INDOLE DERIVATIVES

LXII. SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF TRYPTAMINE HOMOLOGS

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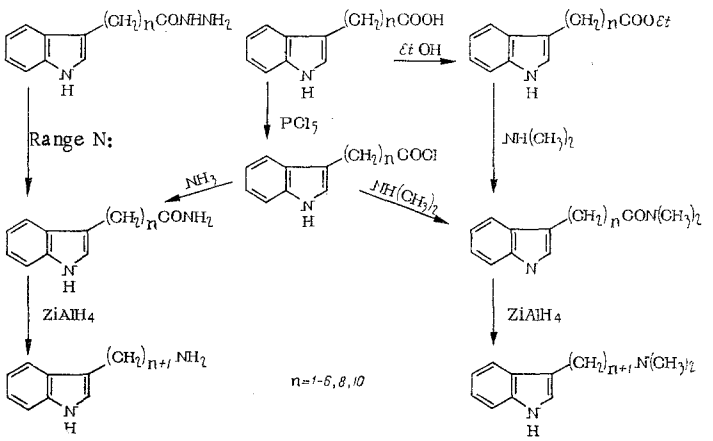
UDC 615.22 :547.75].012.1

Tryptamine is an important biogenic amine. Tryptamine derivatives (serotonin, mexamine, indopan, etc.) possess pronounced pharmacological activity and are used as drugs. N,N-Dimethyltryptamine has a strong effect on the central nervous system.

We synthesized homologs of tryptamine and N,N-dimethyltryptamine according to the scheme cited below and studied the relationship between the structure and the pharmacological action of the compounds obtained. The synthesis was facilitated to a substantial degree by the fact that we had available the starting materials, ω-indolyl-3-alkanoic acids (I), the method of production of which we had developed earlier [1]:



The production of amides and N,N-dimethylamides of ω-indolyl-3-alkanoic acids (V and VI; Table 1) through the acid chlorides is preferable, since in this case purer products can be isolated with better yields. The amides V and VI crystallize well, whereas ω-indolyl-3-alkylamines (VII) and N,N-dimethyl-ω-indolyl-3-alkylamines (VIII) crystallize poorly and darken upon storage. Their salts, hydrochlorides, and adipates can be obtained in the form of crystalline substances, more stable and soluble in water (Table 2).

Pharmacological investigation indicated that lengthening the side chain of tryptamine (compounds VIIb-VIId, VIIf) and conversion to the corresponding tertiary amines (compounds VIIIb-VIIId) leads to a change in its pharmacological activity. With respect to spasmogenic action on the smooth musculature (rat

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TABLE 1. Amides and N,N-Dimethylamides of ω-Indolyl-3-alkanoic Acids (V and VI)

Compound	Found (in %)			Gross formula	Calc., (in %)			Melting point (in degrees)	Yield (in %)
	C	H	N		C	H	N		
Va, n = 1 [3]	—	—	—	—	—	—	—	153,5—154	86,0
Vb, n = 2 [4]	70,48	6,42	15,04	$C_{11}H_{12}N_2O$	70,30	6,40	14,90	134,5—13,5	78,0
Vc, n = 3 [4]	71,33	6,94	14,29	$C_{12}H_{14}N_2O$	71,29	6,93	13,86	117—118,5	77,0
Vd, n = 4 [4]	72,40	7,05	12,90	$C_{13}H_{16}N_2O$	72,20	7,40	12,96	125—6	87,0
Ve, n = 5 [4]	73,06	7,85	12,11	$C_{14}H_{18}N_2O$	73,04	7,82	12,17	132—3	67,0
Vf, n = 6	73,75	8,62	11,52	$C_{15}H_{20}N_2O$	73,77	8,20	11,47	122—4	70,5
Vg, n = 8	75,29	9,05	10,18	$C_{17}H_{24}N_2O$	75,00	8,82	10,30	102—3	67,6
Vh, n = 10	75,87	9,72	9,36	$C_{19}H_{28}N_2O$	76,00	9,33	9,33	104—5	88,0
VIb, n = 2	72,54	7,23	12,98	$C_{13}H_{16}N_2O$	72,20	7,40	12,96	139—140,5	50,5
VIc, n = 3	72,63	7,94	12,21	$C_{14}H_{18}N_2O$	73,04	7,82	12,17	104—105,5	64,5
VId, n = 4	73,93	8,75	11,22	$C_{15}H_{20}N_2O$	73,77	8,20	11,47	133—5	86,0
VIe, n = 5	74,50	8,92	10,61	$C_{16}H_{22}N_2O$	74,41	8,52	10,85	112—4	48,3
VIf, n = 6	74,90	8,78	10,22	$C_{17}H_{24}N_2O$	75,00	8,82	10,30	124—5	72,5
VIg, n = 8	76,37	9,60	9,35	$C_{19}H_{28}N_2O$	76,00	9,33	9,33	96—7	70,0
VIh, n = 10	76,50	10,03	8,12	$C_{21}H_{32}N_2O$	76,83	9,75	8,53	101—2	75,3

horn of the uterus), compound VIIb is ten times less active than tryptamine, and compound VIIc is one thousand times less active. Further lengthening the side chain (compounds VIId, VIIf) leads to a loss of spasmogenic activity. Compounds VIIb-VIId, VIIf are less active than tryptamine, with respect to other indices as well (vasoconstrictive action, contraction of the third eyelid in cats). N,N-Dimethylderivatives possesss antiserotonin activity both in experiments on isolated organs (rat horn of the uterus, vessels of the rabbit ear) and on animals (reduction of diarrhea induced by 5-hydroxytryptophan in mice, reduction of the spasmodic effect of tryptamine in rats). N,N-Dimethyl-ω-indolyl-3-ethylamine and N,N-dimethyl-ω-indolyl-3-propylamine (VIIb) produce a pronounced hyperthermic effect in rabbits, i.e., the effect characteristic of indolylalkylamines (bufotenin, etc.) possessing hallucinogenic properties [2].

EXPERIMENTAL

Amides of ω-Indolyl-3-alkanoic Acids (V). A. To 25 g Raney nickel in 100 ml absolute ethanol, a solution of 0.01 mole of the hydrazide of ω-indolyl-3-alkanoic acid (II) in 150 ml of absolute ethanol was added gradually with good mixing. The amount of the catalyst was taken in a 5-10-fold excess with respect to the weight of the hydrazide. The mixture was cautiously heated to boiling, and boiling was continued with constant mixing for 3 h. After cooling, the nickel was filtered off, washed several times with hot absolute ethanol with 20-25 ml portions, the filtrate combined with the wash liquid, concentrated to 25-30 ml, and cooled for an hour in a mixture of ice and salt. The precipitate formed was suction filtered, washed with water, and dried in a vacuum desiccator.

B. To a suspension of 0.1 mole I in 100 ml absolute diethyl ether, cooled with a mixture of ice and salt, 0.011 mole of phosphorus pentachloride was added in small portions with mixing. The temperature of the reaction mixture should not exceed 5-10°. The reaction is ended in 1.5 h. The solution of the ω-indolyl-3-alkanoyl chloride (IV) obtained was rapidly filtered to remove a small amount of resinous impurities, and added slowly with mixing to 100 ml of 25% aqueous ammonia, cooled with a mixture of ice and salt. The crystalline precipitate formed was filtered and dried.

The amides V were crystallized from ethyl acetate. Data on them are cited in Table 1.

The IR spectra were taken on a UR-10 spectrophotometer in liquid petrolatum: ν 3400 cm^{-2} (in indole); ν_{NH} 3200 cm^{-1} (in amide), ν_{CO} 1640 cm^{-1} (band of the amide–I): 1430 cm^{-1} (band of the amide–V).

N,N-Dimethylamides of ω-Indolyl-3-alkanoic Acids (VI). A. A solution of 0.01 mole of the ethyl ester of ω-indolyl-3-alkanoic acid (III) and about 4 g of dimethylamine in 15 ml absolute ethylene glycol were left for five days at room temperature, then poured out into 150 ml of ice water. The precipitate formed was filtered off, washed with water, and dried.

B. To a solution of IV, prepared according to the method described above, 50 ml of a 33% aqueous solution of dimethylamine was added with cooling and mixing and left for 2 h, then the precipitate removed.

N,N-Dimethylamines VI were crystallized from ethyl acetate or benzene-petroleum ether mixture. Data on them are cited in Table 1.

TABLE 2. ω-Indolyl-3-alkylamines and N,N-Dimethyl-ω-indolyl-3-alkylamines

Compound	Melting point (in degrees)	Found (in %)				Gross formula	Calculated (in %)				Yield (in %)
		C	H	N	Cl		C	H	N	Cl	
XII a, hydrochloride n=1 [5]	244,5—245,5				17,59	$C_{10}H_{12}N_2 \cdot HCl$				18,06	64,0
VII b, hydrochloride n=2 [3]	169—70				16,89	$C_{11}H_{14}N_2 \cdot HCl$				16,87	77,0
VII c, hydrochloride n=3	217—8				15,87	$C_{12}H_{17}N_2 \cdot HCl$				15,78	81,5
VII d, adipate n=4	179—180,5	65,47	8,31	8,34	—	$C_{13}H_{18}N_2 \cdot C_6H_{10}O_4$	65,52	8,04	8,04	—	85,0
VII e, adipate n=5	157—9	66,06	8,23	8,11	—	$C_{14}H_{20}N_2 \cdot C_6H_{10}O_4$	66,30	8,28	7,73	—	59,8
VII f, adipate n=6	80—2	67,07	8,46	7,52	—	$C_{15}H_{22}N_2 \cdot C_6H_{10}O_4$	67,02	8,51	7,44	—	92,0
VII g, adipate n=8	124—5	68,37	9,29	6,08	—	$C_{17}H_{26}N_2 \cdot C_6H_{10}O_4$	68,31	8,91	6,93	—	91,0
VII h, adipate n=10	95—6	69,58	9,28	6,38	—	$C_{19}H_{30}N_2 \cdot C_6H_{10}O_4$	69,39	9,32	6,48	—	94,0
VIII b, hydrochloride n=2	75—6				14,62	$C_{13}H_{18}N_2 \cdot HCl$				14,88	76,6
VIII c, hydrochloride n=3	85—6				14,01	$C_{14}H_{20}N_2 \cdot HCl$				14,06	88,5
VIII d, adipate n=4	93—4	67,11	8,88	7,62		$C_{15}H_{22}N_2 \cdot H_{10}H_4$	67,02	8,51	7,44	—	71,4
VIII e, adipate n=5	111—2	67,64	8,90	7,50		$C_{16}H_{24}N_2 \cdot C_6H_{10}O_4$	67,70	8,81	7,17	—	65,8
VIII f, adipate n=6	87—8	67,91	8,89	6,96		$C_{17}H_{26}N_2 \cdot C_6H_{10}O_4$	68,31	8,91	6,94	—	71,4
VIII g, adipate n=8	90—2	69,33	9,32	6,43	—	$C_{19}H_{30}N_2 \cdot C_6H_{10}O_4$	69,39	9,32	6,48	—	92,0
VIII h, adipate n=10	75—6	70,46	9,61	6,38	—	$C_{21}H_{34}N_2 \cdot C_6H_{10}O_4$	70,40	9,63	6,09	—	88,7

*For compounds VIId-VIIh and VIIId-VIIIh the yields are indicated for the bases.

IR spectra: ν_{NH} 3500 cm^{-1} (in chloroform), 3230-3270 cm^{-1} (in liquid petrolatum), ν_{CO} 1630 cm^{-1} (band of the amide–I, in liquid petrolatum and chloroform).

ω-Indolyl-3-alkylamines and N,N-Dimethyl-ω-indolyl-3-alkylamines (VII and VII). A solution of 0.01 mole VI or V in tetrahydrofuran was gradually added to a suspension of 0.06-0.07 mole lithium aluminum hydride in 115 ml absolute tetrahydrofuran. The reaction mixture was boiled with mixing for 6 h, then cooled with a mixture of ice and salt, and water added to it dropwise in an amount of 5 ml of water per g of lithium aluminum hydride. Mixing was continued for another 40 min, then the solution was filtered, the solvent distilled off, and the oily residue dried in a desiccator.

To obtain the hydrochloride, the amine was dissolve in 5 ml absolute ethanol, and a 50% alcohol solution of hydrogen chloride (about 0.34-0.4 ml) at pH 6.5-7.0 and 35 ml of absolute ehter added with cooling. The precipitate formed was filtered off, washed with ether, and dried in a vacuum desiccator.

Adipates of the amines were prepared as follows. The amine was dissolved in absolute ethanol (3 ml alcohol was taken per 0.01 mole of the amine); a hot solution of an equimolar amount of adipic acid in the minimum quantity of absolute ethanol was also added to the hot solution. The salt that precipitated upon cooling was suction filtered and purified by reprecipitation from an alcohol solution with absolute ether.

Data on the salts VII and VIII are cited in Table 2.

LITERATURE CITED

1. N. N. Suvorov, V. G. Avramenko, and B. Ya. Eryshev, et al., USSR Patent No. 181119. Izobreteniya, No. 9 (1966).
2. J. Jacob and C. Lafilli, Arch. Int. Pharmacodyn., 145, 528 (1963).
3. R. Majima and T. Hoshino, Ber. Dtsch. Chem. Ges., 58, 2042 (1925).
4. D. G. Crosby, J. B. Boyd, and H. E. Johnson, J. Org. Chem., 25, 1627 (1960).
5. A. Ewins, J. Chem. Soc., 99, 270 (1911).