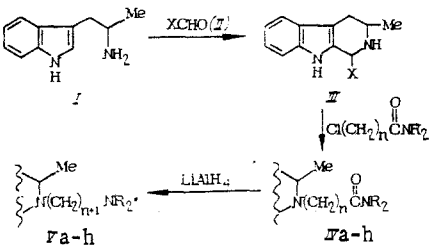
SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF 1,2,3-SUBSTITUTED 1,2,3,4-TETRAHYDRO-β-CARBOLINES

S. A. Pogosyan, L. A. Matevosyan,
A. S. Melik-Ogandzhanyan, R. R. Safrazbekyan,
E. M. Arzanunts, I. S. Sarkisyan,
R. G. Paronikyan, and N. E. Akopyan

UDC 615.214:214:547.562].012.1

β-Carbolines described in the literature have a wide spectrum of pharmacological activity [1, 8-10, 13]; they include phenharman having a psychotropic activity [8]. It was therefore of interest to carry out the synthesis of β-carboline derivatives with an aminoalkyl group in the 2-position (IVa-h, Va-h) and to study their pharmacological properties.

Substituted β-carbolines IVa-h and Va-h were obtained starting from α-methyltryptamine (I) and veratraldehyde (II) according to the following scheme:



IVa, e, Va, e: R=Me; IVb, f, Vb, f: R=Et; IVc, g, Vc, g: R=Pr; IVd, h, Vd, h R+R= $=(CH_2CH_2)_2O$; IVa, d, Va-d $n=1$; IVe, h, Ve, h $n=2$; X = $C_6H_3(OMe)_2$-3,4.

The condensation of I with aldehyde II was carried out by heating equimolar amounts of the components in boiling water in the presence of 2 N H_2SO_4. The structure of β-carboline III was confirmed by IR and PMR spectra, and also by the negative Ehrlich color reaction, indicating the absence of a free 2-position in the indole ring. In the IR spectrum there is an absorption band at 1620 cm^{-1}, characteristic for an aromatic ring and an absorption band at 3300-3350 cm^{-1} indicating the presence of amide and indole NH groups. In the PMR spectrum of III proton signals were detected at 1.25 (d, 3-CH_3), 3.2 (s, 6H, OCH_3), and 6.9-7.4 (m. aom. H) ppm.

Compound III was condensed with N, N-disubstituted chloroacetamides and N, N-disubstituted chloropropionamides in acetone in the presence of Na_2CO_3. In the IR spectra of IVa-h there are absorption bands of the amide carbonyl group at 1660-1680 cm^{-1} and of the indole imino group at 3300-3380 cm^{-1}. Diamines of the β-carboline series Va-h were obtained by reduction of IVa-h by lithium aluminum hydride in an ether—tetrahydrofuran solution. The absence of absorption of the amide carbonyl group in the IR spectra confirms the structure of the compounds obtained. Most of them are oily, undistillable substances, which were identified in the form of dihydrochlorides.

EXPERIMENTAL (CHEMICAL SECTION)

The IR spectra were run on a UR-20 spectrophotometer (GDR) in mineral oil and PMR spectra on a T-60 radiospectrometer (USA) at a working frequency of 60 MHz. The TLC was carried out on Al_2O_3, grade II of activity according to Brockmann: IVa-h in a 8:2 $CHCl_3$ — acetone system of solvents, Va-h in a 9:1 $CHCl_3$ — acetone systems of solvents, with development by iodine vapors.

1-(3,4-Dimethoxyphenyl)-3-methyl-1,2,3,4-tetrahydro-β-carboline (III). A 70-ml portion of water, 11 ml of 2 N H_2SO_4 and 3.32 g (0.02 mole) of veratraldehyde (II) are added to 3.2 g

The A. L. Mndzhoyan Institute of Fine Organic Chemistry, Academy of Sciences of the Armenian SSR, Erevan. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 20, No. 10, pp. 1191-1195, October, 1986. Original article submitted July 7, 1985.

 0091-150X/86/2010-0714$12.50

TABLE 1. N,N-Dialkyl [1-(3,4-Dimethoxyphenyl)-3-methyl-1,2,3,4-tetrahydro-β-carbolyn-2-yl]acetamides and Propionamides IVa-h

Compound	Yield, %	mp, °C (hydrochloride)	R_f	Found, %				Empirical formula	Calculated, %				IR spectrum, cm^{-1}		
				C	H	N	Cl		C	H	N	Cl	C=C	C=O	NH
IVa	44	133—5	0,50	70,44	7,47	10,21		$C_{24}H_{29}N_3O_3$	70,73	7,17	10,31	7,98	1620	1660	3360
		(250—2)				9,20	8,30	$C_{24}H_{30}ClN_3O_3$			9,46				
IVb	90	—	0,58	72,10	7,82	9,66		$C_{26}H_{33}N_3O_2$	71,70	7,63	9,65		1610	1650	3350
		225—7				8,46	7,81	$C_{26}H_{34}ClN_3O_3$			8,90	7,51			
IVc	75	—	0,33	72,30	8,30	8,60		$C_{28}H_{37}N_3O_3$	72,53	8,04	9,06		1600	1670	3360
		(137—40)				8,61	7,25	$C_{28}H_{38}ClN_3O_3$			8,40	7,09			
IVd	60	—	0,23	68,98	6,60	9,08		$C_{26}H_{31}N_3O_4$	69,46	6,95	9,34		1610	1670	3360
		(125—30)				8,76	7,40	$C_{26}N_{32}ClN_3O_4$			8,65	7,29			
IVe	48	150—2	0,69	71,60	7,83	9,65		$C_{25}H_{31}N_3O_3$	71,26	7,36	9,97		1600	1680	3350
		(115—7)				9,68	8,05	$C_{25}H_{36}ClN_3O_3$			9,18	7,76			
IVf	85	110—2	0,70	72,60	7,81	9,80		$C_{27}H_{35}N_3O_3$	72,16	7,78	9,35		1610	1650	3360
		(95—7)				8,80	7,90	$C_{27}H_{36}ClN_3O_3$			8,64	7,39			
IVg	68	—	0,63	73,31	8,00	8,60		$C_{27}H_{33}N_3O_4$	73,56	8,17	8,80		1610	1660	3400
		(125—7)	0,83			8,38	7,54	$C_{27}H_{31}ClN_3O_4$			8,17	6,90			
IVh	80	—	0,73	69,68	7,06	9,13		$C_{27}H_{33}N_3O_4$	69,95	7,17	9,06		1600	1660	3380
		(140—2)				8,30	7,60	$C_{27}H_{34}ClN_3O_4$			8,40	7,10			

TABLE 2. 1-(3,4-Dimethoxyphenyl)-2-[2(3)-dialkylaminoethyl(propyl)]-3-methyl-1,2,3,4-tetrahydro-β-carbolines Va-h

Compound	R_f	Yield, %	mp, °C (hydrochloride)	Found, %				Empirical formula	Calculated, %				IR spectrum, cm^{-1}	
				C	H	N	Cl		C	H	N	Cl	C=C	NH
Va	0,66	52	73—5	72,85	7,43	10,48		$C_{24}H_{31}N_3O_2$	73,25	7,86	10,67		1620	3350
			(155—7)			8,94	15,70	$C_{24}H_{33}Cl_2N_3O_2$			9,01	15,20		
Vb	0,60	50	74—5	73,81	8,06	9,86		$C_{26}H_{35}N_3O_2$	74,07	8,36	9,96		1620	3360
			(176—7)			8,35	13,93	$C_{26}H_{37}Cl_2N_3O_2$			8,50	14,34		
Vc	0,76	56	—	75,30	8,65	9,36		$C_{28}H_{39}N_3O_2$	74,79	8,74	9,34		1610	3370
			(155—60)			8,02	13,66	$C_{28}H_{41}Cl_2N_3O_2$			8,04	13,57		
Vd	0,46	53	—	71,27	7,28	10,02		$C_{26}H_{33}N_3O_3$	71,70	7,64	9,65		1610	3380
			(95—8)			8,03	14,30	$C_{26}H_{35}Cl_2N_3O_3$			8,26	13,94		
Ve	0,77	74	—	73,50	8,10	10,05		$C_{25}H_{33}N_3O_2$	73,72	8,10	10,31		1620	3375
			(119—20)			8,64	15,20	$C_{25}H_{35}Cl_2N_3O_2$			8,74	14,74		
Vf	0,73	57	—	74,30	8,60	9,57		$C_{27}H_{37}N_3O_2$	74,50	8,49	9,72		1620	3400
			(80—3)			8,00	14,40	$C_{27}H_{39}Cl_2N_3O_2$			8,26	13,96		
Vg	0,80	55	—	74,98	8,60	8,98		$C_{29}H_{41}N_3O_2$	75,17	8,87	9,08		1610	3380
	0,62		(85—7)			8,05	13,56	$C_{29}H_{43}Cl_2N_3O_2$			7,83	13,24		
Vh	0,80	82	—	72,21	7,86	9,01		$C_{27}H_{35}N_3O_3$	72,16	7,78	9,35		1620	3390
			(65—7)			7,81	14,02	$C_{27}H_{37}Cl_2N_3O_3$			8,04	13,60		

(0.02 mole) of tryptamine (I). The solution is gradually heated on an oil bath to 100°C, and held at this temperature for 30 min. The solution is cooled, neutralized by Na_2CO_3, decanted, and the residue is treated with 10% HCl. The aqueous layer is neutralized by 5% NaOH, and extracted by ethyl acetate. After distillation of solvent, the yield of III is 3.6 g (56%), mp 197-200°C, R_f 0.33 (Al_2O_3, $CHCl_3$ – acetone, 9:1). Found, %: C 74.70; H 7.56; N 8.22. $C_{20}H_{22}N_2O_2$. Calculated, %: C 74.27; H 7.16; N 8.66. Hydrochloride, mp 221-222°C (dec). Found, %: N 7.80; Cl 9.87; $C_{20}H_{23}N_2O_2Cl$. Calculated, %: N 7.88; Cl 10.20. IR spectrum, ν_{max}, cm^{-1}: 1620 (C=C arom.) 3300-3350 (NH, amine, ind.).

N,N-Dialkyl [1-(3,4-dimethoxyphenyl)-2-methyl-1,2,3,4-tetrahydro-β-carbolin-2-yl]acetamides and Propionamides (IVa-h). A mixture of 3.22 g (0.01 mole) of β-carboline III, 2.12 g (0.02 mole) of Na_2CO_3, and 0.015 mole of N,N-dialkyl monochloroacetamide or β-chloropropionamide in 100 ml of acetone is boiled for 12 h. Acetone is distilled off, the precipitate is extracted by ether, the extract is washed with water, and dried over Na_2SO_4. The solution is concentrated to a 20 ml volume, and passed through a column with Al_2O_3 (80 g). After distillation of ether, the residue is crystallized from absolute ether (Table 1).

1-(3,4-Dimethoxyphenyl)-2-[2(3)-dialkylaminoethyl(propyl)]-3-methyl-1,2,3,4-tetrahydro-β-carbolines (Va-h). A solution of 0.01 mole of IVa-h in 80 ml of dry tetrahydrofuran is added dropwise to 0.1 mole of $LiAlH_4$ in 150 ml of absolute ether. The solution is boiled with stirring for 18 h. When cool, the mixture is decomposed by 19 ml of 5% NaOH, filtered, the precipitate is washed with ether, and the combined ether–tetrahydrofuran solution is evaporated. The residue is treated by 10% HCl, the aqueous layer is neutralized by a NaOH solution and extracted by ether. The ether solution is dried over KOH, concentrated and passed through a column with Al_2O_3 (80 g) (Table 2).

Dihydrochlorides were obtained by adding an ethereal HCl solution to an ether solution of Va-h, and are recrystallized from a 1:1 alcohol–ether mixture.

EXPERIMENTAL (BIOLOGICAL SECTION)

Certain pharmacological properties of compounds IVa-h and Va-h were studied in experiments on nonpedigreed white mice weighing 18-22 g each and rats weighing 150-180 g each of both sexes. The influence of 17 compounds (in doses of 10, 50, and 100 mg/kg) on the motor activity of the animals, body temperature, central depressant effects of reserpine (ptosis, hypothermia, catalepsy, potentiation of Nembutal-induced sleep), and also on the apomorphine effects was studied by methods already described in [3, 4]. The compounds were introduced subcutaneously in a dose of 50 mg/kg, simultaneously with an intraperitoneal injection of reserpine (1.5 mg/kg) to rats, and 30 min before introduction of apomorphine (5 mg/kg) to mice. Indopan was used for comparison.

The antispasmodic activity of the compounds was determined in experiments on mice, using electrical shock as a model of spasm induction, and also Corazol and nicotine-induced spasms and arecoline-induced tremor [2, 6, 11, 12]. The compounds were administered intraperitoneally 30 min before the injection of the spasmodic agents and application of the electrical irritation. The daily acute toxicity (LD_{50}) of the most active compounds Vc,g was also studied. The Litchfield and Wilcoxon method of probit analysis was used to determine the mean effective (ED_{50}) and toxic doses.

The influence of compounds Vc,g on the serotin (5-OT), noradrenalin (NA) and dopamine (DA) contents in the mice brains was also measured by ion exchange chromatography [5]. The compounds were introduced subcutaneously in a dose of 50 mg/kg, 1 h before decapitation.

Compounds Vc, d, h in doses of 50 and 100 mg/kg cause suppression of the motor activity in mice, evaluated as 0.5 point according to [7]; in parallel, a certain decrease in the skin temperature has been noted, within 1-3°C, depending on the dose. The remaining compounds do not appreciably influence the behavior of the body temperature in mice. In the experiments on rats, compounds III, IVd, Va, e in a dose of 100 mg/kg cause ataxia, increase the frequency of respiration, without changing the body temperature of the animals. In their pattern of action, the compounds differ from indopan, which beginning from a dose of 10 mg/kg, causes symptoms of excitation of the central nervous system in mice and rats.

Under the conditions of simultaneous introduction with reserpine to rats, compounds Vc, g, h, in contrast to indopan, hinder only the development of a reserpine-induced blepharoptosis, 4 h after the injection of the neuroleptic. This antagonistic action is most pronounced in compound Vg, which completely eliminates the effect of reserpine. Com-

pounds Vc, h relieve blepharoptosis to the extent of 70 and 56%, respectively. The remaining compounds do not change the reserpine effects. All the compounds also do not influence reserpine potentiation of Nembutal-induced sleep in rats, apomorphine-induced hypothermia, and stereotypy in mice. However, in animals which received compounds Vc, d, g before apomorphine, in contrast to control animals, aggressive behavior and circular movements are absent. Moreover, compound Vc increases the apomorphine hypothermia by 1.6°C.

In a dose of 200 mg/kg, the compounds studied do not exhibit the central p- and m-cholinolytic action, i.e., they do not influence nicotine-induced spasms and arecoline-induced tremor. They also have no anti-Corazol activity. Compounds Vc, g prevent a tonic phase from maximal electrical shock. For compound Vc, ED_{50} is equal to 86 (62-119) mg/kg, LD_{50} — 280 (225-347) mg/kg; for compound Vg — 75 (51.7-108.8) and 430 (333-559) mg/kg, respectively.

One hour after injection, compound Vc increases the 5-OT content in the brain of mice by 36% ($P < 0.001$) and does not change the NA and DA level. Compound Vg does not influence the 5-OT, NA, and DA content in the brain of mice. Under the same conditions, indopan in a dose of 10 mg/kg increases the 5-OT content in the brain by 20% ($P < 0.05$).

Thus, in the series of substituted β-carbolines, only compound Vc with an isopropyl radical at the nitrogen atom of the side chain exhibits an appreciable psychotropic activity: it causes behavioral depression, hypothermia; similarly to the known depressant indopan, compound Vc counteracts reserpine-induced blepharoptosis and selectively increases the 5-OT content in the brain of the mice. In addition, compounds Vc and Vg prevent spasms induced by electrical shock.

LITERATURE CITED

1. N. Bikova, Ek. Denkova, L. Deleva, et al., Trudove N. I. Khim.-farm. In-t, 9, 141-153 (1974); Ref. Zh. Khim., No. 15E92 (1975).
2. M. Ya. Mikhel'son and Ya. R. Savinskii, Farmakol. Toksikol., No. 3, 28-33 (1955).
3. R. R. Safrazbekyan and Arzanunts, Biol. Zh. Arm., 25, No. 2, 102-106 (1972).
4. R. R. Safrazbekyan and É. M. Arzanunts, Biol. Zh. Arm., No. 10, 45-48 (1972).
5. R. R. Safrazbekyan and É. M. Arzanunts, Lab. Delo., No. 4, 226-227 (1977).
6. D. Biret and N. G. Longo, J. Pharmacol. Exp. Ther., 102, 22-30 (1951).
7. M. Cohen and J. N. Nelson, J. Pharm. Sci., 53, 863-868 (1964).
8. J. O. Jilek, J. Pomykacek, J. Jirkovsky, and M. Protiva, Csl. Farm., 3, 229-233 (1964).
9. S. Kenneth and R. Woo-Ming, Heterocycles, 3, 223-264 (1975).
10. J. Sandrin, D. Soerens, P. Mokry, and J. Cook, Heterocycles, 6, 1133-1139 (1977).
11. E. A. Swinjard, W. E. Brown, and L. S. Goodman, J. Pharmacol. Exp. Ther., 106, 319-330 (1952).
12. J. S. P. Toman, E. A. Swinyard, and L. S. Goddman, J. Neurophysiol., 9, 231-239 (1946).
13. M. Von Strandtman, S. Puskalskic, and J. Havel, J. Med. Chem., 7, 141-146 (1964).