SYNTHESIS AND ANTIMONOAMINE OXIDASE ACTIVITY OF HALOGEN SUBSTITUTED 6-, 7- AND 8-(N-METHYL-N-PROPYN-2-YLAMINO-METHYL)QUINOLINES

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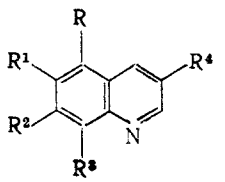
The high effectiveness of some acetylenic inhibitors [1, 13, 14] is a stimulation to carry out searches for new monoamine oxidase (MAO) inhibitors among newly synthesized derivatives of 2-propynylamines. The present work has been done as an extension to earlier investigations that are connected with the synthesis and study of MAO inhibitors, derivatives of 2-propynylamine of the quinoline series [3].

Earlier [2, 3] we showed that introduction off a halogen atom at the 5-position of the quinoline ring leads to an increase in the selectivity of action of inhibitors on MAO of type A, and that introduction of a carbalkoxy, carboxy, or carboxamido group, which are substituents with lower electronegativity, more steric hindrance or are less lipophilic than halogen atoms, leads to a sharp lowering of the inhibitory activity.

To study the relationship between the structure of the quinoline derivatives and the antimonoamine oxidase activity we have synthesized as MAO inhibitors compounds that are derivatives in the series of 6-, 7-, and 8-(N-methyl-N-propyn-2-ylaminomethyl)-quinolines.

The synthesis of MAO inhibitors (IIIa-g, i) was carried out starting from halogen substituted quinolines (Ia-g, i, j) via the corresponding bromomethyl compounds (IIa-g, i, j).



R = Cl (Ia—IIIa), Br (Ib, c, f, g, h, j, IIb, c, f, g, i, IIIb, c, f, g), H (Ie, i —IIIe, i), NO_2 (Id—IIId);
R^1 = H (Ia-e, i, j, IIa, e, i, j, IIIa-e, i), CH_3 (f-h), CH_2Br (IIf, g) $CH_2N(CH_3)CH_2C{\equiv}CH$ (IIIf, g)
R^2 = Cl (Ia, b—IIIa, b), Br (Ic, d—IIIc, d), CH_3 (Ii, j), H (Id-h, IIe, g IIIe-g), CH_2Br (IIi, j), $CH_2N(CH_3)CH_2C{\equiv}CH$ (IIIi).
R^3 = CH_3 (Ia-e), H (If, h IIf, IIIf), Br (Ig, i, j, IIg, and, j, IIIg, i) CH_2Br (IIa-e), $CH_2N(CH_3)CH_2C{\equiv}CH$ (IIIa-e)
R^4 = H (Ia-d, f, g, and IIa-d, f, g, i, Ij, IIj) Br (Ie, h IIe IIIe).

The starting quinoline 5,7-dichloro-8-methylquinoline (Ia) was prepared according to [5, 6] by direct chlorination of 8-methylquinoline in 100% H_2SO_4 in the presence of Ag_2SO_4 at room temperature. 5-Bromo-7-chloro-8-methylquinoline (Ib) was prepared from 7-chloro-8-methylquinoline with N-bromosuccinimide (NBS) in concentrated H_2SO_4. From 8-methylquinoline and its 5-nitro derivative were prepared by the same method 5,7-dibromo-8-methyl-quinoline (Ic) and 5-nitro-7-bromo-8-methylquinoline (Id), and 6- and 7-methylquinoline were converted to the corresponding monobromo and dibromo derivatives: 5-bromo-6-methylquinoline (If), 5,8-dibromo-6-methylquinoline (Ig), 8-bromo-7-methyl-quinoline (Ii), and 5,8-dibromo-7-methylquinoline (Ij) [6].

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TABLE 1. Derivatives of 6-, 7-, and 8-(N-Methyl-N-propyn-2-yl-aminomethyl)quinoline

Compound	Yield, %	mp, °C (from alcohol)		Empirical formula
		free base	hydrochloride	
IIIa	64	40—41	166—168	$C_{14}H_{12}Cl_2N_2$
IIIb	83	39—40	167—169	$C_{14}H_{12}BrClN_2$
IIIc	63	87—88	157—158	$C_{14}H_{12}Br_2N_2$
IIId	82	Oil	115—116	$C_{14}H_{12}BrN_3O_2$
IIIe	48	63—64	181—182	$C_{14}H_{13}BrN_2$
IIIf	53	Oil	172—173	$C_{14}H_{13}BrN_2$
IIIg	85	86	180—182	$C_{14}H_{12}Br_2N_2$
IIIi	56	Oil	164—165	$C_{14}H_{13}BrN_2$

TABLE 2. Influence of Quinoline Derivatives IIIa-g, i on the Activity of Mitochondria of Rat Kidneys

Compound	Concentration of the compound								I_{50}, M	
	$1\cdot10^{-6}$		$1\cdot10^{-7}$		$1\cdot10^{-8}$		$1\cdot10^{-9}$			
	S	P	S	P	S	P	S	P	S	P
IIIa	98,2	92	77	28	3,2	2,0	8,0	—	$2,0\cdot10^{-8}$	$5,0\cdot10^{-7}$
IIIb	100	99	97	63	84	45	3	23	$1,3\cdot10^{-9}$	$2,0\cdot10^{-8}$
IIIc	98	40	61	0	39	—	11	—	$3,2\cdot10^{-8}$	$2,0\cdot10^{-6}$
IIId	37	0	0	0	—	—			$1,6\cdot10^{-6}$	$4,0\cdot10^{-6}$
IIIe	100	63	95	31	69	12	46	—	$2,5\cdot10^{-9}$	$4,0\cdot10^{-7}$
IIIf	100	97	90	79	81	33	0	13	$5,0\cdot10^{-9}$	$1,5\cdot10^{-8}$
IIIg	87	62	79	13	0				$5,0\cdot10^{-8}$	$6,3\cdot10^{-7}$
IIIi	100	86	100	51	66	22	0	0	$6,3\cdot10^{-9}$	$1,0\cdot10^{-7}$

Note. Listed are the mean arithmetic values of the data of five experiments of the inhibition of the deamination of monoamines (in %, in comparison with the control without inhibitor), standard error of the average arithmetic value of the degree of inhibition is 0-12%. S) Serotonin, P) 2-phenylethylamine.

To analyze the dependence of the inhibitory activity on the position of the substituent in the quinoline molecule we have also prepared the compounds with halogen in the heterocyclic part of the nucleus. For the synthesis of 3-bromo substituted methylquinolines we applied the method that was used earlier for the preparation of 3-bromoquinoline [8]. By reacting 8-methylquinoline and 5-bromo-6-methylquinoline (If) with bromine in CCl_4 in the presence of pyridine as HBr acceptor we obtained the corresponding 3-bromo-8-methylquinoline (Ie) and 3,5-dibromo-6-methylquinoline (Ih). Attempts to prepare in this way the 3-bromoderivative of 5-bromo-8-methylquinoline were unsuccessful; only 5-bromo-8-bromomethylquinoline (IV) was isolated in low yield.

Halogen substituted methylquinolines Ia-g, i, j were converted to bromomethyl derivatives IIa-g, i, j by reaction with NBS in CCl_4 under illumination. In the case of derivatives of 6- and 7-methylquinolines a more powerful light source is required in comparison with the bromination of derivatives of 8-methylquinoline.

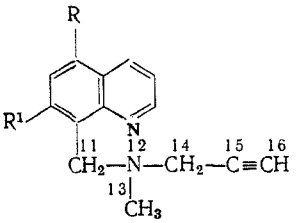
By reaction with N-methylpropargylamine the quinolines IIa-g, i were converted to the propynylated derivatives IIIa-g, i; preparation of propynylated derivatives from bromide Ij were unsuccessful.

In the IR spectra of all the propargylamines (IIIa-g, i are found absorption bands at 3208-3228 cm^{-1}, which are characteristic of a terminal acetylene group (C≡CH). The spectra of compounds IIIa-e contain also bands at 2102-2108 cm^{-1} (C≡C). The PMR spectra contain the following signals of the protons of the side chains of quinolines IIIa-g, i (δ, ppm): 3.4-4.4 (CH_2C, s), 2.3-2.4 (CH_3N, s), 3.2-3.6 (CH_2N, d), and 2.2-2.3 (C≡CH, t).

Yields and properties of the prepared compounds are summarized in Table 1. For the investigation of the antimonoamine oxidase activity, compounds IIIa-g, i were converted to their hydrochlorides by treating them with HCl in ether.

Table 2 lists the inhibition by the synthesized compounds of mitochondrial MAO of types A (substrate: serotonin) and B (substrate: 2-phenylethylamine). Halogen substituted quinolines IIIa-c, e, g, i display powerful

TABLE 3. Distribution of the Charge on the Atoms in Substituted 8-(N-Methyl-N-propyn-2-ylaminomethyl)quinolines



R	R^1	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$	$C_{(11)}$	$N_{(12)}$	$C_{(14)}$	$C_{(15)}$	$C_{(16)}$
Cl	H	—0,0421	—0,0486	—0,0424	0,1649	0,1655	0,2149	0,1875	—0,1437
Cl	Cl	—0,0133	—0,0158	—0,0055	0,1135	0,1149	0,1154	0,1251	—0,1096
H	Cl	—0,0454	—0,0441	—0,0411	0,1653	0,1625	0,2190	0,1865	—0,1461
NO_2	H	—0,0405	—0,0463	—0,0391	0,1036	0,1480	0,1844	0,2671	—0,1355
CN	H	—0,0410	—0,0462	—0,0414	0,1345	0,1545	0,2068	0,1866	—0,1434
$COOC_2H_5$	H	—0,0395	—0,0465	—0,0417	—0,0521	0,0073	0,0103	0,0178	—0,0184
COOH	H	—0,0119	—0,0149	—0,0049	0,0211	0,0941	—0,0196	0,1109	—0,0745
$CONH_2$	H	—0,0388	—0,0475	—0,0424	0,0905	0,0136	0,0238	—0,0075	—0,0265

monoamine oxidase activity. These compounds, in concentrations of $1 \cdot 10^{-6}$ M, completely block the deamination of both amines. Compound IIIb, in a concentration of $1 \cdot 10^{-8}$ M, inhibits the deamination of serotonin by 84%. The inhibitors that contain a bromine atom at positions 3, 5, 7, and 8 of the quinoline ring show a pronounced selectivity to the A form of the enzyme. Thus, compounds IIIc, e, i display an affinity for MAO type A that is 100 times as high as that for MAO type B. Because it is assumed that for MAO type B a simpler binding place is characteristic than is the case for MAO type A [10], it may be assumed that the bulkier inhibitors with a bromine atom approach the less active center of MAO type B with difficulty. Moving the side chain of the inhibitor molecule form position 8 to positions 6 and 7 does not noticeably influence the inhibitory properties of the compound. Thus, compounds IIIf, i are the most powerful inhibitors of the series.

For the derivatives of 8-(N-methyl-N-propyn-2-ylaminomethyl)quinoline that we prepared earlier [3] with chlorine atoms at positions 5 and 7, and also with nitro, cyano, carboxyl, carbethoxy, and carboxamido groups at position 5 we have calculated the charge on the carbon and nitrogen in the quinoline ring and in the side chain that corresponds with the formation of a linkage with the enzyme (Table 3).*

As can be seen from these data there is traced a clear regularity in the change of the charge (in absolute values) at the terminal atom C_{16} of the side chain, which is linked to the isoalloxane ring of FAD, which is part of the active center of the MAO. In inhibitors with chlorine atoms, nitro and cyano groups the value of the charge at the C_{16} atoms is considerably larger than in inhibitors with carboxyl, carboxamido, or carbethoxy groups. The charges at the first atom of the side chain of the inhibitor, C_{11}, also correlate well with the data on the biological activity; for active MAO inhibitors these values are considerably higher. An analogous dependency is also traced for the atoms N_{12} and C_{15}, the charge at the C_{14} atom is for all the compounds considered in active inhibitors ten times as high as in inactive compounds. Apparently, this may serve as a confirmation of model experiments [9] and the role of the C_{14} atom in the interaction of the inhibitor with the enzyme. Thus, the positive influence on the inhibitory activity of such electron-accepting groups as nitro and cyano, and also the chlorine atom found earlier [3] for a group of MAO inhibitors, derivatives of quinoline, is reflected in one of the calculated parameters of the electronic structure of a fragment of the molecules of these compounds, C_{11}—N_{12}—C_{14}—C_{15}—C_{16}, with whose participation a covalent bond of the inhibitor with the isoalloxane ring of FAD is formed.

*Quantum-chemical calculations were carried out with the MINDO-3 method on a high-speed electronic computer BESM-6 using the program system "Viking" [12].

EXPERIMENTAL (CHEMICAL)

IR spectra were taken on a Unicam SP-1000 spectrometer (UK) from KCl disks. PMR spectra were recorded on a Varian-100 spectrometer (USA) at 27°C in $CDCl_3$ with tetramethylsilane as internal standard. Melting points (uncorrected) were determined on a Boetius hot stage (GDR). Control of the course of the reactions and the purity of the prepared compounds was performed on Silufol UV-254 plates; preparative TLC was carried out on silica gel LS 5/40. Eluent systems for chromatography: hexane—ether 10:1 (A), benzene—ethyl acetate—AcOH 100:50:1 (B), and acetonitrile—25% 6:1 NH_4OH (C). Found and calculated values of elemental analyses corresponded.

5,7-Dichloro-8-methylquinoline (Ia). Through a solution of 6.24 g (0.02 mole) of Ag_2SO_4 and 2.86 g (0.02 mole) of 8-methyl-quinoline in 30 ml of sulfuric acid was passed a chlorine stream till disappearance of the starting quinoline, and then an additional 0.8 g of Ag_2SO_4 was added. The mixture was set aside at room temperature for 72 h, poured out in 200 ml of water, the AgCl was filtered off, the filtrate was alkalized with 45% KOH, allowed to stand overnight, and the precipitate was filtered off. Extraction with ether yielded 3.8 g of residue, from which by means of preparative chromatography with system A was isolated 1.22 g (35%) of 5-chloro-8-methylquinoline, mp 31-32°C (from a hexane—ether mixture) (literature: mp 31-32°C [5]), and 1.28 (30%) of dichloroquinoline Ia, mp 95-96°C. $C_{10}H_7Cl_2N$.

3-Bromo-8-methylquinoline (Ie). A mixture of 1.43 g (10 mmoles) of 8-methylquinoline, 1.6 g (10 mmoles) of bromine, and 100 ml of CCl_4 was refluxed for 1 h, during which an orange precipitate was formed gradually. Then 0.8 g (10 mmoles) of water-free pyridine in 2 ml CCl_4 was added, refluxing was continued for 3 h, the mixture was allowed to stand at room temperature overnight, and evaporated. The residue was dissolved in 50 ml of water, extracted with $CHCl_3$ (2 × 50 ml), the organic layer was dried over $MgSO_4$. Yield 1.28 g of a mixture of products, from which by means of preparative chromatography with benzene was isolated 560 mg (31.2%) of quinoline Ie, R_f 0.78, mp 63-64°C (purified by sublimation under vacuum). $C_{10}H_{18}BrN$.

3,5-Dibromo-6-methylquinoline (Ih). From 0.67 g (3 mmoles) of 5-bromo-6-methylquinoline (If) and 0.5 g (3 mmoles) of bromine under the conditions described for the preceding experiment was obtained, after preparative TLC with benzene, 230 mg (32%) of quinoline Ih, R_f 0.47, mp 111-113°C. $C_{10}H_7Br_2N$.

5-Bromo-8-bromomethylquinoline (IV). From 1.1 g (5 mmoles) of 5-bromo-8-methylquinoline under the conditions for the synthesis of quinoline Ie was obtained 0.43 g (28%) of bromomethylquinoline IV. It was isolated by preparative chromatography with benzene, R_f 0.38, mp 111-112°C. Lit.: mp 112-113°C [5].

Substituted 6-, 7-, and 8-bromomethylquinolines (IIa-g, i, j). A mixture of 5 mmoles of the substituted 6-, 7-, and 8-methylquinoline and 0.9 g (5 mmoles) of NBS in 40 ml CCl_4 was refluxed in the presence of a catalytic amount of benzoyl peroxide under illumination with a 200 W lamp till completion of the reaction. The succinimide was filtered off, and the filtrate was evaporated to yield the corresponding bromomethylquinoline. The compounds are homogeneous in system B.

5,7-Dichloro-8-bromomethylquinoline (IIa). Yield 70%, mp 114°C, $C_{10}H_6BrCl_2N$.

5-Bromo-7-chloro-8-bromomethylquinoline (IIb). Yield 76%, mp 137-138°C, $C_{10}H_6Br_2ClN$.

5,7-Dibromo-8-bromomethylquinoline (IIc). Yield 80%, mp 152-153°C, $C_{10}H_6Br_3N$.

5-Nitro-7-bromo-8-bromomethylquinoline (IId). Yield 55%, mp 118-119°C, $C_{10}H_6Br_2N_2O_2$.

3-Bromo-8-bromomethylquinoline (IIe). Yield 64%, mp 143-144°C (Lit.: mp 145°C [11]).

5-Bromo-6-bromomethylquinoline (IIf). Yield 53%, mp 132°C, $C_{10}H_7Br_2N$.

5,8-Dibromo-6-bromomethylquinoline (IIg). Yield 71%, mp 171-172°C, $C_{10}H_6Br_3N$.

8-Bromo-7-bromomethylquinoline (IIi). Yield 48%, mp 164-165°C, $C_{10}H_7Br_2N$.

5,8-Dibromo-7-bromomethylquinoline (IIj). Yield 52% mp 119-120°C, $C_{10}H_6Br_3N$.

Substituted 6- and 8-(N-methyl-N-propyn-2-ylaminomethyl)quinolines (IIIa-g). A mixture of 1 mmole of bromides IIa-g and 1.5 ml of N-methylpropargylamine was stirred at 20°C. After 40 min the solvent was evaporated, the residue was dissolved in ether, the solids were filtered off, and the filtrate was evaporated to yield the propynylated derivatives. The compounds were homogeneous in systems B and C.

8-Bromo-7-(N-methyl-N-propyn-2-ylaminomethyl)quinoline (IIIi). A mixture of 300 mg (1 mmole) of bromide IIi, 1.5 ml of N-methylpropargylamine, and 10 ml of ethanol was set aside for 72 h and worked up as described above to yield 170 mg of propynylated derivative IIIi.

EXPERIMENTAL (BIOCHEMICAL)

Polypropylene test tubes were charged with 60 μl of 0.05 M phosphate buffer (pH 7.6), 20 μl of a mitochondria suspension (40 μg of protein) preincubated with different concentrations of inhibitor for 30 min, and 20 μl of a substrate solution. The mixtures were incubated at 37°C for 30 min, then the reaction was quenched with 20 μl of 2 M citric acid (in the case of determination of the activity with serotonin) or with 20 μl of 0.5 M HCl (in the case of determination of the activity with 2-phenylethylamine). To the test tubes was added 2 ml of scintillator, the tubes were closed with a cap, shaken mechanically for 3 min to extract the products into the scintillator, and placed in a Marck-II counter to determine the radioactivity, which was expressed as impulses per minute.

The final concentrations of ^{14}C-serotonin and ^{14}C-phenylethylamine in the samples was 0.01 mM, the specific radioactivity was 2.5 Ci/mole. As scintillator for the determination of the activity with phenylethylamine we used ZhS-106, and with serotonin a 1:1 mixture of ZhS-106 and ethyl acetate.

We took as 100% the MAO activity in the samples to which in the preincubation the same volume of distilled water was added instead of the inhibitor solution [4].

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