SYNTHESIS AND ANTIMONOAMINE OXIDASE ACTIVITY OF 8-(N-METHYL-N-2-PROPYNYL)AMINOMETHYLQUINOLINES

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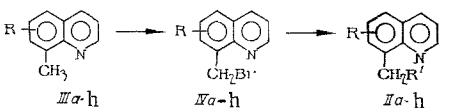
UDC 615.214.32:547.831]012.1

The most powerful and specific inhibitors of mitochondrial monoamine oxidase (MAO) yet known are 2-propynylamine derivatives [1]. Searches have been carried out [2-4] for even more powerful and selective MAO inhibitors in the deprenil and pargilin groups, and the relationships between structure and antimonoamine oxidase activity have been examined.

It has previously been shown [5-7] that quinoline derivatives containing a 2-propynyl group, in particular 8-(N-methyl-N-2-propynyl)aminomethylquinoline (I), are aslo effective MAO inhibitors.

In continuation of these studies, we here report the synthesis of some substituted 8-(N-methyl-N-2-propynyl)aminomethylquinolines (IIa-j), with a variety of substituents in the benzene moiety of the quinoline nucleus, in order to study the relationship between structure and antimonoamine oxidase activity.

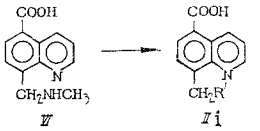
The 5- and 7-halo-, 5-alkoxycarbonyl-, and 5-cyano-(8-N-methyl-N-2-propynyl)aminomethyl quinolines (IIa-h) were synthesized as follows:



IIIa-h IVa-h IIa-h

a: R = 5-F; b: R = 5-Cl; c: R = 7-Cl; d: R = 5-Br; e: R = 5-CN; f: R = 5-$COOCH_3$; g: R = $COOC_2H_5$; h: R = NO_2. Here & subsequently, R^1 = $N(CH_3)CH_2C{\equiv}CH$.

The starting 5-chloro- and 5-bromo-8-methylquinolines (IIIb and d) were prepared by direct halogenation of 8-methylquinoline in concentrated sulfuric acid in the presence of silver sulfate [8]. 7-Chloro-8-methylquinoline (IIIc) was obtained by the Skraup reaction [9], and 5-fluoro-8-methylquinoline (IIIa) by the Baltz–Schiemann reaction [10, 11] from 5-amino-8-methylquinoline [12]. The nitrile (IIIe), esters (IIIf and g), and 8-bromomethyl derivatives (IVa, b, d-h) were obtained as described in [8] and [13]. 7-Chloro-8-bromomethylquinoline (IVc) and 5-nitro-8-bromomethylquinoline (IVh) were synthesized by brominating (IIIc) and (IIIh) with N-bromosuccinimide. The nitro compound (IVh) was also obtained by nitrating 8-bromomethylquinoline as described in [14]. Reaction of quinolines (IVa-h) with N-methylpropargylamine (V) in methanol in the presence of potassium carbonate gave the propynylated derivatives (IIa-h); in the case of (IIc) and (IIh), (V) was used as the solvent. Alkylation of 8-(N-methyl)aminomethyl-5-quinolinecarboxylic acid (VI) [13] with propargyl bromide in the presence of alkali gave the acid (IIi)



VI IIi

The amide (IIj) was obtained by hydrolyzing the nitrile (IIe) with potassium hydroxide in tert-butanol as described in [15] (method A), or by reacting the bromide (IVe) with (V) in tert-butanol in the presence of potassium hydroxide (method B), as follows:

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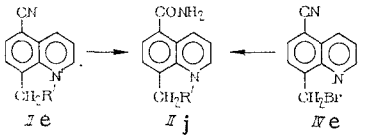
Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 17, No. 9, pp. 1055-1060, September, 1983. Original article submitted November 9, 1982.

0091-150X/83/1709-0625$07.50

TABLE 1. 8-(N-Methyl-N-2-propynyl)aminomethylquinolines (IIa-j)

Compound	mp, °C (from alcohol)		Molecular formula	Found, %				Calculated, %				Yield, %	IR spectrum, cm^{-1}	PMR spectrum, δ, ppm
	base	hydrochloride		C	H	N	halogen	C	H	N	halogen			
IIa	Oil	132—136	$C_{14}H_{13}FN_2$	—	—	12,3	8,9	—	—	12,2	8,6	84	2102 (C≡C) 3223 (C≡CH)	4,2 (CH_2C, s); 2,4 (CH_3N, s); 3,4 (CH_2N, d); 2,2 (C≡CH, t).
IIb	68—69	133—135	$C_{14}H_{13}ClN_2$	68,6	5,5	11,5	14,7	68,7	5,5	11,5	14,7	74	2102 (C≡C) 3223 (C≡CH)	4,6 (CH_2C, s); 2,6 (CH_3N, s); 3,8 (CH_2N, d); 2,4 (C≡CH, t).
IIc	53	185—187	$C_{14}H_{13}ClN_2$	—	—	10,9	14,5	—	—	11,5	14,7	65	2102 (C≡C) 3223 (C≡CH)	4,4 (CH_2C, s); 3,6 (CH_2N, d); 2,5 (CH_3, s); 2,2 (C≡CH, t)
IId	71,5—73*	126—128	$C_{14}H_{13}BrN_2$	58,9	4,3	9,3	...	58,2	4,5	9,7	...	75	2102 (C≡C) 3223 (C≡CH)	4,2 (CH_2C, s); 2,5 (CH_3N, s); 3,6 (CH_2N, d); 2,3 (C≡CH, t).
IIe	93—94	Oil	$C_{15}H_{13}N_3$	76,4	5,5	17,8	—	76,6	5,5	17,8	—	76	2102 (C≡C) 2242 (C≡N) 3237 (C≡CH)	4,3 (CH_2C, s); 2,4 (CH_3N, s); 3,5 (CH_2N, d); 2,2 (C≡CH, t).
IIf	99,5—101	150—152	$C_{16}H_{16}N_2O_2$	71,4	6,0	10,6	—	71,6	6,0	10,4	—	82	1715 (CO) 2103 (C≡C) 3220 (C≡CH)	4,3 (CH_2C, s); 3,4 (CH_2N, d); 2,3 (CH_3N, s); 4,0 (CH_3CO, s); 2,2 (C≡CH, t).
IIg	95—96	117—118	$C_{17}H_{18}N_2O_2$	72,1	6,4	9,6	—	72,3	6,4	9,9	—	69	1713 (CO) 2103 (C≡C) 2237 (C≡CH)	4,2 (CH_2C, s); 2,5 (CH_3N, s); 3,3 (CH_2N, d); 3,8 (CH_2CO, s); 2,3 (C≡CH, t).
IIh	81—82†	158—160	$C_{14}H_{13}N_3O_2$	65,9	5,2	16,5	—	65,9	5,1	16,5	—		1530, 1345 (N...O), 2240 (C≡CH), 2102 (C≡C)	4,4 (CH_2C, s); 3,5 (CH_2N, d); 2,5 (CH_3, s); 2,4 (C≡CH, t).
IIi	Oil	134—136	$C_{15}H_{14}N_2O_2 \cdot 2HCl \cdot 3H_2O$	45,8	7,1	7,2	...	45,1	8,0	7,1	...	83	1717 (COOH) 2043 (C≡C) 3220 (C≡CH)	4,6 (CH_2C, s); 2,5 (CH_3N, s); 3,2 (CH_2N, d); 2,5 (C≡CH, t).
IIj	183—184	Oil	$C_{15}H_{15}N_3O_2$	71,1	5,9	16,7	—	71,1	6,0	16,6	—	56	1632 ($CONH_2$) 2102 (C≡C) 3223 (C≡CH)	

*Purified on Florisil (Merck) (hexane).
†Purified by reprecipitation from ether with alcohol.



IIe IIj IVe

The yields and properties of the products are shown in Table 1. In order to study the antimonoamine oxidase activity of (IIa-j), they were converted into their hydrochlorides by treatment with hydrogen chloride in methanol.

Table 2 gives results for the inhibition by the test compounds of MAO type A (substrate serotonin) and type B (substrate 2-phenylethylamine) from rat liver.

The introduction into the parent molecule (I) of different substituents resulted in changes in the electronic, hydrophobic, and steric properties of the inhibitor, these playing an important part in the binding of the compounds with the enzyme. Assessing the substituents from this viewpoint, it can be assumed that the optimum combination of electronic, hydrophobic, and steric factors will give the most powerful MAO inhibitor [16, 17]. It is, for example, known that in many instances the introduction of halogens results in an increase in inhibitory activity in certain compounds [2, 18-21]. In our experiments, the introduction of F and Br (compounds IIa and IId) in the 5-position of the quinoline nucleus resulted in an increase in the affinity of the compounds for type B MAO, but the affinity for type A MAO remained virtually unchanged. The best effect was obtained by introducing chlorine atoms into the 5- and 7-positions of quinoline (compounds IIb and IIc), the relatively high selectivity towards type A MAO being retained. It appears that in this instance the optimum combination of electronegativity and hydrophobicity is responsible for binding form A of the enzyme. A reduction in hydrophobic properties following the introduction of a nitrile or nitro group in the 5-position (inhibitors IIe and IIh) results in a marked reduction in affinity for type A MAO as compared with the 5-halo derivatives (IIa-d), but nevertheless the inhibitory activity of these compounds is retained even in concentrations of $1 \cdot 10^{-7}$ M, apparently owing to the high electronegativity of these substituents. Introduction into the 5-position of the quinoline ring of less electronegative, more sterically hindered, or less lipophilic substituents such as alkoxycarbonyl, carboxy, or carboxamido results in a considerable reduction in inhibitory activity: Compounds (IIf, g, and j) in concentrations of $1 \cdot 10^{-6}$ M inhibit only slightly the deamination of serotonin, and have no effect on the deamination of 2-phenylethylamine, and (IIi) even in a concentration of $1 \cdot 10^{-3}$ M does not inhibit the deamination of either amine.

The high and selective antimonoamine oxidase activity which has been observed in the halo derivatives (I) thus makes further studies of this group of compounds of considerable interest in the search for selectively-acting MAO inhibitors.

EXPERIMENTAL CHEMISTRY

IR spectra were obtained on a Unicam SP-1000 (Great Britain) as KBr disks, and PMR spectra on a Varian XL-100 instrument (USA) at 27°C in $CDCl_3$, internal standard tetramethylsilane. The TLC solvent systems used on Silufol UV-254 plates (Czech SSR) were benzene—ethyl acetate—acetic acid, 100:50:1 (A), chloroform—methanol, 50:1 (B), acetonitrile—25% NH_4OH (C), acetonitrile—25% NH_4OH, 6:1 (D), and chloroform—acetone, 25:1 (E).

5-Nitro-8-bromomethylquinoline (IVh). To a mixture of 5 ml of concentrated sulfuric acid and 5 ml of nitric acid (d 1.51) was added at 0°C 1.1 g of 8-bromomethylquinoline, obtained from 8-methylquinoline and N-bromosuccinimide, the mixture stirred for 10 min, poured into 100 ml of water, 25% NH_4OH added to pH 9.0, and the nitrobromide (IVh) which separated was filtered off. Yield 0.78 g (58%), mp 112-113°C (from alcohol). The compound was homogeneous in system B. Found, %: C 45.0; H 2.7; Br 30.0; N 10.5. $C_{10}H_7BrN_2O_2$. Calculated, %: C 45.0; H 2.6; Br 29.9; N 10.5.

7-Chloro- and 5-Nitro-8-bromomethylquinoline (IVc and h). A mixture of 5 mmole of (IIIc) or (IIIh) and 0.95 g of N-bromosuccinimide in 40 ml of CCl_4 in the presence of benzoyl peroxide was boiled under irradiation by a 200 W lamp until reaction was complete (4-5 h). The precipitated succinimide was filtered off, and the filtrate evaporated to give (IIIc) or (IIIh) respectively, homogeneous in systems A, B, and E. Yield of (IVc) 63%, mp 122-124°C (from alcohol). Found, %: Br+Cl 44.8; N 5.2. $C_{10}H_7BrCl$. Calculated, %: Br+Cl 45.2; N 5.4. Yield of (IVh) 56%, mp 111-112°C (from alcohol). Their spectral and TLC data were identical with those obtained by the method described above.

TABLE 2. Effect of IIa-j Hydrochlorides on the MAO Activity of Rat Liver Mitochondria

Compound	Final concentration of compound, M			
	$1 \cdot 10^{-6}$	$1 \cdot 10^{-7}$	$1 \cdot 10^{-8}$	$1 \cdot 10^{-9}$
I	100±0 / 82,6±3,7	97,6±1,6 / 35,4±3,4	47,4±1,7 / 15,2±3,75	11,75±4,1 / —
IIi	0 / 0	—	—	—
IIj	14,0±1,25 / 0	—	—	—
IIf	17,0±2,1 / 0	0 / 0	—	—
IIg	13,7±3,4 / 15,7±2,6	7,0±0 / 5,0±3,3	0 / 0	—
IIe	92,2±3,1 / 100±0	38,0±3,9 / 23,4±3,7	13,8±2,2 / 0	16,7±1,8 / —
IIa	100±0 / 100±0	100±0 / 60,8±0,8	30,5±2,4 / 8,0±5,1	12,2±2,5 / —
IId	100±0 / 100±0	100±0 / 82,2±2,6	21,2±0 / 0	0 / 0
IIb	100±0 / 100±0	100±0 / 51,4±1,6	48,5±2,3 / 0	28,0±2,1 / —
IIc	100±0 / 100±0	100±0 / 36,2±3,9	60,0±3,4 / 4,8±2,0	8,0±2,2 / —
IIh	100±0 / 96,8±2,5	44,0±1,6 / 25,0±4,9	0 / 13,8±5,5	0 / 0

Note. Experimental conditions are described in the text. Results shown are the mean arithmetic values for five experiments: standard deviations (serotonin in the numerator, 2-phenylethylamine in the denominator) of the inhibition (as % of the controls, without inhibitor) of the deamination of monoamines.

8-(N-Methyl-N-2-propynyl)aminomethylquinolines (IIa, b, d, and h). A solution of 1.5 mmole of IVa, b, d-h in 30 ml of methanol was stirred for 24 h at 20°C with 1 ml of (V) in the presence of 0.12 g of potassium carbonate. The solvent was evaporated, the residue dissolved in chloroform, the filtrate evaporated, and (IIa, b, d-h) extracted with a mixture of hexane and benzene (1:1). The compounds were homogeneous in systems A, B, and E. The properties of the compounds are given in Table 1.

5-Nitro-8-(N-methyl-N-2-propynyl)aminomethylquinoline (IIh). A mixture of 200 mg of the nitro compound (IIIh) and 1.5 ml of (V) was stirred at 0°C. After 40 min, the solvent was evaporated, the residue treated with ether, the solid filtered off, and the mother liquors evaporated to give (IIh). The compound was homogeneous in systems B and E. Similarly obtained at room temperature was 7-chloro-8-(N-methyl-N-2-propynyl)aminomethylquinoline (IIc).

8-(N-Methyl-N-2-propynyl)aminomethylquinoline-5-carboxylic Acid (IIi). A mixture of 288 mg of the dihydrochloride of acid (VI), 1.2 ml of propargyl bromide, and 80 mg of sodium hydroxide in 50 ml of methanol was boiled for 6 h. The solid was filtered off, washed with methanol, the filtrate evaporated, the solid dissolved in chloroform–methanol (1:1), the solid separated, and the procedure repeated twice more, followed by evaporation of the filtrate to give 200 mg (83%) of the acid (IIi) (hydroscopic oil). The acid was treated with a solution of HCl in methanol, evaporated to dryness, the solid dissolved in 5 ml of a 5:1 mixture of methanol and chloroform, and the filtrate evaporated to give 200 mg of the hydrochloride (see Table 1).

8-(N-Methyl-N-2-propynyl)quinoline-5-carboxamide (IIj). Method A. A mixture of the nitrile (IIe), 112 mg of sodium hydroxide, and 5 ml of tert-butanol was boiled for 10-15 h, 25 ml of water added, and extracted with chloroform to give 142 mg (56%) of the amide (IIj). The compound was homogeneous in system D.

Method B. A mixture of 220 mg of the bromide (IV) with 25 ml of tert-butanol and 0.4 ml

of (V) in the presence of 112 mg of potassium hydroxide was boiled. After 12 h it was worked up as described above (method A) to give 138 mg of the amide (IIj), identical in its TLC data and IR spectrum to the product obtained by method A.

Hydrochlorides of 8-(N-Methyl-N-2-propynyl)aminomethylquinolines. Five mmole of the compound (IIa-j) was treated with 10 ml of a 20% solution of HCl in methanol, the solvent concentrated, and the hydrochlorides which separated were used in the biochemical tests.

EXPERIMENTAL BIOCHEMISTRY

The source of the MAO used was fragments of the mitochondrial membranes of rat liver, obtained as described previously [22]. The incubation samples of volume 1.8 ml contained 50 mM of phosphate buffer, pH 7.4, 3 mg of mitochondrial membrane protein, inhibitor, and substrate. The control samples contained no inhibitor. The suspension of the mitochondrial membranes in the buffer was preincubated with the test compound before adding the substrate for 30 min at ~23°C. The MAO activity was assessed from the amount of free ammonia liberated during incubation of the sample at 37°C in an oxygen atmosphere [23]. The amines used as MAO substrates were taken in optimum concentrations, viz., serotonin creatinesulfate (Reanal, Hungary) 10 μmole, 2-phenylethylamine hydrochloride (home-produced, cp grade) 8 μmole. The protein contents of the samples were determined by Lowry's method, using serum albumin as standard.

LITERATURE CITED

1. T. P. Singer, Monoamine Oxidase: Structure, Function, and Altered Functions, London (1979).
2. J. Knoll, Z. Ecsery, K. Magyar, et al., Biochem. Pharmacol., 27, 1739 (1978).
3. A. Kalir, A. Sabbagh, and M. B. H. Youdim, Br. J. Pharmacol., 73, 55 (1981).
4. K. F. Tipton, J. J. M. Mc Crodder, A. S. Kalir, et al., Biochem. Pharmacol., 31, 1251 (1982).
5. G. A. Davydova, I. A. Red'kin, A. I. Tochilkin, et al., USSR Inventor's Certificate No. 550,385; Otkrytiya, No. 10, 60 (1977).
6. B. A. Grinberga, Kh. B. Uziis, M. A. Pakalka, et al., Izv. Akad. Nauk Latvian SSR, No. 3, 299 (1976).
7. G. A. Davydova, K. K. Shatemirova, and I. V. Verevkina, Vopr. Med. Khim., 23, 609 (1977).
8. I. N. Gracheva and A. I. Tochilkin, Khim. Geterotsikl. Soedin., No. 3, 366 (1980).
9. L. Bradford, T. J. Elliott, and F. M. Rowe, J. Chem. Soc., 437 (1947).
10. A. Roe and G. F. Hawkins, J. Am. Chem. Soc., 71, 1785 (1949).
11. Yu. A. Bankovskii, Z. V. Misulovina, A. F. Nevin'sh, et al., Methods of Preparation of Chemical Reagents and Compounds [in [Russian], Nos. 4-5 (1962), p. 71.
12. E. Noelting and E. Trautmann, Ber. Chem. Ges., 23, 3654 (1890).
13. I. N. Gracheva, I. R. Kovel'man, and A. I. Tochilkin, Khim. Geterotsikl. Soedin., No. 6, 785 (1982).
14. J. Howitz and P. Nother, Ber. Chem. Ges., 39, 2705 (1906).
15. J. H. Hall and G. Matthiass, J. Org. Chem., 41, 3769 (1976).
16. J. G. Topliss, J. Med. Chem., 15, 1006 (1972).
17. J. C. Martin, W. B. Martin, and J. D. Taylor, J. Med. Chem., 18, 883 (1975).
18. G. A. Bremanis, T. T. Dumpis, and B. A. Grinberga, Izv. Akad. Nauk Latvian SSR, No. 5, 597 (1978).
19. D. G. Tsedere, Z. V. Lyansa, B. A. Grinberga, et al., Izv. Akad. Nauk Latvian SSR, No. 2, 223 (1982).
20. L. R. Swett, W. B. Martin, J. D. Taylor, et al., Ann. N.Y. Acad. Sci., 107, 891 (1963).
21. L. Florvall, A. L. Ask, S. O. Orgen, et al., J. Med. Chem., 21, 56 (1978).
22. V. Z. Gorkin and I. V. Verevkina, Vopr. Med. Khim., No. 3, 315 (1963).
23. V. Z. Gorkin et al., in: Modern Methods in Biochemistry [in Russian], Moscow (1968), Vol. 2, p. 155.