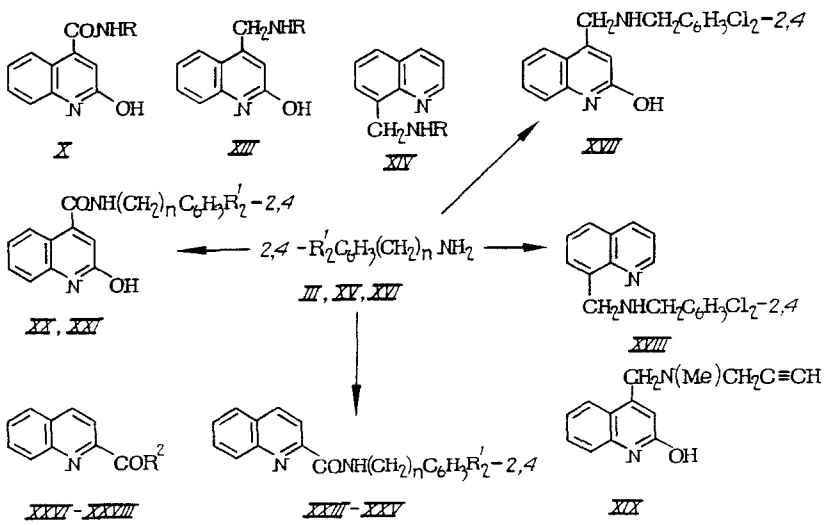
MONOAMINE OXIDASE INHIBITORS BASED ON 2-, 4-, AND 8-SUBSTITUTED QUINOLINES

I. N. Gracheva, D. I. Ioffina,
A. I. Tochilkin, and V. Z. Gorkin

UDC 615.355:577.152.1.042.21.07

The search for new selective inhibitors of monoamine oxidase (MAO) among quinoline derivatives has taken on special interest in recent years in connection with the modern achievements in the study of the chemistry of natural modulators of MAO activity [3]. Continuing the work along this line we synthesized compounds in which the quinoline ring is bonded to aralkylamines of various structures, including those containing aromatically bound chlorine. The selection of these compounds was due to the fact that the aminomethylquinolines with N-propionyl groups that we had produced earlier [2, 6] are effective MAO inhibitors. Moreover, the antimonoamine oxidase activity of benzylamine derivatives is well known [15]. In view of this, the bicyclic compounds that we synthesized might prove useful.

The reaction of 2,4-dichlorobenzyl alcohol with conc. HCl is used to produce 2,4-dichlorobenzyl chloride (I), which is converted to N-(2,4-dichlorobenzyl)phthalimide (II) by the reaction with potassium phthalimide. Hydrazinolysis converts the phthalimide (II) to 2,4-dichlorobenzylamine (III). The reaction of the chloride I with glycol in the presence of NaOH yields 2-hydroxy(2,4-dichlorobenzyl)ethyl ether (IV) [8]. 2-Chloro-(2,4-dichlorobenzyl) ethyl ether (V) is produced by the reaction of the hydroxyether IV with $SOCl_2$. The chloride V is converted by the Gabriel reaction to the corresponding phthaloyl derivatives (VI), hydrazinolysis of which gives 2-(2,4-dichlorobenzyloxy)ethylamine (VII). We used the amine VII as the key compound for further syntheses of reversible and irreversible inhibitors and also studied it as an independent MAO inhibitor. Propargylation of the amine (VII) leads to $2,4\text{-}Cl_2C_6H_3CH_2OCH_2CH_2NHCH_2C{\equiv}CH$ (VIII). The interaction of compound VII with 2-hydroxy-4-quinolinecarboxylic acid (IX) in DMFA in the presence of dicyclohexylcarbodiimide yields 2-hydroxy-4-[N-(2,4-dichlorobenzyloxyethyl)carboxamido]-quinoline (X). The reaction of the amine VII with 2-hydroxy-4-bromoethylquinoline (XI) [7] or with 8-bromomethylquinoline (XII) [12] gives 2-hydroxy-4-[N-(2,4-dichlorobenzyloxyethyl)aminomethyl]quinoline (XIII) or 8-[N-(2,4-dichlorobenzyloxyethyl)aminomethyl]quinoline (XIV).



R = 2-(2,4-dichlorobenzyloxy)ethyl (X, XIII, XIV); R^1 = Cl(III, XX, XXIII), H(XV, XVI, XXI, XXIV, XXV); R^2 = $(NH(CH_2)_2NMe_2$(XXVI), morpholino (XXVII), piperidino (XXVIII), n = 1 (II, XV, XX, XXIII, XXIV), 2 (XVI, XXI, XXV).

Institute of Biological and Medical Chemistry, Academy of Medical Sciences of the USSR, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 25, No. 3, pp. 18-21, March 1991. Original article submitted March 6, 1990.

 0091-150X/91/2503-0160$12.50

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Yield, %	Mp, °C	Gross formula	IR spectrum, ν_{max}, cm^{-1}
II	65	182—4	$C_{15}H_9Cl_2NO_2$	1730, 1780 (CONCO)
III*	96	180—2	$C_7H_8Cl_3N$	1660, 3320 (NH)
IV	91	Oil	$C_9H_{10}Cl_2O_2$	1250 (COC)
V	84	Bp 144-6	$C_9H_9Cl_3O$	1250 (COC)
VI	80	79—1	$C_{17}H_{13}Cl_2NO_3$	1730, 1780 (NCO)
VII*	69	162—5	$C_9N_{12}Cl_3NO$	1660 (CO), 3300 (NH)
VIII	45	Oil	$C_{12}H_{13}Cl_2NO$	2140 (CH≡C), 3340 (C≡CH)
X	40	164—6	$C_{19}H_{16}Cl_2N_2O_3$	1670 (CO)
XIII	51	162—5	$C_{19}H_{18}Cl_2N_2O_2$	1280 (COC)
XIV	47	159—61	$C_{19}H_{17}Cl_2N_2O$	1260 (COC)
XVII	53	228—30	$C_{17}H_{13}Cl_2O$	
XVIII	46	130—2	$C_{17}H_{15}Cl_2N_2$	
XIX	38	Oil	$C_{14}H_{14}N_2O$	2102 (C≡C), 3220 (C≡CH)
XX	43	208—10	$C_{19}H_{18}Cl_2N_2O$	1650 (CO)
XXI	34	95—7	$C_{18}H_{16}N_2O_2$	1650 (CO)
XXIII	61	72—5	$C_{18}H_{16}N_2O$	1680 (CO), 3450 (NH)
XXIV	64	122—4	$C_{19}H_{19}Cl_2N_2O$	1680 (CO), 3480 (NH)
XXV	49	141—3	$C_{17}H_{13}Cl_2N_2O$	1680 (CO), 3480 (NH)
XXVI	52	87—9	$C_{14}H_{17}N_3O$	1680 (CO), 3470 (NH)
XXVII	58	88—9	$C_{14}H_{14}N_2O_2$	1700 (CO)
XXVIII	48	82—4	$C_{15}H_{16}N_2O$	1700 (CO)

*The characteristics are given for the hydrochloride.

A number of inhibitors were synthesized on the basis of benzylamine (XV), phenylethylamine (XVI), and the 2,4-dichlorobenzylamine (III) described above. Alkylation of the latter by bromomethyl derivatives XI or XII yields 2-hydroxy-4-[N-(2,4-dichlorobenzyl)aminomethyl] quinoline (XVII) or 8-[N-(2,4-dichlorobenzyl)aminomethyl]quinoline (XVIII). The bromomethyl derivative XI, reacting with M-methyl-N-2-propynylamine, gives an irreversible MAO inhibitor — 2-hydroxy-4-[N-methyl-N-(2-(2-propynyl)aminomethyl]quinoline (XIX). Condensation of the acid IX with the amine III, analogously to compound X, yields 2-hydroxy-4-[N-(2,4-dichlorobenzyl)carboxamido]quinoline (XX). Analogously, the reaction of the amine XVI with the acid IX leads to 2-hydroxy-4-[N-(2-phenetyl)carboxamido]quinoline (XXI).

Using the acid chloride of quinaldinic acid (XXII) and the amines III, XV, and XVI, we synthesized 2-[N-(2,4-dichlorobenzyl)-, 2-[N-(benzyl)-, and 2[N-(2-phenetyl)carbozamido] quinolines (XXIII-XXV). Analogously, from N,N-(dimethyl)ethylenediamine, morpholine, piperidine, and the acid chloride XXII we obtained 2-[N-(N,N-dimethylaminoethyl)carboxamido]quinoline (XXVI), as well as the morpholide and piperidide of quinoline-2-carboxylic acid (XXVII) and (XVIII).

The characteristics of the compounds synthesized are cited in Table 1.

RESULTS AND DISCUSSION

The compounds obtained were studied as inhibitors of MAO from rat liver mitochondria (Table 2). Although the number and structure of the investigated compounds do not permit an unambiguous estimation of the relationship between the structure and antimonoamine oxidase activity, certain patterns can be noted.

In most cases compounds with a quinoline ring exhibit affinity for type A MAO. For example, quinoline hydrochloride at a concentration of 10^{-5} M inhibits the deamination of serotinin (a substrate of type A MAO) at 28% [6]. Methylquinolines, their quaternary salts, and other derivatives and analogs exhibit the properties of reversible inhibitors of type A MAO from mitochondria of human placenta [5, 9, 10] and, moreover, exhibit the properties of neurotoxins, which is also associated with their antimonoamine oxidase activity [11,14].

Just as we should have expected, the propyl derivatives of 2-hydroxyquinoline XIX exhibits selective affinity for type A MAO: it binds to the enzyme irreversibly and analogously to the acetylenic inhibitors described previously [6]. Among the reversible inhibitors, variation of the substituents leads to a change in the antimonoamine oxidase properties in individual cases. Thus, compounds X, XVII, and XX, substituted in the 4- and 8-positions and containing a dichlorobenzyl fragment, selectively block type B MAO, which is in good agreement with the usual theory of the influence of halogen atoms on selectivity [13]. In view of this, the loss of selectivity of the action of compounds VII and VIII — analogs of

TABLE 2. Antimonoamine Oxidase Activity of the Compounds Synthesized

Compound	Final concentration of inhibitor, M			I_{50}, M
	$1 \cdot 10^{-4}$	$10 \cdot 10^{-5}$	$1 \cdot 10^{-6}$	
VII	75/100	24/38	0/5	$3{,}2 \cdot 10^{-5}/1{,}6 \cdot 10^{-5}$
VIII	98/100	89/100	24/0	$2{,}5 \cdot 10^{-6}/3{,}2 \cdot 10^{-6}$
X	0/72	0/10	—/—	$—/5{,}01 \cdot 10^{-5}$
XIII	0/0	0/0	0/0	—
XIV	0/0	0/0	0/0	—
XVII	0/41	0/0	4/0	—
XVIII	7/73	0/32	0/0	—
XIX	98/2	43/1	2/1	$1{,}3 \cdot 10^{-5}/—$
XX	0/31	0/13	—	—
XXI	74/0	63/0	24/0	$5 \cdot 10^{-6}/—$
XXIII	80/70	74/40	51/0	$1 \cdot 10^{-6}/2{,}2 \cdot 10^{-5}$
XXIV	77/0	55/0	43/0	$4 \cdot 10^{-6}/—$
XXV	80/0	70/0	43/0	$2 \cdot 10^{-6}/—$
XXVI	100/0	86/0	26/0	$2{,}5 \cdot 10^{-6}/—$
XXVII	0/0	0/0	0/0	—
XXVIII	0/0	0/0	0/0	—

Notes. Arithmetic mean values of 5 experiments are presented. In the numerator: values of the substrate serotonin; in the denominator, for 2-phenylethylamine.

chlorgyline [N-(2,4-dichlorophenoxypropyl-3)-N-methyl-2-propynylamine] can be explained, although ambiguously, by changes in the structure of the side chain (replacement of the group $ArOCH_2 \rightarrow ArCH_2O$, where Ar = 2,4-dichlorophenyl). The 2-hydroxyquinoline derivative XXI, structurally close to compounds X, XVII, and XX, extremely selectively blocks the activity of type A MAO. Possibly in this case a vital role is played by the absence of chlorine atoms in the molecule. In most cases, among derivatives substituted in the 4- and 8-positions, the length and structure of the connecting chain is of vital importance for the activity: a bond through the CONH group is preferable (compounds X, XX, and XXI), which corresponds fully to the data of [13]. The manifestation of inhibiting properties by compounds X, XX, and XXI, despite the absence of other basic sites than the quinoline nitrogen atom, additionally confirms the vital role of the quinoline ring in the creation of antimonoamine oxidase activity.

All the derivatives of quinaldinic acid selectively interact with type A MAO. The values of I_{50} for compounds XXIV, XXV, and XXVI is virtually the same ($1 \cdot 10^{-6}$-$4 \cdot 10^{-6}$) and does not depend on the substituent at the CH_2 group of the hydrocarbon chain. Thus, lengthening the connecting chain between the quinoline and benzene rings, for example, in the inhibitors XVII and XVIII, leads to the completely inactive compounds XIII and XIV, respectively. An analogous effect is produced by the presence of voluminous cyclic groups next to the quinoline ring in the case of minimum chain length (compounds XXVII and XXVIII); in the latter case, nonetheless, we cannot exclude the absence of an unsubstituted amide group.

Thus, the synthesis of compounds with various combinations of quinoline and benzene rings, containing definite substituents, may prove useful in the search for new selective MAO inhibitors, close in structure to possible natural modulators of MAO functions.

EXPERIMENTAL (CHEMICAL)

The IR spectra were recorded on a Unicam SP-1000 instrument (Great Britain) in a tablet of KCl. The PMR spectra were obtained on a Tesla BS-567 spectrometer (100 MHz) (Germany) in $CDCl_3$, with a TMS internal standard. The purity of the substances was monitored on Silufol plates. Systems for chromatography: benzene–ethyl acetate–AcOH, 100:50:1 (A), $CHCl_3$–MeOH, 10:1 (B), MeCN – 25% NH_4OH, 9:1 (C). The values found in elementary analyses correspond to those calculated.

N-(2,4-Dichlorobenzyl)phthalimide (II). A mixture of 18.5 g (0.1 mole) 2,4-dichlorobenzyl chloride [8] and 18.5 g (0.1 mole) potassium phthalimide in DMFA was heated at 115-120°C until the initial chloride disappeared (according to thin-layer chromatography), the mixture was poured out into water, the precipitate formed was removed, washed with water, dried over P_2O_5, and a yield of 20 g of the imide II was obtained.

2,4-Dichlorobenzylamine (III). A solution of 5 g (16 mmoles) of the phthaloyl derivative II in 5 ml of alcohol with 5 ml of hydrazine hydrate was boiled. After 30 min, 20 ml of dil. HCl (1:1) was added to pH 1-2, heated for another 30 min, the precipitate formed was removed, washed with hot HCl, with hot water, filtered, 10% NaOH was added to the filtrate to pH 10-11, the mixture was extracted with ether, dried with $MgSO_4$, evaporated, and a yield of 2.75 g 2,4-dichlorobenzylamine III was obtained.

2-Hydroxy-(2,4-dichlorobenzyl)ethyl Ether (IV). To 100 ml (2.8 mmole) of glycol we added 7.6 g of NaOH, mixed until it dissolved completely at 50-60°C, gradually added 33.7 ml (0.17 mole) of 2,4-dichlorobenzyl chloride I to the mixture, heated for 1 h at 80°C, poured out into water, removed the organic layer, extracted the aqueous layer with benzene; the extract was combined with the organic layer, dried with $MgSO_4$, the solvent evaporated, and a yield of 31 g of the ether IV was obtained.

2-Chloro(2,4-dichlorobenzyl)ethyl Ether (V). To 35.5 g (1.6 moles) of the ether IV in 50 ml of dichloroethane we added 12 ml (1.6 moles) of $SOCl_2$, boiled for 1.5 h, poured out into water, removed the organic layer, extracted the aqueous layer with dichloroethane, combined the extracts with the organic layer, washed with a 5% solution of $NaHCO_3$, with water, dried with $MgSO_4$, and obtained a yield of 32.4 g of the ether V. Bp 154°C/10 mm, n_D^{20} 1.5470. According to the data of [8], bp 158-161°C/12 mm, n_D^{20} 1.5483.

2-(2,4-Dichlorobenzyloxy)-N-phthaloylethylamine (VI) was produced analogously to the phthalimide II from the ether V.

2(2,4-Dichlorobenzyloxy)ethylamine (VII) was produced analogously to III from the phthaloyl derivative VI.

N-(2-Propynyl)-2-(2,4-dichlorobenzyloxy)ethylamine (VIII). A mixture of 1.8 g (8.2 mmoles) of the amine VII and 970 mg (8.1 mmoles) of propargyl bromide in benzene was left at ~20°C for 24 h; the precipitate of the hydrobromide of VII that formed was removed and washed with benzene; yield of VII 1.02 g (83%), mp 165-167°C. The filtrate was evaporated, the residue (1.2 g) extracted with 40 ml of 0.1 N HCl, the hydrochloric acid solution extracted with benzene, the extract combined with the oil that formed after treatment with HCl, dried with $MgSO_4$, evaporated, and an unidentified mixture of compounds (720 mg) was obtained. The hydrochloric acid extract was evaporated, and the hydrochloride of VIII was obtained. Yield 610 mg. The hydrochloride was dissolved in 15 ml of water, alkalinized with 250 mg KOH in 2 ml of water, the mixture extracted with benzene, dried with anhydrous Na_2CO_3, evaporated, and 470 mg VIII was obtained in the form of an oil.

2-Hydroxy-4-[N-(2,4-dichlorobenzyloxyethyl)carboxamido]quinoline (X). To 190 mg (1 mmole) of 2-hydroxy-4-quinolinecarboxylic acid (IX) in DMFA we added 220 mg (1 mmole) of the amine VII and 210 mg (1 mmole) dicyclohexylcarbodiimide; after 24 h at ~20°C, the precipitate formed was removed, the mother liquor poured out into 50 ml of water, extracted with ethyl acetate, the extract washed with a 5% solution of $NaHCO_3$, dried with Na_2SO_4, the precipitate triturated with ether, and 200 mg of the quinoline X was obtained and recrystallized from a mixture of alcohol and ether (1:1).

2-Hydroxy-4-[N-(2,4-dichlorobenzyloxyethyl)aminomethyl]quinoline (XIII). A mixture of 520 mg (2.1 moles) 2-hydroxy-4-bromomethylquinoline and 500 mg (2.2 mmoles) of the amine VII in 10 ml of a $CHCl_3$-ethanol mixture (1:1) was boiled; after 2 h the precipitate formed was removed, treated with 25% NH_4OH, extracted with $CHCl_3$, and crystallized from ethanol. Yield 520 mg. PMR spectrum, δ, ppm: 2.2 s (CH_2), 7.5-8.3 m (aromatic protons, ap).

8-[N-(2,4-Dichlorobenzyloxyethyl)aminomethyl]quinoline (XIV) was produced analogously to XIII from 8-bromomethylquinoline (XII) and the amine VII. PMR spectrum, δ, ppm: 2.5 s (CH_2), 3.2 m (NH), 6.9-8.4 m (ap).

2-Hydroxy-4-[N-(2,4-dichlorobenzyl)aminomethyl]quinoline (XVII) was produced analogously from the bromomethyl derivative of XI and the amine III. PMR spectrum, δ, ppm: 2.5 s (CH_2), 3.1 m (NH), 7.4-8.3 m (ap).

8-[N-(2,4-Dichlorobenzyl)aminomethyl]quinline (XVIII) was produced analogously from the bromomethyl derivative of XII and the amine III. PMR spectrum, δ, ppm: 4.1 m (CH_2CH_2), 4.33 s (CH_2NH), 5.16 s (OCH_2), 5.5 s (NH), 7.6-8.2 m (ap.).

2-Hydroxy-4-[(N-methyl-N-2-propynyl)aminomethyl]quinoline (XIX). A mixture of 478 mg (2 mmoles) 2-hydroxy-4-bromomethylquinoline XI and 140 mg (2 mmoles) N-methyl-N-2-propynylamine

in 20 ml MeOH was heated at 50°C in the presence of 280 mg (2 mmoles) K_2CO_3; after 3 h the precipitate was removed, the filtrate evaporated, and 300 mg of the aminomethylquinoline XIX was obtained.

2-Hydroxy-4-[N-(2,4-dichlorobenzyl)carboxamido]quinoline (XX) was produced analogously to compound X from the acid IX and the amine III.

2-Hydroxy-4-[N-2-(phenethyl)carboxamido]quinoline (XXI) was produced analogously to X from the amine XVI and the acid IX.

2-[H-(2,4-Dichlorobenzyl)carboxamido]quinoline (XXIII). To a solution of 280 mg (2 mmoles) of the chloride of 2-quinolinecarboxylic acid (XXII) in dry benzene we gradually added 400 mg (3.5 mmoles) of the amine III. After 24 h the precipitate was removed, and 320 mg of the derivative XXIII was obtained.

2-(N-Benzylcarboxamido)quinoline (XXIV) was produced analogously from the benzylamine XVI [sic] and the acid chloride XII. PMR spectrum, δ, ppm: 3.67 d ($CH_2C_6H_5$) m (ap).

2-(N-Phenetylcarboxamido)quinoline (XXV) was produced analogously from the phenylethylamine XVI [sic] and the acid chloride XII. PMR spectrum, δ, ppm: 3.7 m (CH_2NH), 2.9 m ($CH_2C_6H_5$), 7.4-8.4 m (ap).

2-[N-(N,N-Dimethylaminoethyl)carboxamido]quinoline (XXVI) was produced analogously from N,N-(dimethyl)ethylenediamine and the acid chloride XXII. PMR spectrum, δ, ppm: 2.25 s (CH_3), 2.5 t (CH_2CH_2), 3.57 t (CH_2NH), 8.5 s (NH), 7.2-8.3 m (ap).

The morpholide of quinoline-2-carboxylic acid (XXVII) was produced analogously from morpholine and the acid chloride XXII. PMR spectrum, δ, ppm: 4.0 m (CH_2), 7.2-8.2 m (ap).

The piperidine of quinoline-2-carboxylic acid was produced analogously from piperidine and the acid chloride XII. PMR spectrum, δ, ppm: 1.68 m (CH_2), 7.5-8.6 m (ap).

Compounds II–IV, VI, XIX, XXI are homogeneous in system A, VII, VIII, XXII in system B, and X, XIII, XIV, XVII, XVIII, XX, XXIV–XXVI in system C.

EXPERIMENTAL (BIOLOGICAL)

Fragments of rat liver mitochondrial membranes, produced as described earlier [1], were used as the source of MAO. The MAO activity was determined by a modified method of [4]. The [^{14}C]creatinine sulfate of serotonin was used as the substrate of type A MAO, and [^{14}C] benzylamine hydrochloride was used as the substrate of type M MAO. Preincubation with inhibitors was performed for 30 sec at 25°C; the amount of protein was 0.3 mg/ml, final volume of the samples 0.1 ml in 0.5 M phosphate buffer solution, pH 7.4. The final concentrations of the substrates were $3 \cdot 10^{-5}$ M, time of incubation 30 min at 37°C. Fixation of the samples was performed by adding 20 μl of 2 M citric acid (in experiments with serotonin) or 0.5 M HCl (in experiments with benzylamine). The specific radioactivities of serotonin and benzylamine were 2.64 and 5.5 Ci/mole, respectively.

LITERATURE CITED

1. V. Z. Gorkin, Modern Methods in Biochemistry [in Russian], V. N. Orekhovich (ed.), Vol. 2, Moscow (1968), p. 155.
2. I. N. Gracheva, I. R. Kovel'man, A. I. Tochilkin, et al., Khim.-farm. Zh., No. 9, 1055-1060 (1983).
3. L. N. Ovchinnikova, Vopr. Med. Khim., No. 6, 16-23 (1988).
4. V. A. Pekkel', L. N. Aksenova, and A. N. Boimirzaev, Lab. Delo, No. 7, 491-495 (1987).
5. A. A. Prikulis, B. A. Grinberg, V. N. Bashko, and D. E. Zeilya, Izv. Akad. Nauk LatvSSR, No. 3, 362-364 (1989).
6. K. K. Shatemirova, G. A. Davydova, I. V. Verevkina, and A. I. Tochilkin, Vopr. Med. Khim., 23, No. 5, 609-618 (1977).
7. D. G. Cook, R. E. Bowen, P. Sorter, and E. Daniels, J. Org. Chem., 26, 4949-4951 (1961).
8. M. Kulka and F. G. Van Stouk, Can. J. Chem., 33, 1130-1134 (1955).
9. M. Naoi, Y. Hirata, and T. Nagatsu, J. Neurochem., 48, No. 3, 709-712 (1987).
10. M. Naoi and T. Nagatsu, Life Sci., 40, 1075-1082 (1987).
11. M. Naoi and T. Nagatsu, J. Neurochem., 50, NO. 4, 1105-1109 (1988).
12. B. Prijs, R. Yoll, and R. Ainderling, Helv. Chim. Acta, 37, 90-94 (1954).
13. M. Strolin and B. P. Dossert, Trends Pharm. Sci., 6, 246-251 (1985).

14. S. Vleichka, Farmatsiya, 23, No. 6, 6-8 (1973).
15. C. H. Williams and H. Carvell, Biochem. Pharmacol., 33, No. 2, 334-337 (1984).

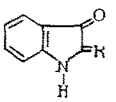
NEW SELECTIVE INHIBITORS OF MEMBRANE-BOUND MONOAMINE OXIDASES IN THE SERIES OF INDOLIN-3-ONE DERIVATIVES

N. S. Kamyshanskaya, V. Yu. Mershakov, and V. Z. Gorkin

UDC 615.214.32:577.152.143].012.1

Monoamine oxidase (MAO) (EC 1.4.3.4) is a family of membrane-bound enzymes, which catalyze the oxidative deamination of biogenic amines, in particular, such indolylalkylamines as tryptamine and 5-hydroxytryptamine (serotonin). The ability to inhibit the action of these enzymes is possessed by a whole series of compounds known as MAO inhibitors, which are used as therapeutic agents in various pathological states. In recent years many reports have been published on the existence of an endogenous factor, also capable of inhibiting monoamine oxidase activity, in the cytosol of various tissues, plasma, urine, and spinal fluid [5-8, 10, 13]. This endogenous inhibitor was named "tribulin" [8, 9]. Subsequently tribulin was identified with isatin [11]. It was established in experiments in vitro that isatin derivatives are reversible, competitive inhibitors of MAO [4], while isatin itself is a more powerful inhibitor of type B MAO (substrate β-phenylethylamine) [11].

The purpose of this work was to search for new, selectively acting MAO inhibitors in the series of indolin-3-one (indoxyl) derivatives.



I - X

R = O(I), CHC_6H_5 (II), CHC_6H_4-4-OMe (III), CHC_6H_3-3,4-$(OMe)_2$ (IV), CHC_6H_4-2-OMe (V), CHC_6H_4-4-iso-Pr (VI), CHC_6H_4-4-Br (VII), CHC_6H_4-2-F (VIII), CHC_6H_4-4-NO_2 (IX), furyl-2-methylene (X), cyclohexene (XI), acetylethoxycarbonylmethylene (XII), and cyanoethoxycarbonylmethylene (XIII).

The investigated 2-arylmethyleneindolin-3-ones (I-IX), 2-(2-furyl)-methyleneindolin-3-one (X), 2-cyclohexeneindolin-3-one (XI), 2-acetylethoxycarbonylmethyleneindolin-3-one (XII), and 2-cyanoethoxylcarbonylmethylene-indolin-3-one (XIII) were described previously and were synthesized according to the well known procedures [2, 12].

EXPERIMENTAL (BIOLOGICAL)

The mitochondrial fractions of rat brain homogenates were isolated by the method of differential centrifugation [1]. The action of inhibitors was studied within a wide range of concentrations (10^{-6}-10^{-3} M), dissolving them in dimethyl sulfoxide; their ability to inhibit monoamine oxidase activity was measured by a radiometric method [3]. The substrates used were [^{14}C]serotonin and [^{14}C]-β-phenylethylamine (from Amersham, England); the final concentrations and specific radioactivities were 27.8 μM, 58 Ci/mole, and 13.8 μM, 60 Ci/mole, respectively. Extraction of the oxidation products of serotonin was performed with a mixture of ethyl acetate and scintillation liquid ZhS-106 (1:1), while β-phenylethylamine

Institute of Biological and Medical Chemistry, Academy of Medical Sciences of the USSR. S. Ordzhonikidze All-Union Scientific-Research Chemicopharmaceutical Institute, Moscow.
Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 25, No. 3, pp. 22-23, March, 1991. Original article submitted April 4, 1990.

0091-150X/91/2503-0165$12.50