INDOLE DERIVATIVES

XXIX. SYNTHESIS AND ANTISEROTONIN PROPERTIES OF CERTAIN NEW INDOLE DERIVATIVES

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It is known that serotonin in small doses stimulates the receptors of the heart and lungs, as a result of which the frequency of the heartbeat decreases, as does the arterial pressure [1, 2]. These reflex reactions are not inhibited by lysergic acid derivatives, morphine, and other classical serotonin antagonists, which prevent the appearance of its myotropic and ganglionic effects [3-5]. In our previous investigations [4-6], we demonstrated that serotonin-reactive structures of the cardiac-pulmonary reflexogenic zone are blocked by typindole (1,3,4,5-tetrahydrothiopyrano[4,3-b]indolecarboxylic-8 acid dimethylaminoethyl ester hydrochloride) [7]. The purpose of this work was to synthesize compounds structurally close to typindole and to study their influence upon the reflexes induced by serotonin.

Derivatives of 1,3,4,5-tetrahydrothiopyrano[4,3-b]indole (I), tetrahydro-γ-carboline (II), tetrahydrocarbazole (III), hexahydrocycloheptindole (IV), 2,3-dimethylindole (V), and 2-methyl-3-ethylindole (VI), possessing a carbethoxyl group in the p-position to the indole nitrogen (Table 1), were synthesized by Fischer cyclization of p-carbethoxyphenylhydrazones of tetrahydrothiopyrone-4, N-methylpiperidone-4, cyclohexanone, cycloheptanone, methyl ethyl ketone, and methyl propyl ketone.

6-Carbomethoxy-1,3,4,5-tetrahydrothiopyrano[4,3-b]indole (VII) was produced by cyclization of the o-carbomethoxyphenylhydrazone of tetrahydrothiopyrone-4. In the alkylation of Na derivatives of carbethoxyindoles (produced using sodium hydride in dimethylformamide) with alkyl halides and dialkylaminoalkyl chlorides, carbethoxyindoles (VIII-XIII), substituted as the indole nitrogen, were synthesized (Table 2).

All the indole derivatives, possessing carbethoxyl or carbomethoxyl groups, were transesterified with dialkylaminoalkanols to the corresponding amino esters (XIV-XXVI). Transesterification was performed by boiling the ethyl (methyl) esters in toluene with an excess of amino alcohol in the presence of catalytic amounts of the alcoholate of the investigated amino alcohol with azeotropic distillation of the ethanol formed with toluene. The yields and constants of the amino alcohols obtained are cited in Table 3.

Some of the synthesized preparations were subjected to pharmacological study. The experiments were conducted on cats, narcotized with urethane (600 mg/kg) and chlorazole (40 mg/kg). The arterial pressure was measured in the common carotid artery with a mercury manometer. The heartbeat was computed according to the curve of the arterial pressure. Serotonin and its antagonists were injected intravenously. The dose in which the antagonist doubles the threshold of reflex reactions to serotonin was determined. For typindole, this dose is 0.35 ± 0.08 mg/kg. Our experiments indicated that changing from typindole to analogous compounds of the tetrahydrocarbazole and cycloheptindole series—the hydrochlorides (XX) and (XXI)—does not significantly change the antiserotonin properties. Changing to the corresponding derivative of tetrahydro-γ-carboline (XIX) weakens the ability to inhibit reflexes.

The relative activity of the hydrochloride of XIX is 0.54 in comparison with the activity of typindole, taken as 1. A slight weakening of the antiserotonin properties is observed for 2,3-dialkylindole derivatives. Thus, the relative activity of the hydrochlorides of XXIV and XXII is 0.78 and 0.9, respectively. Thus, a change from typindole to the corresponding derivatives of tetrahydrocarbazole, tetrahydro-γ-carboline, cycloheptindole, and 2,3-dialkylindole does not change or only slightly weakens the ability of the preparations to inhibit the "serotonin" reflexes. This ability is also sharply weakened when hydrogen at the indole nitrogen is replaced by a benzyl group and especially by a β-dimethylaminoethyl group. Thus, the N-benzyl analog of typindole (the hydrochloride of XVIII) halves the threshold of reflex bradycardia at a

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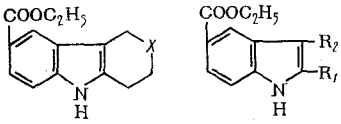
TABLE 1



I-IV V, VI VII

Compound	X or R_1, R_2	Yield (in %)	Melting point (in degrees)	Literature references
I	S	62,9	158—9	[7]
II	NCH_3	48	145—6	[8]
III	CH_2	50	116—7	[9]
IV[1]	$(CH_2)_2$	28	97—8	
V	$R_1=R_2=CH_3$	86	113—4	
VI	$R_1=CH_3$, $R_2=C_2H_5$	80	98,5—99	[10]
VII[2]		56,7	150—1	[11]

[1]Found, %: C 74, 73, 74, 90; H 7.53, 7.68; N 5.32, 5.38. $C_{16}H_{19}NO_2$. Calculated, %: C 74.69; H 7.44; N 5.45.
[2]Found, %: N 5.55, 5.53; S 13.16, 13.27. $C_{13}H_{13}N_2O_2S$. Calculated, %: N 5.67; S 12.96.

dose of 3.6 mg/kg (its activity is 0.12 in comparison with typindole). The corresponding β-dimethylaminoethyl derivative (hydrochloride of XVII) does not inhibit the reflex even at a dose of 5 mg/kg. The replacement of hydrogen at the indole nitrogen by a methyl group does not weaken the ability of the substances to inhibit reflexes. The antiserotonin properties of the preparations are substantially weakened by the replacement of the β-dimethylaminoethoxycarbonyl group in the 8-position of thiopyranoindole by an amino group. The hydrochloride of 8-amino-1,3,4,5-tetrahydrothiopyrano[4,3-b]indole [7] does not inhibit the reflexes at a dose of 5 mg/kg. Nor does 2-ethyl-3-methyl-5-aminoindole inhibit the reflexes at this dose.

As a result of our investigations, we established that the ability to inhibit reflexes induced by serotonin is possessed by derivatives of tetrahydrothiopyranoindole, tetrahydro-γ-carboline, tetrahydrocarbazole, cycloheptindole, and 2,3-dialkylindole, possessing a hydrogen atom or a methyl group on the indole nitrogen and a β-dimethylaminoethoxycarbonyl group in the para-position to the indole nitrogen.

EXPERIMENTAL

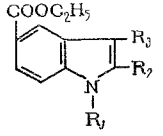
o-Carbomethoxyphenylhydrazine hydrochloride (mp 174-175°) was synthesized from the methyl ester of anthranilic acid analogously to the production of o-carbethoxyphenylhydrazine [12]. Found, %: Cl 17.71, 17.75. $C_{18}H_{11}ClN_2O_2$. Calculated, %: Cl 17.50.

o-Carbomethoxyphenylhydrazone of Tetrahydrothiopyrone-4. A mixture of 14 g o-carbomethoxyphenylhydrazine hydrochloride, 5.4 g tetrahydrothiopyrone-4, and 100 ml of alcohol was boiled for 30 min; after cooling, the precipitate was filtered off, washed with water, and crystallized from alcohol. Yield 17 g (93%) of the hydrazone, mp 90-91°. Found, %: N 10.42, 10.51; S 12.25, 12.41. $C_{13}H_{16}N_2O_2S$. Calculated, %: N 10.60; S 12.14.

Fischer Cyclization. p-Carbethoxyphenylhydrazones of tetrahydrothiopyrone-4, N-methylpiperadone-4, cyclohexanone, and cycloheptanone and the o-carbomethoxyphenylhydrazone of tetrahydrothiopyrone-4 were cyclized by 10-15 min boiling with concentrated hydrochloric acid; the p-carbethoxyphenylhydrazones of methyl ethyl ketone and methyl propyl ketone were cyclized by 15 min boiling with a mixture of glacial acetic and concentrated sulfuric acid (19:1). Data on the substances I-VII obtained are cited in Table 1.

Alkylation of V-VII. To 30 ml of freshly redistilled dimethylformamide, 0.9 g sodium hydride was added, and then 0.028 mole of the indole derivative V-VII in 50 ml of dimethylformamide was added with mixing, the mixture mixed for 1.5 h at 30-40°, then 0.028 mole of the alkyl halide added, mixed for 1.5-2 h at room temperature, and poured out into water. The precipitate formed was filtered off, washed with water, dried, and recrystallized from aqueous alcohol or heptane. Information on the substances VIII-XIII obtained is cited in Table 2.

TABLE 2



Compound	R_1	R_2	R_3	Base (in %)	Temp. (in degrees)	Found (in %) C	Found (in %) H	Found (in %) N	Found (in %) Cl	Gross formula	Calculated (in %) C	Calculated (in %) H	Calculated (in %) N	Calculated (in %) Cl
VIII	CH_3	CH_3	CH_3	79	92—3	72.84 73.00	7.46 7.44	6.37 6.20		$C_{14}H_{17}NO_2$	72.69	7.41	6.06	
IX	CH_3	CH_3	C_2H_5	77.5	72—3			6.04 6.09		$C_{15}H_{19}NO_2$			5.71	
X	$CH_2C_6H_5$	CH_3	C_2H_5	55.5	63—4			4.55 4.51		$C_{21}H_{23}NO_2$			4.36	
XI	$CH_2CH_2N(CH_3)_2$ ·HCl	CH_3	CH_3	85	210—1			8.56 8.68	11.45 11.50	$C_{17}H_{25}N_2O_2Cl$			8.63	10.91
XII	$CH_2CH_2N(CH_3)_2$ ·HCl	R_2+R_3 $=CH_2SCH_2CH_2$		74.1	118—9	64.85 64.64	7.17 7.11	8.77 8.72	9.48 9.41	$C_{18}H_{24}N_2O_2SCl$	65.02	7.27	8.42	9.64
XIII	$CH_2CH_2N(CH_3)_2$[1] ·HCl	CH_3 CH_3		95	215—7			9.96 9.77	12.55 12.57	$C_{15}H_{23}N_2OCl$			9.90	12.54

[1]Contains the OCH_3 group instead of $COOC_2H_5$.

TABLE 3. Dialkylaminoalkyl Esters

Compound	Base											Hydroxide					
	yield (in %)	melting point (in deg.)	found (in %)				gross formula	calculated (in %)				melting point (in deg.)	found (in %)		gross formula	calculated (in %)	
			C	H	N	S		C	H	N	S		N	Cl		N	Cl
β-Dimethylaminoethyl ester of 1, 3, 4,5-tetrahydrothiopyrano [4,3-b]indole-1-carboxylic-6 acid (XIV)	52,6	117—8			9,00 8,75	10,78 10,85	$C_{16}H_{20}N_2O_2S$			9,27	10,53	234—6	7,92 8,14		$C_{16}H_{21}N_2O_2ClS$ [1]	8,22	
β-(N-Piperazinyl)ethyl ester of 1,3,4, 5-tetrahydrothiopyrano[4, 3-b]indolecarboxylic-8 acid (XV)		176—8			12,03 12,27	9,32 9,36	$C_{18}H_{23}N_3O_2S$			12,16	9,27	246—247,5		16,85 16,62	$C_{18}H_{25}N_3O_2SCl_2$		16,94
β-(N)Morpholyl)ethyl ester of 1,3,4, 5-tetrahydrothiopyrano[4, 3-b]indolecarboxylic-8 acid (XVI)	57,5	159—61			8,13 8,27	9,46 9,47	$C_{18}H_{22}N_2O_3S$			8,09	9,26						
β-Dimethylethyl ester of 5-(β-dimethylaminoethyl)-1,3,4,5-tetrahydrothiopyrano[4,3-b]indolecarboxylic-8 acid (XVII)	69,4											273—5	9,58 9,45	15,44 15,35	$C_{20}H_{31}O_2N_3SCl_2$	9,37	15,81

TABLE 3 (continued)

Compound	Base										Hydroxide					
	yield (in %)	melting point (in deg.)	found (in %)				gross formula	calculated (in %)				melting point (in deg.)	found (in %)		gross formula	calculated (in %)	
			C	H	N	S		C	H	N	S		N	Cl		N	Cl
β-Dimethyl-aminoethyl ester of 5-benzyl-1,3,4,5-tetrahydro-thiopyrano[4,3-b]-indole-carboxylic-8 acid (XVIII)	65,3[2]											209—10	6,32 6,53	8,00 8,11	$C_{23}H_{27}O_2N_2SCl$	6,50	8,22
β-Dimethyl-aminoethyl ester of 1,2,3,4-tetrahydro-γ-carboline-carboxylic-6 acid (XIX)	70,4	148—9	68,33 68,31	7,76 7,83	13,96 13,66		$C_{17}H_{23}N_3O_2$	67,74	7,69	13,94		269—70		18,63 18,63	$C_{17}H_{25}N_3O_2Cl_2$		18,94
β-Dimethyl-aminoethyl ester of 1,2,3,4,tetrahydro-carbazolecar-boxylic-6 acid (XX)	67,0	151—2	71,54 71,26	7,62 7,83	9,80 9,89		$C_{17}H_{22}N_2O_2$	71,29	7,74	9,78		209—10		10,88 11,10	$C_{17}H_{23}N_2O_2Cl$		10,98

TABLE 3 (continued)

Compound	Base											Hydroxide					
	yield (in %)	melting point (in deg.)	found (in %)				gross formula	calculated (in %)				melting point (in deg.)	found (in %)		gross formula	calculated (in %)	
			C	H	N	S		C	H	N	S		N	Cl		N	Cl
β-Dimethyl-aminoethyl ester of 5,6,7,8,9,10-hexa-hydrocyclohept (b)-indolecar-boxylic-2 acid (XXI)	80,0	124—5	71,14 71,36	8,04 7,91	9,85 9,87		$C_{18}H_{24}N_2O_2$	71,95	8,06	9,34		183—4	8,39 8,41	10,49 10,27	$C_{18}H_{25}N_2O_2Cl$	8,32	10,52
β-Dimethyl-aminoethyl ester of 2,3-dimethylin-dolecarboxylic-5-acid (XXII)	60,6	136—7	69,44 69,57	7,80 7,85	10,50 10,58		$C_{15}H_{20}N_2O_2$	69,24	7,75	10,76		203—4	9,56 9,60	11,76 11,78	$C_{15}H_{21}N_2O_2Cl$	9,44	11,93
β-Dimethyl-aminoethyl ester of 1,2,3-trimethylindole-carboxylic-5 acid (XXIII)	72,1	72—3	69,99 70,15	8,04 8,22	10,19 10,25		$C_{16}H_{22}N_2O_2$	70,03	8,08	10,21		198—200	8,73 8,85	11,30 11,44	$C_{16}H_{23}N_2O_2Cl$	9,01	11,41
β-Dimethyl-aminoethyl ester of 2-methyl-3-ethylindole-carboxylic-5 acid (XXIV)	70,0	110—1	70,10 70,30	8,19 8,33	10,45 10,60		$C_{16}H_{22}N_2O_2$	70,03	8,08	10,21		176—8	8,63 8,81	11,37 11,64	$C_{16}H_{23}N_2O_2Cl$	9,01	11,41

TABLE 3 (continued)

Compound	Base										Hydroxide								
	yield (in %)	melting point (in deg.)	found (in %)					gross formula	calculated (in %)					melting point (in deg.)	found (in %)		gross formula	calculated (in %)	
			C	H	N	S			C	H	N	S			N	Cl		N	Cl
β-Dimethyl-aminoethyl ester of 1,2-dimethyl-5-indolecarboxylic-5 acid (XXV)	80,0[2]													216—7	8,64 8,77	10,57 10,35	$C_{17}H_{25}N_2O_2Cl$	8,63	10,91
β-Dimethyl-aminoethyl ester of 1-benzyl-2-methyl-3-ethylindole-carboxylic-5 acid (XXVI)	95,0[2]													205—6	7,16 7,33	8,64 8,75	$C_{23}H_{29}N_2O_2Cl$	6,99	8,84

[1]Found, %: S 10.02, 9.98. Calculated, %: S 9.40.
[2]Yield on the basis of the hydrochloride.

Transesterification. To 0.01 mole of the carbethoxyindole in 100 ml of absolute toluene we added 5 ml of the amino alcohol, 10 mg of sodium, and boiled for 2 h with slow distillation of the toluene. Then another 5 ml of the amino alcohol was added, and 50 ml of absolute toluene, and the mixture again boiled for 1.5-2 h, distilling off the toluene. The remains of the toluene and amino alcohol were distilled off under vacuum, and the oil remaining dissolved in 50 ml of ether, washed with water, and dried. The base was isolated by evaporating the ether extract, or the corresponding amino ester hydrochloride was precipitated with a solution of hydrogen chloride in ether. Data on the substances XIV-XXVI obtained are cited in Table 3.

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