SYNTHESIS AND PSYCHOTROPIC ACTIVITY OF FUNCTIONALLY SUBSTITUTED DIAZIRIDINES AND BISDIAZIRIDINES

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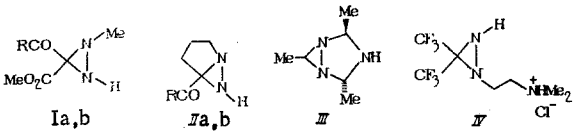
Of interest for study as potential antidepressants are inhibitors of brain monoamine oxidase (MAO), together with compounds which influence the reverse capture of monoamine mediators by the presynaptic nerve endings [6, 10]. Diaziridines are MAO inhibitors [16]. For this reason, we have examined the psychotropic activity of the diaziridines (Ia, b)-(Va,d), which differ considerably in their structures ((Ia, b) and (IV) are monocyclic, and (IIa, b) and (III) are bicyclic) and in the C- and N-substituents (Tables 1 and 2).



Ia,b IIa,b III IV

Ia: R = MeO; Ib: R = (R)-PhCH(Me)NH; IIa: R = MeO; IIb: R = MeNH

We have previously described the synthesis of the diester (Ia) [3], the 1R,2R,3S,αR-α-phenylethylamine (Ib) [8], and the 1,6-diazabicyclo[3.1.0]-hexane-5-carboxylic acids (IIa, b) [12]. The 1,3,5-triazabicyclo[3.1.0]hexane (III) was synthesized as its d,l-isomer by reaction of 2,4,6-trimethyl-1,3,5-triazacyclohexane with tert-BuOCl in methanol in the presence of sodium carbonate [14]. The hydrochloride (IV) was obtained from the base, described in [13].

It was expected that biological activity would be enhanced on introducing two aziridine rings into the molecule. In the case of the bisdiaziridine (Vd), derived from 1,10-diaza-18-crown-6, it was also expected (findings reported in [5]) that the compound would pass readily through the blood–brain barrier. For this purpose, a modification of the Mannich reaction was examined [7].

In contrast to the usual method of aminomethylating diaziridines by heating with the amine and formaldehyde in aqueous medium [2, 16], the reaction was effected under mild conditions (20°C) to give high yields. The synthesis of (Vb, c) has been described by us previously [7]; we now give the synthesis of (Va, d).

TABLE 1. Acute Toxicities and Some Pharmacological Effects of Diaziridines

Compound	LD_{50}, mg/kg (intraperitoneally in mice)	Changes in duration of effect as % of controls				
		hexenal (hexobarbital) sleep	stereotypy			arecoline hyperkinesis
			phenamine amphetamine	apomorphine	L-DOPA	
Ia	1100	−18	+19	+14	+8	+61
Ib	380	+75	+35	+20	+18	+17
IIa	1000	+8	+15	+5	0	+3
IIb	1150	+300	+57	+14	+15	+50
III	1100	+5	+14	+4	+5	0
IV	350	−40	+22	+8	+5	+50
Va	1200	−20	+29	+17	+10	+10
Vb	750	+102	+16	+4	+8	+30
Vc	1100	+40	+35	+26	+20	+30
Vd	75	−20	+28	+26	+22	+10
Imipramine	150	+110	+60	+22	+15	−32
Iproniazid	640	+40	+10	−10	+10	0

Note. Here and in Table 2, the doses used were 10% of the LD_{50}.

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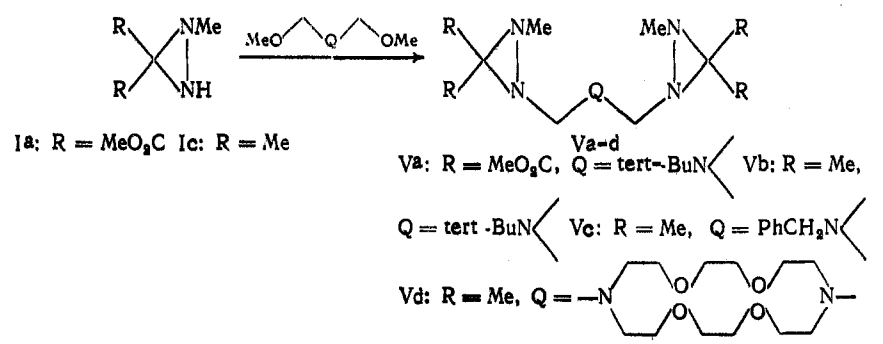
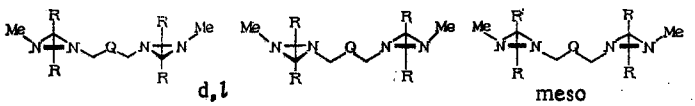
TABLE 2. Effect of Functionally Substituted Diaziridines (Ib, IIb, III, and Vb) on the Effects of Reserpine, 5-Hydroxytryptophan, Tryptamine, Corazole, and Apomorphine Hypothermia

Compound	Reserpine		5-Hydroxytryptophan	Triptamine	Corazole	Apomorphine
	ptosis, points	hypothermia, °C	extent of hyperkinesis, points		threshold convulsant dose, ml of 1% solution	reduction in hypothermia, °C
Ia	3.1±0.05	2.5±0.25*	2±0.05*	1.8±0.04*	0.095±0.006*	1.8
IIb	3±0.05*	2.8±0.4	1.9±0.2*	2±0.95*	0.101±0.005*	2.2
III	3.2±0.15	2.7±0.25	1.6±0.05*	1.5±0.04	0.112±0.01	1.4
Vb	3.3±0.25	3±0.4	1.4±0.08	1.3±0.08	0.111±0.009	1.2
Imipramine	2.5±0.3*	2.2±0.17	1±0.05	1.1±0.05	0.158±0.02*	2.2
Iproniazid	2.1±0.15	2.5±0.25*	2.8±0.2*	2.2±0.05*	0.089±0.007	1.5
Control	3.5±0.36	3.2±0.39	1.2±0.04	1±0.05	0.111±0.007	0



The bisdiaziridines (Va-d) were obtained as mixtures of the d,l- and meso-isomers (in a ratio of 1:1), these differing in their ^1H and ^{13}C NMR spectra.



The ability to observe these isomers under normal conditions is due to the high configurational stability of the nitrogen atoms in diaziridines [3, 8].

EXPERIMENTAL CHEMICAL PART

^1H (400.13 MHz) and ^{13}C (100.61 MHz) NMR spectra were measured on a Bruker WM-400 spectrophotometer (West Germany), with TMS as internal standard.

1-β-Dimethylaminoethyl-3,3-bis(trifluoromethyl)diaziridine Hydrochloride (IV). Into a solution of 2.51 g (10 mmole) of 1-β-dimethylaminoethyl-3,3-bis(trifluoromethyl)diaziridine [13] in 50 ml of dry ether was passed an excess of dry hydrogen chloride gas. The solid which separated was filtered off, washed with ether, and dried in vacuo. Recrystallization from a mixture of acetone and 2-propanol gave 2.67 g (90%) of (IV), mp 184-186°C (decomp.). Found, %: C 29.38; H 4.25; N 14.42. $C_7H_{12}N_3F_6Cl$. Calculated, %: C 29.23; H 4.20; N 14.60.

Bis-(2-methyl-3,3-bismethoxycarbonyldiaziridino-1-methyl)-tert-butylamine (Va). A solution of 1.08 g (6.2 mmole) of (Ia) [3] and 0.5 g (3.1 mmole) of bis(methoxymethyl)-tert-butylamine [7] in 3 ml of dry benzene was kept for 12 h at 20°C. Removal of the solvent and reprecipitation of the solid from CCl_4 with pentane gave 1.36 g (91%) of (Va) as an oil, n_D^{20} 1.5369. NMR spectrum (C_6D_6), δ, ppm: (^1H) 1.24 (Me_3C), 2.35 and 2.40 (MeN), 3.14, 3.15, 3.22, 3.27 (MeO), 3.88 and 3.89 (H_A), 4.20 and 4.22 (H_B) (NCH_2N, J_{AB} 13.4 Hz); (^{13}C) 29.45 and 29.52 (Me_3C, $^1J_{CH}$ 125.7 Hz), 42.43 and 42.46 (MeN, J 136.7 Hz), 52.41, 52.53, 52.57 (MeO, $^1J_{CH}$ 147.7 Hz), 69.64 and 69.90 (NCH_2N, $^1J_{CH}$ 146.5, $^4J_{CH}$ 6.10Hz), 54.22 and 54.31 (CMe_3, $^2J_{CH}$ 3.8 Hz), 66.90 and 66.96 (C_{ring}, $^3J_{CH}$ 3.7 Hz), 165.03 and 165.29 (CO, $^3J_{CH}$ 3.7 Hz). Found, %: H 7.18; C 48.62; N 16.10. $C_{18}H_{31}N_5O_8$. Calculated, %: H 7.02; C 48.53; N 15.72.

1,10-Bis-(2,3,3-trimethyldiaziridino-1-methyl)-1,10-diaza-18-crown-6 (Vd). Similarly, from 0.4 g (4.6 mmole) of (Ic) [15] and 0.8 g (2.3 mmole) of 1,10-bis(Methoxymethyl-1,10-

diaza-18-crown-6 ether [11] in 1 ml of ethanol there was obtained 1 g (95%) of (Vd) as a colorless oil, n_D^{20} 1.5821, NMR spectrum ($CDCl_3$), δ, ppm: (^1H) 1.25 and 1.27 (Me_2), 2.42 (MeN), 3.32 (H_A) and 3.63 (H_B) (NCH_2N, J_{AB} 12.7 Hz), 2.99 (CH_2N, $^3J_{HH}$ 5.9 Hz), 3.66 (CH_2O), 3.65 [$O(CH_2)_2O$]; (^{13}C) 18.73 and 19.49 (Me_2C), $^1J_{CH}$ 126.3, $^4J_{CH}$ 3.7 Hz), 39.73 (MeN, $^1J_{CH}$ 134.9 Hz), 74.3 (NCH_2N, $^1J_{CH}$ 144.7, $^3J_{CH}$ 3.1 Hz), 52.21 (CH_2N, $^1J_{CH}$ 133.1 Hz), 70.08 (CH_2O, $^1J_{CH}$ 141.1 Hz), 70.63 [$O(CH_2)_2O$], $^1J_{CH}$ 140.4 Hz, 59.34 (CMe_2, $^2J_{CH}$ 3.7 Hz). Found, %: C 57.65; H 10.56; N 18.38. $C_{22}H_{46}H_6O_4$. Calculated, %: C 57.61; H 10.11; N 18.32.

EXPERIMENTAL

Pharmacological activity was studied in male mice weighing 18-22 g, by means of the following tests [4]: determination of acute toxicity by a single intraperitoneal administration, examination of effects on the spontaneous behavior of the animals, induced reactions, vegetative symptoms and body temperature, and orientational activity; modification of the effects of hexenal (60 mg/kg), apomorphine (2 mg/kg), phenamine (6 mg/kg), L-DOPA (300 mg/kg), 5-hydroxytryptophan (300 mg/kg), tryptamine (80 mg/kg), corazole (150 mg/kg interperitoneally, or a 1% solution intravenously), and maximum electroshock (50 mA, 0.2 sec, 50 Hz). The drugs were given intraperitoneally 45 min after administration of the test compound, and reserpine 4 h before beginning the experiment. Comparisons were made with the antidepressants imipramine and iproniazid.

In the case of the two most active compounds (Ib) and (IIb), the effects of the compounds on MAO activity in mitochondrial fractions of the brain of rats weighing 200-250 g were studied [1] (Table 3). MAO activity was assessed by the amount of ammonia liberated using creatine sulfate (3 mM, "Reanal," Hungary) or tryamine hydrochloride (3 mM, Merck, West Germany) as the serotonin substrate. The reaction was carried out for 20 min at 37°C in 0.2 M Na, K phosphate buffer of pH 7.4. Optical densities were measured with an SF-26 spectrophotometer at 410 nm.

Discussion of Results. The toxicities of the diaziridines are given in Table 1. These compounds displayed effects characteristic of antidepressants on the behavior of the animals: having weak or moderate stimulant activity, increasing motor activity, enhancing reactions to irritants in low doses, and showing sedative activity in higher doses. In the latter case, reduction in motor activity and diminution in reactions to irritants were seen. In the case of the diester (Ia), the bistrifluoromethyl compound (IV), and the bisaziridines (Va, d) stimulant activity predominated at the doses studied, the animals becoming excited with increased motor orientational activity and increased reactions to irritants. In doses approaching toxic levels, clonic convulsions occurred.

As in the case of the classical antidepressants, the interactive tests showed the following conjunction of effects: potentiation of the stimulant effects of phenamine, apomorphine, and L-DOPA, decrease in apomorphine hypothermia, enhancement of the hypnotic-sedative effects of hexenal, and a weakening of the depressant hypothermic effects of reserpine (Tables 1 and 2). It is well known that antidepressants which are MAO inhibitors potentiate the effects of 5-hydroxytryptophan [9]. The diaziridines studied here also enhance and prolong the hyperkinesis induced by 5-hydroxytryptophan and tryptamine. In these tests, the most active compounds were (Ib) and (IIb), which were found to be inhibitors of mitochondrial brain MAO, although less active in this respect than iproniazid (Table 3). The test compounds either had no effect on, or enhanced the effects of convulsants, behavior which is also characteristic of some antidepressants which are MAO inhibitors.

TABLE 3. Effects of the Most Active Compounds on MAO Activity in Rat Brain

Compound	Concentration, $M \cdot 10^{-4}$	% inhibition of MAO*	
		substrate	
		serotonin	tyramine
Ib	1	55	70
	0.1	40	58
IIb	1	65	80
	0.1	52	66
Iproniazid	1	95	100
	0.1	88	92

*Means of 4-6 measurements.

Hence, functionally substituted diaziridines (Ia, b-IV) and bisdiaziridines (Va-d) possess a number of properties typical of antidepressants. The most active of these, the amides (Ib) and (IIb), are inferior to imipramine, although in several tests they are superior to the typical MAO inhibitor iproniazid (Table 1). They are, however, inferior to these antidepressants in tests for interaction with reserpine (Table 2). It is also noteworthy that in contrast to antidepressants of the imipramine type [6, 9], the diaziridines have no cholinolytic properties, some of them (Ia,b—Va-d), on the other hand, stimulating the central m-cholinergic systems and potentiating the effects of the m-cholinomimetic arecoline.

Examination of the diaziridine-3-carboxylic acids (Ia) and (IIa), and (Ib) and (IIb), shows that replacement of the ester group by amide results in considerable enhancement of antidepressant properties, and in the case of (I), a weakening of stimulant effects. Comparison of the derivatives (Ia, c) and (Va-d) shows that the introduction of two diaziridine residues does not, contrary to expectation, result in any marked changes in activity (Tables 1 and 2).

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