NEW SIMPLE LABORATORY METHOD FOR THE SYNTHESIS OF PIRAZIDOL

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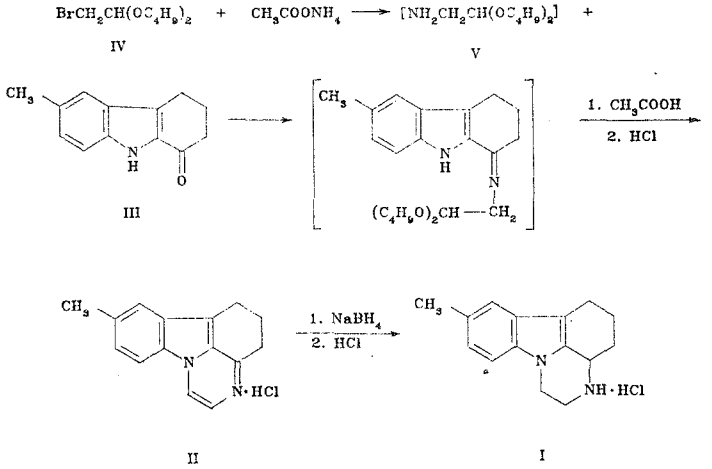
5,6-Dihydro-8-methyl-4H-pyrazino[3,2,1-j,k]carbazole was obtained by the reaction of α-bromoacetaldehyde dibutylacetal, ammonium acetate, and 1,2,3,4-tetrahydro-6-methyl-1-ketocarbazole in acetic acid. The reduction of 5,6-dihydro-8-methyl-4H-pyrazino[3,2,1-j,k]carbazole or its hydrochloride with sodium borohydride leads to 2,3,3a,4,5,6-hexahydro-8-methyl-1H-pyrazino[3,2,1-j,k]carbazole hydrochloride — the medicinal preparation pirazidol.

The original Soviet antidepressant pirazidol — 2,3,3a,4,5,6-hexahydro-8-methyl-1H-pyrazino[3,2,1-j,k]carbazole hydrochloride (I) — has found wide application in medical practice [1]. The starting compound for the synthesis of pirazidol I is 5,6-dihydro-8-methyl-4H-pyrazino[3,2,1-j,k]carbazole hydrochloride (II). We found that the latter is formed in the reaction of 1,2,3,4-tetrahydro-6-methyl-1-ketocarbazole (III), α-bromoacetaldehyde dibutylacetal (IV), and ammonium acetate in acetic acid. The reaction evidently proceeds initially through a step involving the formation of aminoacetaldehyde dibutylacetal (V) — the reagent used in the Pomeranz–Fritsch reaction — via the scheme



Hexahydropyrazinocarbazole I is obtained in the reduction of dihydropyrazinocarbazole II with sodium borohydride in formic acid or in the reduction of dihydropyrazinocarbazole hydrochloride II with sodium borohydride in acetic acid.

In contrast to the method that we described in [2, 3], the proposed variants of the method of reduction make it possible to obtain N-unsubstituted 2,3,3a,4,5,6-hexahydro-8-methyl-1H-pyrazino[3,2,1-j,k]carbazole hydrochloride (pirazidol).

EXPERIMENTAL

5,6-Dihydro-8-methyl-4H-pyrazino[3,2,1-j,k]carbazole Hydrochloride (II). A mixture of 5 g (25 mmole) of ketocarbazole III, 6.3 g (25 mmole) of dibutylacetal IV, 40 ml of acetic acid, and 20 g (0.260 mmole) of ammonium acetate was heated with stirring at 120°C for 10 h, after which it was cooled and poured into 200 ml of water. The unchanged ketocarbazole III was removed by filtration, and the filtrate was extracted with five 50-ml portions of carbon tetrachloride. The extract was acidified to pH 3 with hydrochloric acid, and the resulting

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precipitate was removed by filtration, washed on the filter with 20 ml of acetone, and dried to give 1.36 g (22%) of II with mp 200-203°C [4] (dec., from water). Found: C 69.3; H 5.7; Cl 13.8; N 10.6%. $C_{15}H_{14}N_2 \cdot HCl$. Calculated: C 69.6; H 5.8; Cl 13.7; N 10.8%.

2,3,3a,4,5,6-Hexahydro-8-methyl-1H-pyrazino[3,2,1-j,k]carbazole Hydrochloride (I). A) A 13-g (50 mmole) sample of sodium borohydride was added in portions with stirring at 15°C to a suspension of 13 g (50 mmole) of the hydrochloride of III, and the reaction mixture was stirred at this temperature for 30 min. It was then heated to 80°C, and stirring was continued for 30 min. The mixture was cooled and poured into 300 ml of water, and the aqueous mixture was made alkaline to pH 8 with sodium hydroxide solution and extracted with three 50-ml portions of chloroform. The extract was dried with sodium sulfate and evaporated, and the residue was dissolved in 60 ml of acetone. A solution of hydrogen chloride in ether was added to the acetone solution until the mixture had pH 3, and the resulting precipitate was removed by filtration to give 10.0 g (76%) of hydrochloride I with mp 260-264°C [dec.; mp 250-252°C after crystallization from acetone–water [4]]. Found: C 68.5; H 7.1; Cl 13.6; N 10.9%. $C_{15}H_{18}N_2 \cdot HCl$. Calculated: C 68.6; H 7.3; Cl 13.5; N 10.7%.

B) A 4.4-g sample of sodium borohydride was added in portions with stirring at 10°C to a suspension of 4.4 g (20 mmole) of base III in 50 ml of dry dioxane and 25 ml of 99% formic acid, after which the mixture was heated at 80°C for 1.5 h. It was then cooled and diluted with 150 ml of water, and the aqueous mixture was made alkaline to pH 8-9 with sodium hydroxide and extracted with three 50-ml portions of chloroform. The extracts were dried with sodium sulfate and evaporated, and the residue was dissolved in 25 ml of acetone. A solution of hydrogen chloride in ether was added to the acetone solution until the mixture had pH 5, and the resulting precipitate was removed by filtration, washed with acetone, and dried to give 2.4 g (46%) of hydrochloride I with mp 260-263°C [dec.; mp 241-242°C after crystallization from acetone–water [5]]. No melting-point depression was observed for a mixture of this product with a sample obtained by method A.

LITERATURE CITED

1. M. D. Mashkovskii, Medicinals [in Russian], Meditsina, Moscow (1977), Part 1, p. 102.
2. V. I. Shvedov, É. S. Krichevskii, O. B. Romanova, A. N. Grinev, N. I. Andreeva, and M. D. Mashkovskii, Khim.-farm. Zh., No. 5, 85 (1978).
3. A. N. Grinev, O. B. Romanova, É. S. Krichevskii, M. D. Mashkovskii, and N. I. Andreeva, Khim.-farm. Zh., No. 8, 32 (1980).
4. V. I. Shvedov, L. B. Altukhova, and A. N. Grinev, Khim.-farm. Zh., No. 3, 25 (1967).
5. V. I. Shvedov, L. B. Altukhova, N. I. Andreeva, M. D. Mashkovskii, and A. N. Grinev, Khim.-farm. Zh., No. 10, 14 (1972).