Like sydnocarb, compounds (IIa, c) were insoluble in water, i.e., they possessed hydrophobic properties and displayed activity peculiar to sydnocarb. Compounds (IIi, j, k) were readily soluble in water, possessed hydrophilic properties, and had no central stimulant activity. Compounds containing a carboxyl group in positions ortho, meta, and para of the benzene ring of the carbanoyl residue, although insoluble in water, must in practice be in the ionized form at a pH in the medium of about 7.5 (i.e., conditions in the organism) which is characteristic of hydrophilic substances.

Consequently, the imparting of hydrophilic properties to a sydnocarb analog by introducing a hydroxy or a carboxy group into the benzene ring of the phenylcarbamoyl substituent led to loss of the pharmacological activity characteristic of sydnocarb. An increase in the distance between the phenyl radical and the exocyclic nitrogen atom led to disappearance of central stimulant activity.

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SYNTHESIS AND ANTIMONOAMINE OXIDASE ACTIVITY OF INKASAN AND ANALOGS OF IT

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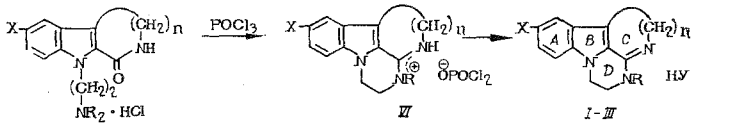
UDC 615.214.32.012.1

During a directed search for new psychotropic agents among tri- and tetracyclic compounds which has been carried out in the All-Union Scientific-Research Institute for Pharmaceutical Chemistry, a series of representatives of new heterocyclic systems which include an indole fragment in their structure have been synthesized. The original antidepressant inkasan was found as a result of the pharmacological investigation (Academicians, M. D. Mashkovskii, N. I. Andreeva of the Academy of Medical Sciences of the USSR) of this group of compounds. Inkasan is 3-methyl-8-methoxy-3H,1,2,5,6-tetrahydropyrazino[1,2,3-ab]-β-carboline hydrochloride (I).

The synthesis of (I) and its analogs (II, III) was effected from the hydrochlorides of N,N-dialkylaminoethyl substituted β-carbolines (IIa, b) and azepino[3,4-b]indole (V) by cyclization of the latter with phosphorus oxychloride and decomposition of the resulting dichlorophosphonates (VI) to the tetracyclic compounds (I-III). The developed scheme for the synthesis of (I-III) has a general nature and is applicable to the preparation of various analogs of (I) including compounds with various sizes of rings C and D:



IV: n=2, R=Me
a) X=OMe, b) X=H
V: n=3, X=H, R=Et

VI

I: n=2, X=OMe, R=Me, HY=HCl
II: n=2, X=H, R=Me, HY=HCl
III: n=3, X=H, R=Et, HY= tartaric acid

Since assessment of the inhibitory action of psychotropic agents in relation to monoamine oxidase (MAO) is one of the most important characteristics of their biological activity,

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TABLE 1. Inhibition of Rat Liver MAO Activity by (I) and Its Analogs (1 mM)

Inhibitor	Inhibition of deamination, % (M ± m)		
	serotonin	tyramine	β-phenylethylamine
Hydrochloride I	76±6	73±4,4	54±2,65
Hydrochloride II	83±4	68±5,8	28±2*
Tartrate III	62±4,2	67±6,2	25±3,1*
Hydrochloride IV	18±4,1**	44±5,8*	42±2,5

Note. Arithmetic mean values of the data of 4 parallel determinations are shown. In control samples (without inhibitor) with serotonin (3 mM), tyramine (3 mM), or β-phenylethylamine (1 mM) as substrate 13.5, 38.2, and 9.3 mole ammonia per mg protein per minute were liberated, respectively. The duration of preincubation of the mitochondrial fraction with inhibitors was 20 min. P was calculated in relation to the percent inhibition with compound (I). One asterisk denotes P = 0.05, two asterisks P = 0.01.

the inhibition of mitochondrial MAO by (II-IV), which are structural analogs of (I), has been studied in comparison with (I) in the present work in continuation of the investigations carried out by us [1].

EXPERIMENTAL (BIOCHEMICAL)

White random-bred male rats weighing 160-180 g were used in experiments. A liver mitochondrial fraction was obtained by differential centrifugation in 0.25 M sucrose of the combined homogenate of the livers of 20-30 animals. The mitochondrial fraction precipitate was suspended in 0.01 M Na, K-phosphate buffer pH 7.4 and was stored frozen at −20°C. Protein content was determined by the method of Lowry [2].

The quantity of ammonia liberated during incubation of the mitochondrial fraction with serotonin creatine sulfate (Reanal, Hungary), tyramine hydrochloride (Merck, West Germany), or β-phenylethylamine hydrochloride at 37°C for 20 min in 0.2 M Na, K-phosphate buffer pH 7.4 served as a measure of MAO activity. Other conditions of the incubation, fixation of samples, and ammonia determination with the aid of Nessler reagent have been described previously in [3].

RESULTS AND DISCUSSION

All the investigated compounds inhibited MAO activity at a concentration of 1 mM (Table 1). However, compound (II), which differed from (I) by the absence of a methoxy group, inhibited the deamination of β-phenylethylamine to a greater extent than (I). Compound (IV), which in contrast to (I) is a tricyclic and not a tetracyclic compound, inhibited only the deamination of serotonin to a smaller extent but retained the inherent property of (I) to inhibit the deamination of β-phenylethylamine to a significant degree.

According to contemporary ideas [4] serotonin is a specific substrate for type A MAO, β-phenylethylamine is specifically deaminated by type B MAO, while tyramine is a substrate of both basic types of MAO.

In subsequent experiments we investigated the dependence of the degree of inhibition of the oxidative deamination of serotonin (Fig. 1) or β-phenylethylamine (Fig. 2) on the final molar concentration in the test sample of (I) or its structural analog. As follows from the results obtained the investigated structural analogs of (I) were superceded by it in the expression of the property to inhibit MAO activity. According to our data (Fig. 3) (I) is a

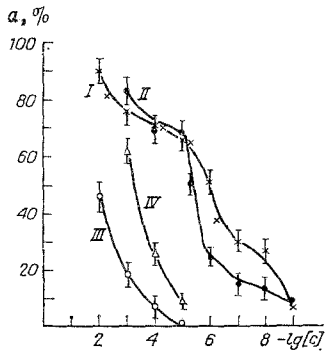

Fig. 1

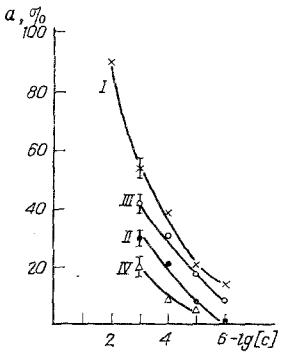

Fig. 2

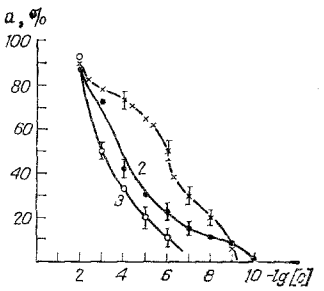

Fig. 3

Fig. 1. Dependence of the degree of inhibition of serotonin (3 mM) deamination by rat liver mitochondrial MAO on concentration of (I) and its structural analogs. Here and in Figs. 2 and 3 the negative logarithm of the concentration of compound (−log[C]) is on the abscissa, inhibition of deamination (a, %) is on the ordinate. Numbering of compounds and preincubation conditions are shown in Table 1.

Fig. 2. Dependence of the degree of inhibition of β-phenylethylamine (1 mM) deamination by rat liver mitochondrial MAO on the concentration of (I) and its structural analogs.

Fig. 3. Dependence of the degree of inhibition of the deamination of 1) serotonin; 2) tyramine; and 3) β-phenylethylamine by rat liver mitochondrial MAO on the concentration of (I).

selective inhibitor of type A MAO activity. To inhibit by 50% the deamination reaction of serotonin a concentration of (I) of 1 μM is adequate but to inhibit the deamination of β-phenylethylamine to the same extent the concentration of (I) in the system must be increased 1000 times. To inhibit by 50% the deamination of tyramine in rat liver mitochondrial fraction samples, the final concentration of (I) must be increased to only 100 times the concentration of this inhibitor which blocks the deamination of serotonin by 50% (Fig. 3). These data are in accordance with the generally accepted concept [4] of tyramine as a substrate oxidized by MAO of types A and B.

It was established by us previously [1] that inhibition of mitochondrial MAO was not detected during preincubation of (I) with mitochondria. In the course of further study it was noted that dialysis of samples containing (I) (10 mM) increased the tyramine deaminase activity by 69% towards the initial level while the serotonin or β-phenylethylamine deaminase activity under the same conditions of analysis returned towards the initial level by only 34 or 23% (Table 2). These data contradict the generally accepted opinion on the matter of MAO multiplicity and may be explained on the concept of the existence of an independent active center (or form) of the enzyme participating in the deamination of tyramine [5]. In accordance with contemporary ideas [6] specific inhibitors of type A MAO activity both irreversible (chlorgilin, derivatives of N-substituted cyclopropylamine such as the inhibitor Lilly 51641 [7], and reversibly (derivatives of β-carboline such as harmine or harmaline, of oxazolidinone such as MD 780515, or 4-aminophenylethylamine) [8-10] are preferred for expression of antidepressant effect over specific type B MAO inhibitors. Consequently in any plan for the design of new highly effective psychotropic agents the search for selective inhibitors of type A MAO activity is an urgent problem.

EXPERIMENTAL (CHEMICAL)*

IR spectra of the synthesized compounds were taken on a Perkin–Elmer (England) and UR-10 (East Germany) instruments and UV spectra on an EPF-3 spectrophotometer.

1-Keto-10-[β-(N,N-dimethylamino)ethyl]-1H,2,3,4,5-tetrahydroazepino[3,4-b]indole (V). Sodium hydride (3 g) was added in portions to a suspension of 1-keto-1H,2,3,4,5-tetrahydroazepino[3,4-b]indole (20 g) in dry dimethylformamide (120 ml) at 25°C and the mixture was heated at 30°C for 2 h (50°C, 30 min). β-Dimethylaminoethyl chloride (14 g) was added drop-

*A. V. Zaitseva participated in carrying out the experimental section.

TABLE 2. Reversibility of Inhibition of Rat Liver Mitochondrial MAO Activity by Inkasan (10 mM)

Substrate	Inhibition of deamination, %		Δ
	before dialysis	after dialysis	
Serotonin	90	56	—34
Tyramine	94	25	—69
β-Phenylethylamine	87	64	—23

Note. Mean values of data of 4 parallel determinations are given. Dialysis was carried out for 48 h against 5 changes of a 50-fold volume of 0.1 M Na, K-phosphate buffer pH 7.4.

wise to the reaction mass which was heated to 50-55°C, stirred for 4 h, and then cooled. The mixture was pured into 50% acetic acid (100 ml), filtered, the solution made alkaline (pH 9.0) with 15% aqueous ammonia, and extracted with benzene. The extract was washed with water, dried with calcined potassium carbonate, evaporated to dryness in vacuum, the solid rubbed with ether, filtered, and dried. Base (V) was obtained in 52.4% yield, mp 122-123°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 3070, 3200 (NH), 1660 (CO amide). UV spectrum (alcohol), λ_{max}, nm (log ε): 228 (4.4), 294 (4.17). Found, %: C 70.83; H 7.50; N 15.56. $C_{16}H_{21}N_3O$. Calculated, %: C 70.84; H 7.75; N 15.50. Hydrochloride of (V) mp 253-254°C (from alcohol). Found, %: Cl 11.28; N 14.00. $C_{16}H_{21}N_3O \cdot HCl$. Calculated, %: Cl 11.55; N 13.65.

3-Methyl-8-methoxy-3H,1,2,5,6-tetrahydropyrazino[1,2,3-ab]-β-carboline Dichlorophosphate (VI) (n = 2, x = OMe, R = Me). A mixture of (IVa) hydrochloride (33.65 g) and phosphorus oxychloride (280 ml) was boiled for 4 h. A solution formed while heating from which a bright yellow solid precipitated. After cooling, the solid was filtered off, washed with ether, and dried. Compound (VI) (n = 2, x = OMe, R = Me) was obtained in 81.4% yield, mp 196-198°C. IR spectrum, ν, cm^{-1}: 1660 (C=N), 3130, 3190 (NH). The compound was hygroscopic. Found, %: C 46.48; H 4.78; N 10.94; P 7.96. $C_{15}H_{18}Cl_2N_3O_3P$. Calculated, %: C 46.15; H 4.61; N 10.76; P 7.94.

3-Methyl-8-methoxy-3H,1,2,5,6-tetrahydropyrazino[1,2,3-ab]-β-carboline Hydrochloride (I). A mixture of (VI) (n = 2, x = OMe, R = Me) and absolute alcohol (200 ml) was boiled for 1 h. A solution was formed during heating from which a solid precipitated after 5-10 min. The mass was cooled in ice, filtered, the solid washed with absolute alcohol, and dried. Compound (I) was obtained in 95% yield, mp 310-312°C (from alcohol). IR spectrum, ν, cm^{-1}: 1660 (C=N). Found, %: C 61.65; H 6.00; Cl 12.11; N 14.37. $C_{15}H_{17}N_3O \cdot HCl$. Calculated, %: C 61.75; H 5.83; Cl 12.17; N 14.40.

Compound (I) base was obtained by treating a solution of (I) hydrochloride in water with dilute ammonia in 100% yield, mp 174-176°C (from absolute alcohol). IR spectrum, ν, cm^{-1}: 1600 (C=N). UV spectrum (alcohol), λ_{max}, nm (log ε): 322 (4.3), 234 (4.28). Found, %: C 70.40; H 6.74; N 16.50. $C_{15}H_{17}N_3O$. Calculated, %: C 70.58; H 6.66; N 16.47.

Compound (II) base was synthesized in a similar manner in 70% yield, mp 102-103°C. Found, %: C 74.90; H 6.53; N 18.70. $C_{14}H_{15}N_3$. Calculated, %: C 74.66; H 6.66; N 18.66.

Compound (II) hydrochloride had mp above 350°C. Found, %: Cl 13.56; N 15.65. $C_{14}H_{15}N_3 \cdot HCl$. Calculated, %: Cl 13.57; N 16.06. Compound (III) base was synthesized in a similar manner from (V) in 40% yield mp 131-132°C (from aqueous alcohol). Found, %: C 76.12; H 7.73; N 16.86. $C_{16}H_{19}N_3$. Calculated, %: C 75.88; H 7.51; N 16.60.

Compound (III) tartrate had mp 194-195°C (from alcohol). Found, %: C 59.57; H 6.43. $C_{20}H_{25}N_3O_6$. Calculated, %: C 59.55; H 6.23.

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SYNTHESIS AND STUDY OF THE BIOLOGICAL PROPERTIES OF DERIVATIVES OF 5-CARBOXYMETHYLTHIAZOLIDINE-2,4-DIONE AND OF THIOCARBOHYDRAZIDE

M. A. Kaldrikyan, A. V. Khekoyan, Yu. Z. Ter-Zakharyan, R. V. Paronikyan, and G. M. Stepanyan

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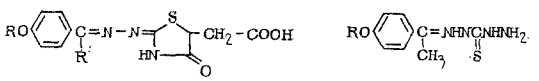
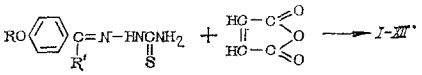
It is known that the thiosemicarbazones of various carbonyl compounds are biologically active substances, and, in particular, possess antiviral properties [1]. The majority of thiosemicarbazones with a high antiviral activity, and also some thiosemicarbazones of α-(N-heteryl)carbaldehydes with antitumoral activity [2], contain free =NNHC(S)NH_2 groupings. It has been established that the introduction of the latter into a cyclic system leads to heterocyclic compounds with a thiourea skeleton which are interesting subjects of pharmacological investigation [3].

On the basis of the above facts, we have found it desirable to use 4-alkoxybenzaldehydes and 4-alkoxyacetophenones in the synthesis of new derivatives of 5-carboxymethylthiazolidine-2,4-dione and of thiocarbohydrazide with the general formulas:



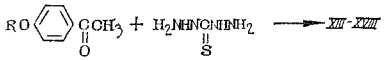
I — XII (for R and R' see Table 2) XIII — XVIII (for R and R' see Table 2)

The main starting materials for the synthesis of compounds (I-XII) were the thiosemicarbazones of 4-alkoxybenzaldehydes and of 4-alkoxyacetophenones obtained by boiling equimolar amounts of the carbonyl compounds with thiosemicarbazide in aqueous alcoholic solution [1, 5]. The latter were caused to react with maleic anhydride in chloroform.



The synthesis of analogous compounds in benzene has been described in the literature [1], but our experiments showed that this always gives mixtures of the initial compounds and the final products. The use of chloroform in place of benzene leads to fairly pure derivatives of 5-carboxymethylthiazolidine-2,4-dione with high yields.

The thiocarbohydrazones of 4-alkoxyacetophenones were obtained by the reaction of the 4-alkoxyacetophenones with thiocarbohydrazide as described in the literature [6].



A. L. Mndzhoyan Institute of Fine Organic Chemistry of the Academy of Sciences of the Armenian SSR, Erevan. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 15, No. 5, pp. 62-66, May, 1981. Original article submitted July 9, 1980.

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