SYNTHESIS AND INVESTIGATION OF 8-(QUINUCLIDIN-3-YL)-CONTAINING ANALOG OF PYRAZIDOLE

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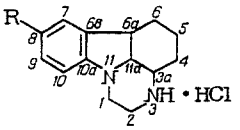
We have previously found a new antidepressant pyrazidole (I) in the series of pyrazino[3,2,1-j,k] carbazoles [2, 5].

In continuation of the systematic investigation of the pyrazidole analogs we synthesized and studied a new derivative hexahydro-1H-pyrazino[3,2,1-j,k]carbazole having a quinuclidin-3-yl residue (II) in the 8-position. It was assumed that the introduction of the quinuclidinyl substituent, which is bulkier than the methyl group, would make it possible to magnify its antidepressant action, increase the solubility in water, decrease the stimulating effect and introduce a sedative component of activity characteristic for the quinuclidine compounds [7].



I, II

I:R = methyl; II:R = quinuclidin-3-yl

We expected that the synthesis of compound II could be carried out by two alternative variants: from p-(quinuclid-3-yl)aniline according to the scheme for the preparation of pyrazidole [4], or from 6-bromoketocarbazole (III), wherein the formation of the C–C bond of the tetracyclic fragment with the quinuclidine residue takes place at the later stages of the synthesis. To solve the problem set forth, we chose the second scheme, in which bromoketocarbazole III is obtained by the modified [2] scheme in a substantially higher yield than according to the previously described method [8].

To add the piperazine fragment onto the tetrahydrocarbazole system, we used an alternative approach proposed for the synthesis of pyrazidole [1]: the ketocarbazole III was converted into an imine (IV), and then into chloroethylimine (V), which was reduced by means of $NaBH_4$ into amine (VI). Under interphase catalysis conditions in a benzene medium, by the action of an aqueous alkali, an intramolecular alkylation of VI was carried out with the formation of pyrazinocarbazole (VII), which was obtained in an overall yield of 36.2%, based on III.

The NH-fragment was then protected by alkylation of VII with benzyl chloride and the compound VIII formed was converted into an organo-lithium derivative (IX), which (without isolation) was converted into a quinuclidinyl carbinol (X). Acid dehydration of X led to the unsaturated derivative (XI) in a 70% yield. During the reduction of XI by palladium on carbon in the presence of ammonium formate (28 h, ~50°C) two reactions take place: removal of the N-benzyl protection and reduction of the $\Delta^{2'}$-double bond of the dehydroquinuclidine ring. The overall yield of the desired end product II is 64%. The two reduction processes can be separated: the N-debenzylation proceeds by the action of Pd/C in alcohol, while further heating with ammonium formate [9] results in the reduction of the $\Delta^{2'}$-dehydroquinuclidine ring into a quinuclidine ring. However, it is more expedient to combine these two reactions into a single process. The base of compound II isolated after alkalinization

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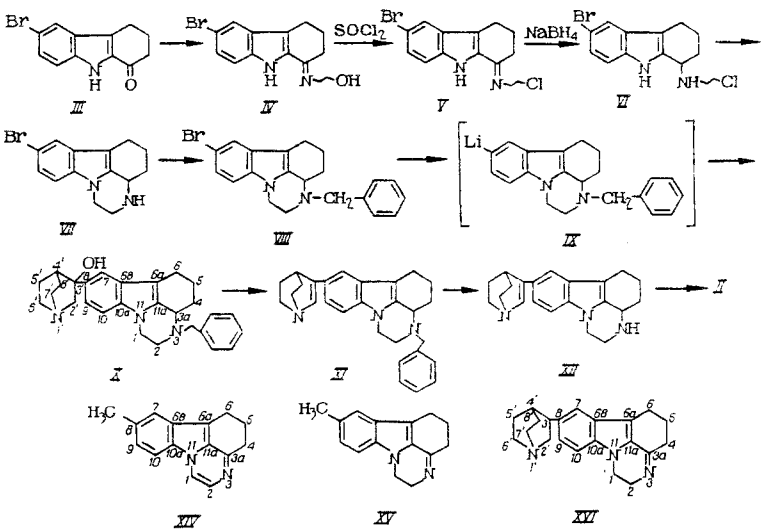
TABLE 1. Chemical Shifts of ^{13}C Nuclei of Pyrazino[3,2,1-j,k]-carbazole

Compound (solvent)	^{13}C nuclei in position							
	1,2,2′,6′7′[a]	4,5,6,5′,8′[a]	7,9,10[a]	6a,8,10a,11a[a]	6a	3a	3′	4′
I ($CDCl_3$)	43,4; 43,9; —, —, —	30,3; 20,8; 22,4; —, —	118,1; 122,1; 108,6	120,0; 128,5; 136,3; 133,8	106,8	52,6	—	—
I(CF_3COOH) / $CDCl_3$	39,6; 43,3; —, —, —	26,7; 19,8; 21,3; —, —	119,0; 124,6; 109,4	128,1; 130,6; 137,0; 126,9	112,8	53,4	—	—
II crude ($CDCl_3$)[b]	52,0; 47,6; 47,3; 42,9; 40,5	27,2; 24,5; 22,0; 20,4; 18,5	123,4; 117,9; 111,6	138,1; 133,1; 130,2; 128,5	112,6	52,7	38,9	27,6
X ($ClCl_3$)[d]	42,6; 47,0; 46,5; 49,8; 62,9	32,7; 22,7; 22,2; 21,9; 20,5	115,2; 119,1; 108,7	127,4; 136,1[e]; 136,3; 137,1; 138,4	107,0	59,4	72,9	28,2
XI ($CDCl_3$)[d]	42,5; 49,3; 49,8	20,5; 22,2; 28,3; 28,4	114,5; 118,2; 109,0	128,4; 135,5[e,f]; 136,9; 138,5	108,1	59,4	147,4	29,9
XIV ($CDCl_3$)	113,9; 123,3; —, —, —	31,3; 20,5; 23,0; —, —	118,7; 123,1; 110,0	125,5; 131,3; 127,2; 126,7	106,8	156,9	—	—
XIV (CF_3 COOH)	118,1; 110, 3; —, —, —	26,4; 20,0; 21,9; —, —	119,7; 131,2; 110,9	127,4; 135,9; 131,6; 124,1	123,0	155,6	—	—
XV ($CDCl_3$)	39,3; 48,1; —, —, —	32,2; 20,9; 24,6; —, —	119,7; 125,4; 109,0	126,5; 128,8; 135,5; 126,2	116,9	160,5	—	—
XV (CF_3 COOH)	39,0; 42,1; —, —, —	27,0; 20,0; 23,0; —, —	120,8; 133,5; 109,9	126,5; 132,6; 140,7; 136,8	123,5	165,9	—	—
XVI ($CDCl_3$)	51,4; 43,2[c]; 38,1	28,2; 24,3[c]; 21,4; 18,3	131,3; 120,6; 113,0	140,8; 135,1; 134,3; 126,9	125,2	167,4	38,7	27

Notes. [a]The assignment of signals was not carried out in these groups. [b]The average value of the chemical shift in diastereomers. [c]The signals of the remaining ^{13}C nuclei are masked by the more intense signals of the crude compound II. [d]Signals of the ^{13}C nuclei of the benzyl residue: 57.2; 126.8; 128.0; 128.4 (XI) and 57.2; 126.9; 128.1; 128.7 (X). [e]The ^{13}C signal I of the benzyl residue is present in this region. [f]The ^{13}C signal at 2′ is observed at 134.5.

with ammonia and extraction with benzene is converted into dihydrochloride by precipitation with alcoholic HCl from an ethereal solution, and the crude II (XIII) is recrystallized from absolute ethanol.

The structure of compounds X, XI, XII, and II was confirmed by the ^{13}C NMR spectra. The bases of I, XIV and XV were used as model compounds for comparison, the ^{13}C NMR spectra of which are described in the preceding publication [6].



In the spectrum of compound X (see Table 1) there are signals of carbon atoms of the quinuclidine and carbazole parts of the molecules. On transition to the dehydrated product XI, the signals at 62.9 and 72.9 ppm, characteristic of the 3-hydroxyquinuclidine residue, disappear and signals of the quinuclidine $C(2)^1$ and $C(3)^1$ carbon atoms at the double bond appear (147.4 and 134.5 ppm). In the ^{13}C NMR spectra of the unpurified product II (XIII), groups of two signals with approximately equal intensity and with similar chemical shifts ($\Delta\delta_{max}$ 0.15 ppm) correspond to each of the carbon atoms. This shows that XIII is a mixture of approximately equal amounts (a 1:1 ratio) of diastereomers. Compound XVI is possibly

the main impurity in the unpurified XIII. It was not isolated in an individual state and was identified from the presence in the ^{13}C NMR spectrum of a δC(3a) signal at 167.4 ppm, the absence of the CH group atom signals in the 45-60 ppm region and a considerable weak-field shift of the C(6a) signal (112.6 in XIII and 125.2 in XVI). Similar differences are observed in the ^{13}C NMR spectra of the previously described carbazoles [6].

The purification of crude grade compound II from XVI is accompanied by a change in the ratio of diastereomers to ~3:1.

A peak of a molecular ion is observed in the mass spectrum of compound XII with m/z 319 (100°C), which is smaller by two units than the mass of the desired end product II. This conforms with the presence in the spectrum of an ion with m/z 108 corresponding to the dehydrated quinuclidine fragment and confirms the structure of XII. A peak of molecular ion with m/z 321 is observed in the mass spectrum of compound II, the decomposition of which, caused mainly by the elimination of the neutral C_2H_4 particle and to a slight extent by the elimination of the quinuclidine fragment, is characteristic for polycyclic compounds containing aromatic and saturated heterocyclic rings and confirms its structure: $M^{+\cdot}$ 321 (48%), 293 $[M - C_2H_4]^{+\cdot}$, (100%), 211 $[M - C_7H_{12}N]^{+\cdot}$, (17%), 210 $[M - C_7H_{13}N]^{+\cdot}$, (18%), 96 $[C_6H_{10}N]^{+\cdot}$

EXPERIMENTAL (CHEMICAL)

The ^{13}C NMR spectra were run on a XI-200 ("Varian," Switzerland) spectrometer (50 MHz) using dioxane as internal standard, the mass spectra on a MAT-112 ("Varian," Switzerland) chromatomass spectrometer, with direct introduction of the sample into the ion source. The temperature of the ionization chamber was 180°C and the energy of the ionizing electrons 30 eV. The results of the elemental analyses correspond to the calculated data.

8-Bromo-2,3,3a,4,5,6-hexahydro-1H-pyrazino[3,2,1-j,k]carbazole (VII) was obtained in a similar way as compound I [1] from ketone III [8]. Yield, 36.2%, mp 101-104°C (from ether), mass spectrum: $M^{+\cdot}$ 290.

3-Benzyl-8-bromo-2,3,3a,4,5,6-hexahydro-1H-pyrazino[3,2,1-j,k]carbazole (VIII). A mixture of 22.1 g (0.076 mole) of VII, 21 ml of Et_3N, 12 ml of benzyl chloride and 70 ml of acetonitrile was heated to boiling for 2 h. The suspension that formed was cooled, the precipitate was filtered, washed with 15 ml of acetonitrile, 100 ml of water and dried in vacuum. After recrystallization from benzene, 24.9 g (86.2%) of VIII was obtained, mp 164-166°C, mass spectrum: $M^{+\cdot}$ 380. $C_{21}H_{21}BrN_2$.

3-Benzyl-8-(3-hydroxyquinuclidin-3-yl)-2,3,3a,4,5,6-hexahydro-1H-pyrazino[3,2,1-j,k] carbazole (X). A solution of 15.2 g (0.04 mole) of VIII in 100 ml of hot THF was added to 0.8 g of lithium, while maintaining a temperature of 0°C in the flask. After standing for 1 h, the solution of the organolithium compound IX was cooled to −50°C and a solution of 5.0 g (0.04 mole) of 3-quinuclidone in 15 ml of THF was added in the course of 10 min. The reaction mixture was allowed to warm up to room temperature, the excess of lithium was separated, and 3 ml of water was added to the solution. Tetrahydrofuran was evaporated under vacuum, the residue was dissolved in benzene, the benzene solution was washed with water, dried over Na_2SO_4 and evaporated under vacuum. The precipitate that separated out was filtered off, washed with hexane and dried. The yield of X in the form of a solvate with benzene was 10.1 g (54.2%), mp 130-135°C (dec.). Mass spectrum: $M^{+\cdot}$ 427. $C_{31}H_{36}N_3O \cdot 1/2C_6H_6$.

3-Benzyl-8(Δ²-dehydroquinuclidin-3-yl)-2,3,3a,4,5,6-hexahydro-1H-pyrazino-[3,2,1-j,k] carbazole (XI). A solution of 16.4 g (0.035 mole) of X in 170 ml of 25% H_2SO_4 was heated for 1 h at 50°C, then cooled, 100 ml of benzene was added, and then a solution of NaOH (50 g in 90 ml of water) to pH 10 at a temperature of the reaction mixture not higher than 30°C. The benzene layer was separated, washed with water, dried over Na_2SO_4, and benzene was evaporated under vacuum. The residue was dissolved in 25 ml of THF and the solution was chromatographed on a column with silica gel L 40/100 (CSSR), using a THF-Et_3N (50:1) mixture as eluent. The solution was evaporated under vacuum, and the residue was recrystallized from i-PrOH. The yield of XI was 10.0 g (70.0%) mp 136-140°C (dec.); mass spectrum: $M^{+\cdot}$ 409. $C_{28}H_{31}N_3$.

The compound is readily soluble in $CHCl_3$, benzene, soluble in ethanol, and slightly soluble in i-PrOH and acetone. R_f 0.43 (Et_3N–THF, 1:3), Merck plates, silica gel $60F_{254}$.

8-(Quinuclidin-3-yl)-2,3,3a,4,5,6-hexahydro-1H-pyrazino-[3,2,1-j,k]carbazole dihydrochloride (II). A 0.5 g portion of a 5% Pd/C and 1 g (15.8 mmoles) ammonium formate were added to a solution of 1 g (2.4 mmoles) of XI in 10 ml of absolute alcohol. The mixture was stirred for 28 h at 50°C. The catalyst was filtered off and the solution was evaporated under vacuum. A 5-ml portion of distilled water was added to the residue, the solution was made alkaline to pH 9 with 25% NH_4OH and extracted with benzene. The extract was dried over $MgSO_4$ and evaporated. The oily residue was converted into a hydrochloride by adding an alcoholic solution of HCl to the solution of the base to pH 3-4. The precipitate of crude II was filtered, dried and recrystallized from 5 ml of absolute alcohol. The yield was 0.5 g (yield 64%), mp 292-293°C, mass spectrum: $M^+ \cdot 321$. $C_{21}H_{27}N_3 \cdot 2HCl$.

EXPERIMENTAL (PHARMACOLOGICAL)

The quinuclidine analog of pyrazidole II was subjected to pharmacological investigation in comparison with pyrazidole with respect to several indices of psychotropic, especially its antidepressant action [3]. The reaction of compound II was studied with reserpine [blepharoptosis, 2.5 mg/kg, intraperitoneally (i/p)], ℓ-DOPA (hypothermia, 200 mg/kg, i/p), phenamine (motoric activity, 2.5 mg/kg, i/p), clonidine (motoric activity, 0.2 mg/kg, i/p), 5-hydroxytryptophan (head shaking, 50 mg/kg, i/p), apomorphine (hypothermia, 25 mg/kg, subcutaneously, (s/c)), tremorine (hypothermia, 20 mg/kg, s/c), scopolamine (amnesia, 1 mg/kg, s/c), thiopental (soporific action, 30 mg/kg, intravenously (i/v)), corazole (spasms, 125 mg/kg, s/c), and thiosemicarbazide (spasms, 20 mg/kg, s/c). The experiments were carried out on nonpedigree white mice of both sexes, each weighing 18-20 g, and on male rats, each weighing 150-180 g.

It was found that compound II in doses of 5, 10, and 25 mg/kg (perorally), similarly to pyrazidole, has an antireserpine effect, intensifies the action of ℓ-DOPA and 5-hydroxytryptophan, but in contrast to pyrazidole, these effects were not dose-dependent. Thus, in all three doses of compound II, the decrease in reserpine ptosis was ~40%, decrease in hypothermia due to ℓ-DOPA was equal to 1.7-1.8°C, and the appearance of head shaking caused by 5-hydroxytryptophan was observed in 40% of the mice.

When II was used in a lower dose (1 mg/kg) only a small (~20%) antireserpine action was noted, while the compound was practically inactive with respect to remaining indices. Compound II, also dose-independently, somewhat decreased the phenamine-induced hyperlocomotion on the Animex apparatus (on the average 816 runs per group of three control mice, and 430-470 runs on preliminary administration of II) and practically did not influence clonidine-induced hypolocomotion.

In similar experiments, pyrazidole did not display an appreciable influence on the action of phenamine, but decreased the sedative hypolocomotoric effect of clonidine. The latter effects of II indicate the absence in it of a stimulating action and presence of elements of a sedative effect. However, according to experimental data with thiopental and Corazole, no clear-cut sedative action in II was noted: compound II did not intensify the soporific action of thiopental, did not lessen the spasmodic action of Corazole, and in this respect was similar to pyrazidole. Similarly to pyrazidole, II had no noticeable influence on the hypothermal effects of apomorphine and tremorine. While being as active as pyrazidole, II decreased the amnestic effect of scopolamine: while in control mice the conditional passive avoidance reaction after training was reproduced in 60% of the animals (n = 30) and by the action of scopolamine – only in 20% (n = 30), then after a single administration of scopolamine and II it was observed also in 60% of mice (n = 30).

The influence of II on the functional state of CNS was studied on kept-awake rats by recording the overall spontaneous and bioelectrically induced activity (EEG) in various cortical and subcortical structures of the brain. The EEG evaluation was carried out on the basis of a computerized compression analysis on a Berg–Fourier analyzer from the firm OTE "Biomedica" (Italy). The action of II was compared with the activity of pyridazole I.

In contrast to pyridazole I, which according to the EEG analysis data displayed a dose-dependent stimulating action on the CNS, compound II in a dose of 10 and 15 mg/kg (intraperitoneally) 30-60 min after the administration displayed only an inappreciable activating action, which was expressed in a certain intensification in the rating of the theta-range (4-6 Hz) and weakening of the alpha-rhythm (8-10 Hz) of the EEG frequency spectrum, especially in the cortical brain structures. Compound II thus did not display a pronounced

synchronized rhythm in the subcortical structures (the limbic system) on the background of a desynchronized reaction in the cortical regions of the brain. The suppression of the alpha-range (8-12 Hz) of the EEG indicated an increase in the CNS activity. However, in contrast to pyrazidole I, which caused a prolonged (4-6 h) activation, 2-3 h after the administration of II, the activation reaction changed into a slight depressant action. This was expressed in the intensification of the rhythmical activity of the alpha-range, and also in a certain intensification of the rating of the delta range (1-3 Hz) of the EEG frequency spectrum in the cortical structures of the brain. The duration of the depressant action of II was 1-2 h. With increase in the dose of II to 20 mg/kg, the depressant action did not intensify substantially and the duration of the effect did not change.

Thus, beside the activation action of the CNS (less pronounced than in the case of pyridazole), compound II displayed a certain nonprolonged sedative effect.

The data obtained may indicate an influence of compound II on the central catecholaminergic systems of the organism. However, judging from the influence indices on the CNS studied, compound II shows no substantial advantages over pyrazidole.

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