ether, benzene, chloroform, and water. Found %: C 61.81; H 5.53; N 15.40. $C_{14}H_{15}N_3O_3$. Calculated %: C 61.55; H 5.51; N 15.44.

5-Acetyl-6-methoxy-1,2,3,4-tetrahydro-β-carbolin-1-one Hydrazone (IV). A solution of triacetate (I) (0.3 g) in hydrazine hydrate (3 ml) was refluxed for 3 h. The reaction mixture was evaporated under vacuum and the residue was distilled with alcohol to give hydrazone (IV) (0.21 g, 91%) mp 216-217°C (from alcohol). Found %: C 62.14; H 5.81; N 20.20. $C_{14}H_{16}N_4O_2$. Calculated %: C 61.76; H 5.88; N 20.58%.

Hydrochloride, mp 241-242°C (from alcohol). Found %: Cl 11.72; 18.25. $C_{14}H_{16}N_4O_2 \cdot HCl$. Calculated %: Cl 11.57; 18.15.

5-Ethyl-6-methoxy-1,2,3,4-tetrahydro-β-carbolin-1-one (V). To a solution of triacetate (I) (1 g) in ethyl alcohol (100 ml) was added a solution of palladium chloride (0.5 g) in 18% hydrochloric acid (5 ml). Hydrogenation was carried out at room temperature (18-20°C) under an excess pressure of 20-30 mm H_2O until the absorption of hydrogen ceased. The palladium was filtered off. The solution was evaporated under vacuum to give 5-ethyl-6-methoxy-1,2,3,4-tetrahydro-β-carbolin-1-one (V) (0.6 g, 85%), mp 204-205°C (from ethanol). The compound was soluble in common organic solvents but poorly soluble in water. Found %: C 68.62; H 6.23; N 11.13. $C_{14}H_{16}N_2O_2$. Calculated %: C 68.71; H 6.58; N 11.51.

LITERATURE CITED

1. K. Rehse, H. Schulte-Sienbeck, and R. Horwski, Arch. Pharm., 311, 228 (1978).
2. M. Protiva, J. Jilik, E. Hachova, et al., Chem. Listy, 51, 1915 (1957).
3. R. J. Gryglewski, S. H. Misztal, J. A. Splawiński, and B. Panczenko, J. Med. Chem., 9, 471 (1966).
4. V. Z. Gorkin, L. V. Tat'yanenko, D. M. Krasnokutskaya, et al., Biokhimiya, 32, 510 (1967).
5. L. N. Yakhontov, M. Ya. Uritskaya, O. S. Anisimova, et al., Khim. Geterotsikl. Soedin., 1975, 1270.

SYNTHESIS AND NEUROTROPIC PROPERTIES OF SOME α-AMINOBENZYLPIPERIDINES

É. K. Orlova, V. M. Bulaev, A. I. El'kin, L. M. Meshcheryakova, and V. A. Zagorevskii

UDC 615.21:547.821

The piperidine ring is a structural fragment of a series of substances active on the central nervous system (CNS) such as, for example, neuroleptics of the butyrophenone series, agents for the treatment of parkinsonism, and narcotic analgesics of natural and synthetic origin.

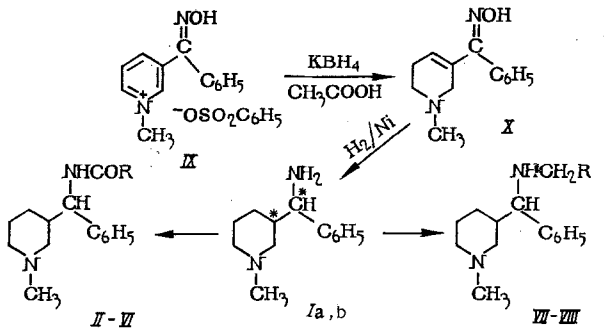
In order to further study the connection between the structure of piperidine derivatives incorporating a phenyl radical and neurotropic activity, we synthesized the previously unknown 1-methyl-3-(α-aminobenzyl) piperidine in the form of two individual diastereoisomers (Ia, b) and a series of N-acyl and N-alkyl derivatives of the latter (IIa, b, IIIa, b, and IVa-VIIIa). Up to now, substances with this molecular skeleton have not been studied pharmacologically.

Amines Ia, b were obtained by stepwise reduction of the oxime of 1-methyl-3-benzoylpyridine benzenesulfonate (IX) with potassium borohydride in acetic acid to the oxime of 1-methyl-3-benzyl-1,2,5,6-tetrahydropyridine (X), and subsequent hydrogenation over Raney nickel under the usual conditions. The structure of oxime X was confirmed by molecular weight determination (mass-spectrometrically), IR spectrum [ν ($CHCl_3$): 3570 (OH), 1645 (C=N) cm^{-1}], and PMR spectrum [δ ($CDCl_3$): 6.0 (1H, singlet, C_4), 3.8 (2H, multiplet, C_2) ppm]. The amines Ia, b were formed in a ratio of about 1:1 (by GLC), and their acid maleates were fractionally crystallized to give the individual isomers. Isomers Ia and Ib were distinguished by the chemical shifts of their N-CH_3 protons (δ 2.0 and 2.4 ppm, respectively, in CCl_4), as well as by their IR spectra in the 500-1000 cm^{-1} region.

Institute of Pharmacology, Academy of Medical Sciences, Moscow.

Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 13, No. 1, pp. 47-51, January, 1979. Original article submitted June 26, 1978.

In the hydrogenation of oxime X, particularly in the presence of acid, to give amines Ia, b, hydrolysis of the oxime group resulted in the concurrent formation of the known 1-methyl-3-benzoylpiperidine (XI) [1].



IIa, b: R = CH_3, IIIa, b: R = C_2H_5, IVa: R = OC_2H_5, Va: R = C_6H_5, VIa: R = 3-pyridyl, VIIa: R = C_6H_5, VIIIa: R = —CH=CHC_6H_5.

Acylation of the amines Ia, b gave the corresponding acyl derivatives (IIa, b, IIIa, b, IVa-VIa). Reaction of isomer Ia with benzaldehyde and cinnamaldehyde, and subsequent reduction of the intermediate Schiff bases with potassium borohydride gave compounds VIIa-VIIIa.

Compounds I-IIIa, b, IV-VIIIa, and XI were studied by tests characterizing their influence on CNS. Compounds Ia, IIIa, and VIIa showed a weak disruptive activity on the CNS. Of most interest were compounds Ia, b, and IIa, which showed a significant antimorphine effect. Thus we have found a new morphine antagonist group not containing a specific substituent on the nitrogen atom, as for example, alkyl, cyclopropylmethyl, etc.

EXPERIMENTAL PHARMACOLOGICAL PART

The influence of compounds I-IIIa, b, IV-VIIIa, and XI on the CNS was studied by the following tests: potentiation of the narcotic effect of thiopental sodium (35 mg/kg), muscle-weakening effect (retention on rotating rod), influence on body temperature, influence on simple conditioned reflexes and defense avoidance reflexes, interaction with convulsive poisons (corazole, 100 mg/kg), analgesic and morphine antagonist activity, and acute toxicity. The property of these substances to influence the simple conditioned reflexes as well as analgesic and morphine antagonist activity were studied in experiments with rats, and the remaining investigations were carried out on mice. None of the compounds studied caused a reduction in body temperature or showed muscle-weakening effects, and none had an influence on the defense avoidance reflex at a dose of 50 mg/kg or more. Interestingly, compounds Ia, IIIa, and VIIa in dosages of 112, 75, and 72 mg/kg, respectively, doubled the length of thiopental-sodium sleep, showed an anticorazole effect (increased the latent period by 2.5 times), and depressed simple conditioned reflexes, i.e., showed a weakly disruptive influence on the CNS. The toxic effects of these compounds appears in significantly large doses (by intraperitoneal introduction, the LD_{50} for Ia was 745 mg/kg; for IIIa, 530 mg/kg; for VIIa, 290 mg/kg).

Analgesic and antimorphinic activity of the indicated compounds was studied by electric-pain stimulation of the tail [2]. It was determined that none of the substances studied possessed analgesic activity by enteral introduction at doses of from 10 to 50 mg/kg. For the determination of antimorphinic activity, it was found that compounds Ia, b and IIa at a dose of 10 mg/kg by enteral introduction produced a distinct weakening of morphine analgesia. The most significant antimorphine effect was shown by compound Ib, which lowered the pain threshold by 2 times at a dose of 10 mg/kg, but this effect was not as pronounced as that of nalorfine (2 mg/kg). The action was not strengthened by increasing the dosage up to 30 mg/kg.

EXPERIMENTAL CHEMICAL PART

1-Methyl-3-benzoylpyridine Oxime Benzenesulfonate (IX). A mixture of 61 g of 3-benzoylpyridine oxime in 500 ml of anhydrous acetone and 65 g of methyl benzenesulfonate was boiled for 3 h, cooled, and the resulting precipitate was filtered off and recrystallized from absolute alcohol to give 81 g (64%) of the benzenesulfonate salt of IX, decomposition temperature 162°C. Found %: S 8.90; N 7.68. $C_{19}H_{18}N_2O_4S$. Calculated %: S 8.65; N 7.56.

1-Methyl-3-benzoyl-1,2,5, 6-Tetrahydropyridine Oxime (X). To a stirred solution of 81 g of IX benzenesulfonate in 400 ml of glacial acetic acid was introduced 70 g of potassium borohydride in small portions. After 36 h, 150 ml of water was added with external cooling, the solution was made basic with 40% sodium hydroxide

and extracted with ether. The extract was concentrated to one-third volume, and 25 g (54%) of the product (X) was filtered off, mp 147-149°C (from a mixture of benzene and petroleum ether). Found %: C 72.10; H 7.51; N 12.71. $C_{13}H_{16}N_2O$. Calculated %: C 72.18; H 7.46; N 12.95.

1-Methyl-3-(α-aminobenzyl)piperidine (Ia, b). The oxime X was hydrogenated in alcohol at room temperature and atmospheric pressure over Raney nickel until hydrogen uptake ceased. The catalyst was separated, the alcohol was evaporated, and benzene was added. The residue was dissolved in absolute ether, and 28 g of maleic acid in absolute alcohol was added. After 16 h the precipitate was filtered off and recrystallized from alcohol to give 20 g (38.5%) of the Ia acid maleate, decomposition temperature 162°C. Found %: C 57.65; H 6.35; N 6.49. $C_{13}H_{20}N_2 \cdot 2H_4C_4O_4$. Calculated %: C 57.77; H 6.47; N 6.42. The mother liquor after removal of Ia was treated with absolute ether, the residue was filtered off, and crystallized from absolute alcohol to give 13 g (25%) of the acid maleate of Ib, decomposition temperature 144°C. Found %: C 57.63; H 6.46; N 6.38. $C_{13}H_{20}N_2 \cdot 2H_4C_4O_4$. Calculated %: C 57.77; H 6.47; N 6.42.

If the hydrogenation of the oxime X is conducted after addition of a catalytic amount of chloroplatinic acid, the production of the amines Ia, b is accompanied by about 10% of the maleate of the ketone XI, decomposition temperature 137°C (from absolute alcohol). Found %: C 63.76; H 6.65; N 4.47. $C_{13}H_{17}NO \cdot H_4C_4O_4$. Calculated %: C 63.92; H 6.63; N 4.39.

1-Methyl-3-(α-acetylaminobenzyl)piperidine (IIa). To 1.5 g of amine Ia, externally cooled with ice, was rapidly added 5 ml of acetic anhydride. The solution was heated for 1 h on a water bath, cooled, treated with 2 ml of 2 N hydrochloric acid, and after approximately 15 min, was made basic with 2 N sodium hydroxide and extracted with benzene to give 1.2 g of the base IIa, mp 144°C (from benzene), which was converted to the maleate of IIa, decomposition temperature 180°C. Found %: C 62.94; H 7.01; N 7.69. $C_{15}H_{22}N_2O \cdot H_4C_4O_4$. Calculated %: C 62.96; H 7.23; N. 7.73. IR spectrum of IIa maleate ν: 3325 (NH), 1672 (C=O) cm^{-1}, in potassium bromide.

1-Methyl-3-(α-acetylaminobenzyl)piperidine (IIb) was obtained analogously with IIa from 1.9 g of amine Ib, yield 50%, mp 137.5-138.5°C (from a mixture of benzene and petroleum ether). Found %: C 73.42; H 8.88; N 11.18. $C_{15}H_{22}N_2O$. Calculated %: C 73.13; H 9.00; N 11.37. IR spectrum ν: 3450 (NH), 1670 (C=O) cm^{-1}, in chloroform.

1-Methyl-3-(α-propionylaminobenzyl)piperidine (IIIa) was obtained analogously to IIa from 2 g of amine Ia and 6 ml of propionic anhydride. The IIIa free base was dissolved in absolute alcohol and to this solution was added 2.5 g of maleic acid in absolute ether, the mixture was boiled for 1 h, the residue was separated, and reprecipitated with ether from a solution in absolute alcohol to give 2.6 g (69%) of IIIa maleate, decomposition temperature 176°C. Found %: C 63.69; H 7.40; N 7.38. $C_{16}H_{24}N_2O \cdot H_4C_4O_4$. Calculated %: C 63.81; H 7.50; N 7.44.

1-Methyl-3-(α-propionylaminobenzyl)piperidine (IIIb) was obtained analogously to IIIa from 1.8 g of amine Ib, yield 1.4 g (60%), mp 130-131°C (from a mixture of benzene and petroleum ether, treated with charcoal). Found %: C 73.95; H 9.10; N 10.70. $C_{16}H_{24}N_2O$. Calculated %: C 73.79; H 9.28; N 10.76.

1-Methyl-3-(α-benzylaminobenzyl)piperidine (Va). After Schotten–Bauman benzoylation (from 2 g of amine Ia, 1.5 g of benzoyl chloride, and 1.4 g of potassium carbonate stirred for 1.5 h at 20°C), the amide was separated, dissolved in absolute ether and precipitated from the ether solution with hydrogen chloride to give 2.0 g (59%) of Va hydrochloride, decomposition temperature 300°C (from absolute alcohol). Found %: C 67.58; H 7.78; Cl 8.99; N 7.10. $C_{20}H_{24}N_2O \cdot HCl \cdot C_2H_5OH$. Calculated %: C 67.57; H 8.00; Cl 9.07; N 7.17.

1-Methyl-3-(α-ethoxycarbonylaminobenzyl)piperidine (IVa). The acetylation was carried out as in the preparation of Va from 2 g of amine Ia, 2.3 g of ethyl chloroformate and 1.4 g of potassium carbonate. The reaction mixture was extracted with benzene, the extract was concentrated under vacuum, the residue was dissolved in absolute ether, and to this solution was added a solution of 2 g of maleic acid in absolute ether to give 2.2 g (54%) of IVa maleate, decomposition temperature 177°C (precipitated from absolute alcohol with ether). Found %: C 61.24; H 7.19; N 7.22. $C_{16}H_{24}N_2O_2 \cdot H_4C_4O_4$. Calculated %: C 61.22; H 7.19; N 7.14.

1-Methyl-3-(α-nicotinoylaminobenzyl)piperidine (VIa). A suspension of nicotinoyl chloride (1.23 g of nicotinic acid and 5 ml of thionyl chloride was heated for 2 h, after which the excess thionyl chloride was removed under vacuum) in anhydrous chloroform was added portionwise with external cooling to a mixture of 2.3 g of amine Ia and 2.8 g of potassium carbonate in wet chloroform. After 2 h, the chloroform was separated and concentrated. The residue was washed with a mixture of alcohol and ether (1:1) to give 1.5 g (49%) of compound VIa, mp 150°C (with decomposition at 178°C; from a mixture of benzene and petroleum ether). Found %:

C 70.04; H 7.66; $C_{19}H_{23}N_3O \cdot H_2O$. Calculated %: C 69.71; H 7.70. Found %: H_2O 5.62 (by Fischer). Calculated %: H_2O 5.50.

1-Methyl-3-(α-benzylaminobenzyl)piperidine (VIIa). To a solution of 2 g of amine Ia in methanol was added 1g of benzaldehyde in methanol. After about 16 h, the solution was diluted with water (1:1) and 3 g of potassium borohydride was added in portions, heated for 20 min and extracted with chloroform. The extract was concentrated under vacuum and the solution residue in anhydrous benzene was treated with an ether solution of hydrogen chloride to give 1.8 g (50%) of VIIa dihydrochloride, decomposition temperature 233°C. Found %: C 64.60; H 7.71; Cl 19.17; N 7.59. $C_{20}H_{26}N_2 \cdot 2HCl \cdot 0.25\ H_2O$. Calculated %: C 64.60; H 7.63; Cl 19.06; N 7.54.

1-Methyl-3-(α-cinnamylaminobenzyl)piperidine (VIIIa) was prepared analogously with VIIa from 1.7 g of amine Ia, 1.23 g of cinnamaldehyde and 3 g of potassium borohydride; yield of VIIIa dihydrochloride, 2.4 g (75%), decomposition temperature 230°C (from a mixture of absolute alcohol and ether). Found %: C 66.82; H 7.90; Cl 17.87; N 6.90. $C_{22}H_{28}N_2 \cdot 2HCl$. Calculated %: C 67.16; H 7.69; Cl 18.03; N 7.12.

LITERATURE CITED

1. E. Smissman and G. Hilfe, J. Am. Chem. Soc., 81, 1201 (1959).
2. G. Paalzow and L. Paalzow, Psychopharmacologia (Berlin), 45, 9-20 (1975).

SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF 2-AMINOMETHYL DERIVATIVES OF BENZOFURAN

A. N. Grinev, S. A. Zotova, A. A. Stolyarchuk, V. P. Gaevoi, and V. V. Matsak

UDC 615.22:547.722].012.1

In recent years drugs with cardio-dilating, spasmolytic, and antiarrhythmic activity have been found among benzofuran derivatives [1, 2]. In this context we decided to make a further search for cardiovascular drugs in the benzofuran series. Here we report the syntheses of 2-aminomethyl derivatives of benzofuran and a study of their pharmacological properties.

The starting compounds were α-phenoxypropiophenones (I)-(IV). We used the literature method [3] to convert them to 2-methyl-3-phenylbenzofuran (V) and its 5-substituted derivatives (VI)-(IX).

We found that 2-methyl-3-phenylbenzofurans, like 2-methyl-3-ethoxycarbonyl-5-methoxybenzofuran [4], are easily brominated at the methyl group by N-bromosuccinimide. Bromination of (VIII) gave 2-bromomethyl-3-phenyl-5-chlorobenzofuran (X). The other 2-bromomethyl-3-phenylbenzofurans were used for the synthesis of the aminomethyl derivatives without purification. We prepared the 2-aminomethyl derivatives (XI)-(XVIII) by reaction of the 2-bromomethyl derivatives with secondary amines. Bromination of 2,5-dimethyl-3-phenylbenzofuran (VII) with two moles of N-bromosuccinimide formed 2,5-bis(bromomethyl)-3-phenylbenzofuran, which was used without isolation for the synthesis of the bis(aminomethyl) derivatives (XIX). (See scheme on following page).

EXPERIMENTAL PHARMACOLOGICAL PART

We evaluated the antiarrhythmic, spasmolytic and local anesthetic action of the synthetic 2-aminomethyl derivatives of benzofuran. We examined compounds (XI)-(XVII) as the hydrochlorides and compounds (XVIII)-(XIX) as the bases.

We determined the indices of toxicity by Litchfield and Wilcoxon's method [5]. The antiarrhythmic action was examined against aconitine-induced disruption of the rhythm in rats [6]. We examined the surface anesthesia

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. N. I. Pirogov Vinnitsa Medical Institute.

Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 13, No. 1, pp. 51-54, January, 1979. Original article submitted May 30, 1978.

0091-150X/79/1301-0044$07.50