIRO ANALOGS OF LILOLIDINE ALKALOIDS

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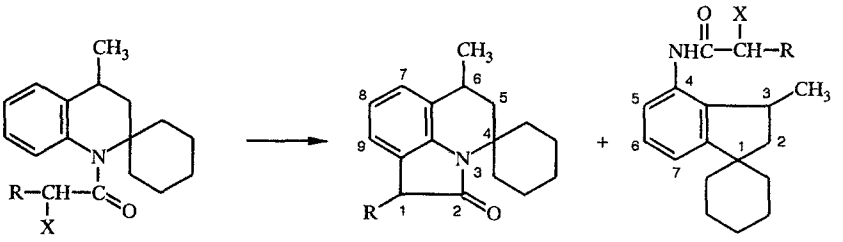
The Friedel–Krafts intramolecular cyclization of N-chloroacetyl- and N-α-bromopropionyl-4-methylspiro[tetrahydroquinoline-2-cyclohexanes] was used to obtain 2-oxo-1,2,5,6-tetrahydro-4H-spiro[pyrrolo(3,2,1-i,j)quinoline-4,1'-cyclohexanes] — spiro analogs of lilolidine alkaloids.

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-α-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-1,6-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.



I, II III, IV V, VI

I, III, V R = H; II, IV, VI R = CH_3; I, V X = Cl; II, VI X = Br

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 pyrrolidone ring.

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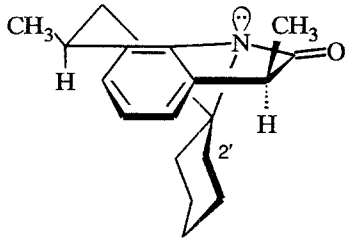
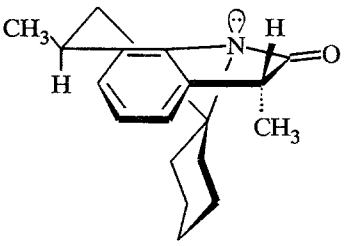
The aromatic part of the PMR spectrum of compounds III and IV (Table 1) is characterized by the presence of signals of three interacting protons, 7-, 8-, and 9-H. In contrast to recyclization products V and VI [5], where in the PMR spectra, because of the anisotropy of the acylamine substituent in the $C_{(4)}$ 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-CH_3 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.



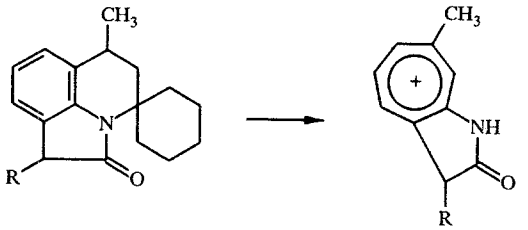
cis–IV



trans –IV

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 $[M-CH_3]^+$, $[M-C_2H_5]^+$, $[M-C_3H_7]^+$, $[M-C_4H_8]^+$. The other direction of fragmentation of M^+ ions is due to the elimination of the C_7H_{11} 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 pyrrolidonotropylium cations.



M^+ $\quad$ $[M - C_7H_{11}]^+$

In the second stage of fragmentation, the $[M-C_3H_7]^+$ and $[M-C_2H_5]^+$ 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].

TABLE 1. Parameters of the PMR Spectra of 4H-Tetrahydrospiro[pyrrolo(3,2,1-i,j)quinoline-4-cyclohexanes] III, IV

Compound	δ, ppm (J, Hz)											
	1-H	5-H_e	5-H_a	6-H	7-H	8-H	9-H	1-CH_3	6-CH_3	Cyclohexane protons		
										2'-H_a	2'-H_e	other
III	3,38	2,55	1,31	2,82	7,14	6,97	7,05	—	1,39	3,49	2,05	1,43...
	3,58	(13,96;	(13,96;			(7,60;			(6,72)	(13,95;	(13,95;	1,87
	(22,10)	4,38)	1,82)			7,60)				14,0;	4,30;	
										5,04)	4,10)	
IV	3,31	2,54	1,23	2,83	7,14	6,97	7,07	1,42	1,39	3,50	2,05	1,50...
	3,45	2,56	(13,90)		7,22	(7,33;	(1,1)	1,46	(6,64)	(13,79;	(13,90;	1,86
		(13,89;			(1,1;	7,33)		(7,85)		13,79;	4,30;	
		4,89)			1,2)					7,50)	4,10)	

EXPERIMENTAL

The mass spectra of the synthesized compounds were obtained with an LKB-9000 instrument provided with a system of direct introduction of the sample into the ion source at an ionizing voltage of 70 eV. The IR spectra were recorded in KBr in a UR-20 spectrophotometer. The PMR spectra were recorded in $CDCl_3$ with a Bruker WM-400 instrument, with TMS as the internal standard. For column chromatography, use was made of alumina of activity grade II according to Brockmann, and for TLC, Alufol plates were used. The development was done with iodine vapor.

The data of the ultimate analysis of the synthesized compounds for C, H, and N correspond to the calculated data.

2-Oxo-1,2,5,6-tetrahydro-6-methyl-4H-spiro[pyrrolo(3,2,1,i,j)quinoline-4-cyclohexane] (III, $C_{17}H_{21}NO$). A. To a boiling solution of 0.7 g (2.3 mmoles) of N-chloroacetylated spiro compound I in 15 ml of heptane is added in portions 0.95 g (7.1 mmoles) of aluminum chloride. The reaction mass is boiled for 1 h (with TLC control), cooled, poured onto ice (15 g), and alkalized to pH 10 with a solution of soda. The mixture is extracted with ethyl acetate (3 × 50 ml) and magnesium sulfate. After the ethyl acetate is driven off, the residue is crystallized from heptane. Compound III in the form of colorless crystals is obtained in the amount of 0.45 g (75%), m.p. 151-153°C, R_f 0.33 (4:1 heptane–ethyl acetate). IR spectrum: 1710 cm^{-1} (C=O). Mass spectrum, m/z (intensity, %): 255 (100) M^+, 240 (68), 212 (70), 199 (3), 184 (25), 170 (5), 160 (16), 156 (6), 132 (5).

B. A mixture of 0.5 g (1.7 mmoles) of compound I and 0.7 g (5.2 mmoles) of aluminum chloride are heated for 0.5 h at 100-105°C, then cooled, ice (20 g) and 50 ml of chloroform are added, and the mixture is alkalized with aqueous ammonia to pH 10. The separated chloroform solution is washed with water and dried with magnesium sulfate. After the chloroform is driven off, the residue is chromatographed on a column (1.5 × 40 cm), the eluent being 10:1 heptane–ethyl acetate. First, 0.1 g (27%) of 1,2,3,4-tetrahydro-4-methylspiro[quinoline-2-cyclohexane] is eluted, which in its physicochemical and spectroscopic characteristics is analogous to that described previously [7]. Then, 0.24 g of a mixture of compound III and spiro[indanecyclohexane] V is washed out. Rechromatographing of this mixture yielded 0.14 g (28%) of 4-chloroacetylaminospiro[indane-1-cyclohexane] V, which in its physicochemical properties is analogous to that described previously [5]. Compound III in pure form was not isolated in this experiment.

2-Oxo-1,2,5,6-tetrahydro-1,5-dimethyl-4H-spiro[pyrrolo(3,2,1,i,j)quinoline-4-cyclohexane] (IV, $C_{18}H_{23}NO$). A. To a boiling solution of 0.4 g (1.1 mmoles) of N-α-bromopropionyl-substituted spiro compound II in 10 ml of heptane is added in portions 0.46 g (3.4 mmoles) of aluminum chloride, then the mixture is boiled for 1 h and treated as described above in an analogous experiment. After the solvent is driven off, the residue is chromatographed on a column (1 × 60 cm), first with a 30:1 heptane–ethyl acetate mixture, and is then washed with 0.1 g (40%) of 1,2,3,4-tetrahydro-4-methylspiro[quinoline-2-cyclohexane]. A mixture of the same solvents in the ratio 15:1 is then eluted with 0.1 g (33.3%) of spiro compound IV, and

a brown oily liquid of R_f 0.85 (8:1 heptane–ethyl acetate) is obtained. IR spectrum: 1710 cm^{-1} (C=O). Mass spectrum, m/z (intensity, %): 269 (100) M^+, 254 (68), 240 (4), 226 (71), 214 (4), 213 (3.5), 198 (37), 184 (4), 182 (4.5), 174 (20), 170 (12), 156 (6). Finally, a 5:1 heptane–ethyl acetate mixture is used to wash out of the column 0.1 g (25%) of the recyclization product, N-α-bromopropionylaminospiro[indanecyclohexane] VI, which is identical with the compound described in [5].

B. A mixture of 0.7 g (2 mmoles) of spiro compound II and 0.8 g (6 mmoles) of aluminum chloride is heated for 0.5 h at 100-105°C and treated as described above. The residue is chromatographed on a column (1 × 62 cm) with a 10:1 heptane–ethyl acetate mixture, and 0.1 g (23%) of 1,2,3,4-tetrahydro-4-methylspiro[quinoline-2-cyclohexane] is separated. A mixture of these solvents in the ratio 5:1 is then used to elute 0.11 g (20%) of spiro compound IV, which is a viscous brown oil, R_f 0.85 (8:1 heptane–ethyl acetate), M^+ 269. IR spectrum: 1710 cm^{-1} (C=O).

To a solution of 1 g (2.9 mmoles) of spiro compound II in 20 ml of Freon-113 is added 1.14 g (8.6 mmoles) of aluminum chloride, and the mixture is boiled for 10 h (TLC control). After the Freon is driven off, the residue is treated with a 10% aqueous solution of soda to pH 8-10 with cooling. The reaction products are extracted with ether (4 × 50 ml) and dried with magnesium sulfate. After the ether is driven off, the residue is chromatographed on a column (1.5 × 65 cm) with a heptane–ethyl acetate mixture, the ratio being varied from 15:1 to 5:1, and 0.18 g (23%) of compound IV, R_f 0.85, M^+ 269, is separated.

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