SYNTHESIS AND PHARMACOLOGICAL STUDY OF SUBSTITUTED 1,2,3,4-TETRAHYDRO-β-CARBOLIN-1-ONES

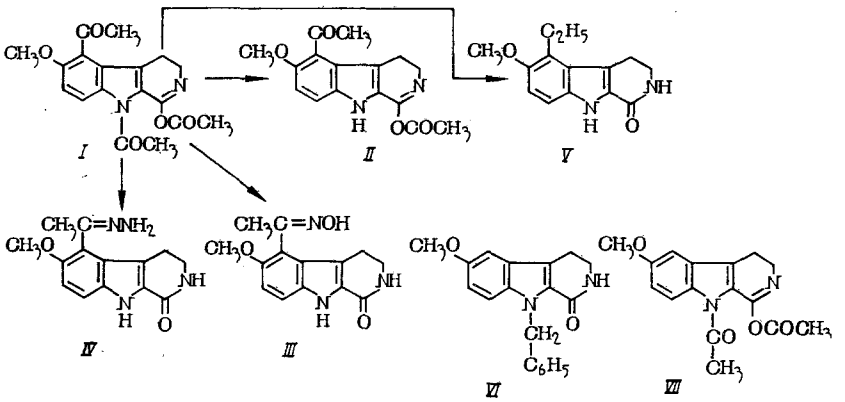
M. Ya. Uritskaya, N. I. Andreeva,
M. D. Mashkovskii, and L. N. Yakhontov

UDC 615.214.24: 547.759].012.1

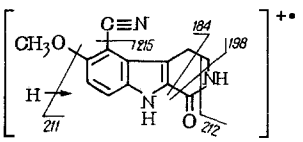
Various 1,2,3,4-tetrahydro-β-carboline derivatives are known to have considerable psychotropic activity [1-4].

Our recently developed method for introducing an acetyl group into position 5 of the tetrahydrocarboline system [5] has opened the way to the synthesis and pharmacological study of the hitherto difficultly accessible 5,6-disubstituted 1,2,3,4-tetrahydro-β-carbolin-1-ones. Here we describe the synthesis and study of some new compounds of this series.

Our starting compound for the preparation of these compounds was 1-acetoxy-5,9-diacetyl-6-methoxy-3,4-carboline (I) [5].



Treatment of the triacetate with an equimolar quantity of hydroxylamine hydrochloride selectively cleaved the N-acetyl group to give 1-acetoxy-5-acetyl-3,4-dihydro-β-carboline (II) in 85% yield. Excess hydroxylamine hydrochloride removed both N- and O-acetyl groups and oximated the keto group of the C_5 acetyl in the β-carboline system. The yield of 5-acetyl-6-methoxy-1,2,3,4-tetrahydro-β-carbolin-1-one oxime (III) was 61%. The equivalent reaction of triacetate (I) with excess hydrazine hydrate gave 5-acetyl-6-methoxy-1,2,3,4-tetrahydro-β-carbolin-1-one hydrazone in 91% yield (IV). The mass spectrum of hydrazone (IV) has an intense molecular peak at m/e 272. The molecular ion fragments by cleavage of the side chain in the aromatic part of the molecule to form the $(M-NH_2-CH_3)^{+\cdot}$ ion (m/e 241). The subsequent fragmentation of the m/e 241 ion is:



Reduction of triacetate (I) in alcoholic solution in the presence of a palladium catalyst involves N- and O-deacetylation and reduction of the keto group to methylene, forming 5-ethyl-6-methoxy-1,2,3,4-tetrahydro-β-carbolin-1-one (V) in 85% yield. The most intense peaks in the mass spectrum of compound (V) belong to the ions $M^{+\cdot}$ (m/e 244) and $(M-CH_3)^{+\cdot}$ (m/e 229). The abundance of the m/e 229 ion points to the presence of an ethyl

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 13, No. 1, pp. 44-47, January, 1979. Original article submitted June 19, 1978.

0091-150X/79/1301-0039$07.50

group on the aromatic ring. As in compound (IV), the subsequent fragmentation is mainly due to cleavage of the saturated part of the molecule.

For a comparison of the pharmacological activity of the 5,6-disubstituted 1,2,3,4-tetrahydro-β-carbolin-1-ones (I)-(V), we also examined the 5-unsubstituted compounds, 6-methoxy-9-benzyl-1,2,3,4-tetrahydro-β-carbolin-1-one (VI) and 1-acetoxy-6-methoxy-9-acetyl-3,4-dihydro-β-carboline (VII), whose syntheses we described in our previous report [5].

For pharmacological evaluation compounds (I)-(III) and (V)-(VII) were administered internally as suspensions in 1% methylcellulose solution; compound (IV) was administered subcutaneously as an aqueous solution.

We examined the general action, toxicity, and psychotropic activity in white mice from symptoms that included the effects on the central adrenergic (interaction with phenamine, L-DOPA, reserpine, and tetrabenazine), serotoninergic (interaction with apomorphine), and cholinergic structures (interaction with arecoline and nicotine). We also examined the effect of compounds (I)-(VII) on the soporific effect of hexenal in rats and the analgesic action of promedol in white mice.

Our results showed that the water-insoluble compounds (I)-(III) and (V)-(VII) are relatively nontoxic: They neither caused the death of mice nor produced appreciable changes in the state and behavior of the animals in doses of 500-600 mg/kg (internally). The water-soluble compound (IV) is quite toxic: LD_{50} on subcutaneous administration to white mice is 30 mg/kg.

All the test compounds (I)-(VII) displayed a tendency to enhance the depressant effect of reserpine and tetrabenazine; this was most apparent in compounds (IV) and (V). Thus in the control mice the ptosis was 0.5 (0.1-0.9) points 1 h after administration of reserpine (2 mg/kg intraperitoneally) and 1.6 (1.0-2.2) points after 2 h. When compound (IV) (10 mg/kg subcutaneously) was administered 30 min before reserpine the reserpine ptosis was 1.7 (1.1-2.3) and 2.1 (1.7-2.5) points respectively. The hypothermal effect of tetrabenazine (40 mg/kg intraperitoneally) increased from 32 (30.1-33.9°C) in the control to 27 (26.7-28.3°C) in mice that had received compound (V) (100 mg/kg internally) 60 min before tetrabenazine.

The same compounds, (IV) and (V), slightly reduced phenamine hyperthermia. Thus, in the control mice the body temperature reached 39.4 (39-39.8°C) 30 min after administration (7.5 mg/kg subcutaneously) while when compound (IV) (10 mg/kg subcutaneously) or compound (V) (100 mg/kg internally) were administered 30 min before phenamine, the body temperature was respectively 37.8 (36.8-38.6) and 38 (36.1-39.9°C). The group toxicity of phenamine was not markedly modified by the test compounds.

Compounds (IV) and (V) in the same doses enhanced the hypothermal action of 5-hydroxytryptophan in mice (120 mg/kg intraperitoneally) by 1.5-2°C but did not substantially affect head shaking induced by 5-hydroxytryptophan. Compounds (I)-(VII) did not markedly affect apomorphine hypothermia in mice or alter the intensity and duration of the convulsant effects of nicotine and arecoline.

Compound (III) increased the duration of the soporific effect of hexenal in rats. Thus the length of hexenal-induced sleep (50 mg/kg intraperitoneally) was 15 (9.4-20.9) min in the control animals and 28 (19.5-36.5) min in rats that had first received compound (III) (200 mg/kg internally).

Thus these symptoms of psychotropic action imply that the test compounds are relatively inactive; only some, compounds (III)-(V), showed any elements of sedative action.

EXPERIMENTAL

1-Acetoxy-5-acetyl-6-methoxy-3,4-dihydro-β-carboline (II). To a solution of triacetate (I) (0.34 g) in a mixture (5 ml) of alcohol (4 ml) and water (1 ml) was added a solution of hydroxylamine hydrochloride (0.07 g) and ammonium acetate (0.07 g). The reaction mixture was refluxed for 3 h and the precipitate was filtered off to give diacetate (II) (0.22 g, 85%), mp 214-215°C (from methanol). The compound did not depress the melting point of a mixture with a sample of (II) prepared by the method described earlier [5] and had an identical mass spectrum.

5-Acetyl-6-methoxy-1,2,3,4-tetrahydro-β-carbolin-1-one Oxime (III). To a solution of triacetate (I) (0.34 g) in a mixture of alcohol (7 ml) and water (2 ml) were added hydroxylamine hydrochloride (0.21 g) and ammonium acetate (0.24 g). The reaction mixture was refluxed for 30 h; the end of the reaction was detected by thin-layer chromatography on Silufol (methanol–chloroform, 1:4). The precipitate formed on cooling was filtered off to give oxime (III) (0.16 g, 61%), mp 233-234°C (from ethanol). The compound was poorly soluble in

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.