AZAINDOLE DERIVATIVES

XLVII. SYNTHESIS AND PHARMACOLOGICAL STUDY OF 3-AMINOALKYL DERIVATIVES OF AZAINDOLES*

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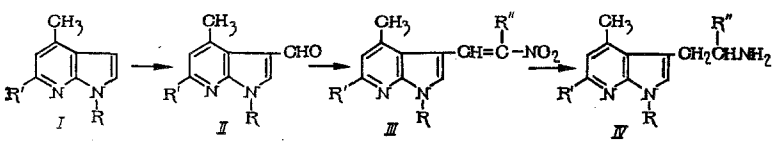
Various 3-aminoalkyl derivatives of indole have attracted the attention of many investigators over the last ten years. The importance of this type of substance in the biogenesis of indole alkaloids, the wide distribution of 3-(β-aminoethyl)-5-hydroxyindol (serotonin), one of the most important biogenous amines, in plant and animal organisms, and also the pronounced hallucinogenic and psychomimetic activity of such 3-aminoalkyl derivatives of indole as psilocin, psilocybin, and bufotenine are well known. Among the synthetic compounds of this series, substances are found which calm the central nervous system and are characterized by a pronounced hypotensive action (the compound BAS and others). 3-(β-Aminoethyl)-5-methoxyindole (mexamine), which is permitted by the Pharmacological Committe as a radiation shielding compound, and 3-(β-aminopropyl)indole (indolan) permitted as a central nervous system stimulator, have found practical application in the USSR.

The high pharmacological effectiveness of 3-aminoalkyl derivatives of indole and also of imidazolylalkylamines, among which belongs histamine, one of the most active of the biogenous amines, stimulated the growth of studies on the synthesis and biological investigation of substances which are aminoalkyl derivatives of different heterocycles [2]. Also up to the present the aza analogs of 3-aminoalkylindoles have not been subjected to a broad biological study though it is known that substitution of $-CH=$ or $-CH_2-$ groups by a nitrogen atom, i.e., the transformation to aza analogs, is accompanied by an increase and sometimes also a change of pharmacological activity.

In the course of a systematic study of isomeric 7-azaindoles general methods have been developed by us for the synthesis of 3-(β-aminoalkyl) derivatives of these compounds according to the scheme [3-7]:



The substituted or unsubstituted 7-azaindoles (I) were converted by the Vilsmeier reaction into the corresponding 3-formyl derivative (II, Table 1) which on reacting with the various nitroalkanes (nitromethane, nitroethane, and nitropropane) formed 3-(β-nitrovinyl)-7-azaindoles (III, Table 2). The latter were converted by reduction with lithium aluminium hydride into 3-(β-aminoalkyl)-7-azaindoles (IV) which formed hydrochloride salts poorly soluble in alcohols and readily soluble in water.

This scheme proved to be unsuitable for 4-azatryptamine (V) because of the difficult accessibility of the 3-formyl derivative, and compound V was prepared from 4-azaindole (VI) via 3-cyanomethyl-4-azain-

*For Part XLVI, see [1].

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TABLE 1. 3-Formylazaindoles

Compound	R	R′	Yield (in %)	Melting point (in degrees)[1]	Found (in %) C	Found (in %) H	Found (in %) N	Empirical formula	Calculated (in %) C	Calculated (in %) H	Calculated (in %) N
IIa	H	H	25	220—1	67,38	5,26	17,57	$C_8H_8N_2O$	67,38	5,26	17,57
IIb	H	Cl	25	264—5	55,49	3,74	14,26	$C_8H_7ClN_2O$[3]	55,53	3,60	14,40
IIc	CH_3	H	17	89—90	68,56	5,80	16,20	$C_{10}H_{10}N_2O$	68,96	5,75	16,00
IId	C_4H_9	H	48	150—3 (0,5 mm)[2]	72,04	7,68	12,61	$C_{13}H_{16}N_2O$	72,23	7,40	12,96
IIe	C_6H_5	H	76	141—2	76,35	5,22	12,08	$C_{15}H_{12}N_2O$	76,27	5,08	11,86
IIf	p-$CH_3OC_6H_4$	H	71	129—130	71,77	5,25	10,70	$C_{16}H_{14}N_2O_2$	72,16	5,30	10,52
IIg	$C_6H_5CH_2$	H	38	82—3	76,86	5,66	10,97	$C_{16}H_{14}N_2O$	76,80	5,60	11,20

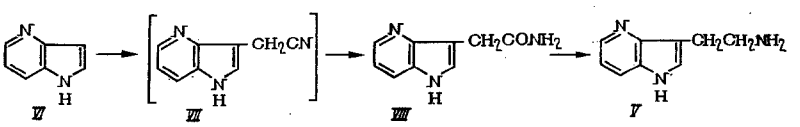
[1]Compound IIa and f were crystallized from alcohol, IIb from benzene, IIc and e from heptane, and IIg from methanol.
[2]Boiling point.
[3]Found, %: Cl 17.38. Calculated, %: Cl 18.24

TABLE 2. 3-(β-Nitrovinyl)azaindoles

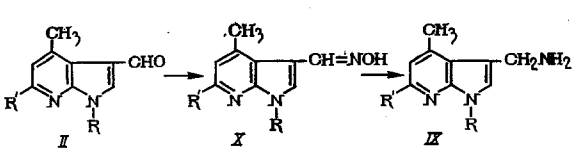
Compound	R	R′	R″	Yield (in %)	Melting point (in degrees)[1]	Found (in %) C	Found (in %) H	Found (in %) N	Empirical formula	Calculated (in %) C	Calculated (in %) H	Calculated (in %) N
III a	H	Cl	H	73	248—9	50,48	3,53	17,28	$C_{10}H_8ClN_3O_2$[2]	50,53	3,37	17,68
III b	H	Cl	CH_3	68	273—4	52,61	3,93	16,51	$C_{11}H_{10}ClN_3O_2$[3]	52,48	3,98	16,70
III c	H	Cl	C_2H_5	69	252—3	54,31	4,74	15,51	$C_{12}H_{12}ClN_3O_2$[4]	54,24	4,52	15,82
III d	CH_3	H	H	54	196—7	60,59	4,88	19,54	$C_{11}H_{11}N_3O_2$	60,83	5,06	19,35
III e	C_4H_9	H	H	34	113—4	64,66	6,74	15,84	$C_{14}H_{17}N_3O_2$	64,86	6,56	16,22
III f	C_6H_5	H	H	81	179—180	68,64	4,73	14,87	$C_{16}H_{13}N_3O_2$	68,82	4,66	15,05
III g	C_6H_5	H	CH_3	84	177—8	69,48	5,12	14,26	$C_{17}H_{15}N_3O_2$	69,62	5,12	14,33
III h	C_6H_5	H	C_2H_5	79	150—1	70,31	5,54	13,70	$C_{18}H_{17}N_3O_2$	70,35	5,54	13,68
III i	p-$CH_3OC_6H_4$	H	H	78	187—8	66,04	4,97	13,24	$C_{17}H_{15}N_3O_3$	66,01	4,89	13,59
III j	p-$CH_3OC_6H_4$	H	CH_3	85	179—180	67,02	5,30	13,36	$C_{18}H_{17}N_3O_3$	66,86	5,30	13,00
III k	$C_6H_5CH_2$	H	H	53	160—1	69,25	5,17	13,98	$C_{17}H_{15}N_3O_2$	69,62	5,12	14,33

[1]Compounds IIId and h were crystallized from alcohol and IIIe from benzene.
[2]Found, %: Cl 15.35. Calculated, %: Cl 14.93.
[3]Found, %: Cl 14.14. Calculated, %: Cl 14.11.
[4]Found, %: Cl 13.63. Calculated, %: Cl 13.37

dole (VII) and (4-azaindolyl-3)-acetamide (VIII) and reduction of the latter with lithium aluminium hydride in boiling tetrahydrofuran [8]:



The corresponding 3-aminomethyl derivatives of the 7-azaindoles (IX) were synthesized from the aldehydes (II) through their oximes (X) and subsequent reduction by zinc in hydrochloric acid [3-5].



The 3-dimethylaminomethyl derivatives of the azaindoles (XI) were prepared from the corresponding azaindoles (I) by the Mannich reaction [3, 6, and 9].

TABLE 3. 3-Aminoalkylazaindoles

Compound	R	R′	R″	Yield (in %)	Melting point (in degrees)[2]	Found (in %) C	Found (in %) H	Found (in %) Cl	Found (in %) N	Empirical formula	Calculated (in %) C	Calculated (in %) H	Calculated (in %) Cl	Calculated (in %) N
IVa	H	H	CH_3	44	323—4	58,18	7,34	—	18,48	$C_{11}H_{15}N_3 \cdot HCl$	58,54	7,09	—	18,63
IVb	H	H	C_2O_5	49	328—9	59,74	7,58	14,96	17,41	$C_{12}H_{17}N_3 \cdot HCl$	60,12	7,51	14,82	17,54
IVc	H	Cl	CH_3	84	298—9	50,75	5,46	27,38	16,28	$C_{11}H_{14}ClN_3 \cdot HCl$	50,77	5,77	27,31	16,15
IVd	H	Cl	C_2O_5	91	314—5	52,51	5,82	25,70	15,03	$C_{12}H_{16}ClN_3 \cdot HCl$	52,55	6,20	25,91	15,33
IVe	CH_3	H	H	75	219—220	50,27	6,80	26,70	15,99	$C_{11}H_{15}N_3 \cdot 2HCl$	50,39	6,48	27,09	16,03
IVf	n-C_4H_9	H	H	78	199—200	63,05	8,29	13,36	15,66	$C_{14}H_{23}N_3 \cdot HCl$	62,83	8,22	13,27	15,7
IVg	C_6H_5	H	H	66	252—3	53,23	6,52	19,68	11,74	$C_{16}H_{17}N_3 \cdot 2HCl \cdot 2H_2O$	53,34	6,38	19,72	11,67
IVh	C_6H_5	H	CH_3	69	267—8	60,54	6,13	20,82	12,25	$C_{17}H_{19}N_3 \cdot 2HCl$	60,54	6,13	21,00	11,86
IVi	C_6H_5	H	C_2H_5	70	268—9	61,11	6,73	19,88	11,81	$C_{18}H_{21}N_3 \cdot 2HCl$	61,36	6,53	20,17	12,43
IVj	p-$CH_3OC_6H_4$	H	H	60	208—9	57,45	5,93	—	11,86	$C_{17}H_{19}N_3O \cdot 2HCl$	57,63	5,98	—	11,93
IVk	p-$CH_3OC_6H_4$	H	CH_3	57	235—7	63,88	6,76	10,68	12,43	$C_{18}H_{21}N_3O \cdot HCl \cdot 0.5H_2O$	63,42	6,80	10,40	12,83
IVl	$C_6H_5CH_2$	H	H	72	187—8	54,41	6,62	18,56	11,45	$C_{17}H_{19}N_3 \cdot 2HCl \cdot 2H_2O$	54,54	6,68	18,98	11,23
V	—	—	—	85	257—8	46,50	5,88	30,37	17,85	$C_9H_{11}N_3 \cdot 2HCl$	46,16	5,60	30,29	17,95
IXa	n-C_4H_9	H	—	63	191—2	53,83	7,25	24,03	14,40	$C_{13}H_{19}N_3 \cdot 2HCl$	53,79	7,24	24,45	14,50
IXb	C_6H_5	H	—	65	228—9	57,85	5,43	22,83	13,49	$C_{15}H_{15}N_3 \cdot 2HCl$	58,06	5,48	22,90	13,55
XIa	H	Cl	—	60	161—2	59,02	6,37	16,06	19,01	$C_{11}H_{14}ClN_3$	59,06	6,26	15,88	18,79
XIb	n-C_4H_9	H	—	64	163—4	63,97	8,45	12,80	14,87	$C_{15}H_{23}N_3 \cdot HCl$	63,94	8,52	12,61	14,92
XIc	C_6H_5	H	—	72	215—6	54,41	6,68	18,84	11,31	$C_{17}H_{19}N_3 \cdot 2HCl \cdot 2H_2O$	54,54	6,68	18,98	11,23

[1]Compounds IVa and IVb were prepared by the dehalogenation of IVc and IVd respectively [5].

[2]All substances melted with decomposition.

The 18 aminoalkyl derivatives of the azaindoles IVa-1, V, IXa-b, and XIa-c (Table 3) were subjected to a pharmacological study as hydrochloride salts.

The study was carried out in accordance with a number of properties characteristic for 3-aminoalkyl derivatives of indoles. During this it was established that the azaindole analogs of tryptamine [3-(β-aminoethyl)indole] and compounds similar to it are essentially different from the indoles in activity and nature of action.

Tryptamine-like properties are displayed by 1-phenyl-3-aminomethyl-4-methyl-7-azaindole dihydrochloride (IXb). The compound causes spasm of the vessels and of the bronchial musculature; however, it is 10 times or more inferior in activity to tryptamine. On introducing the dihydrochloride of 4-azatryptamine (V) to narcotized cats starting with doses of 0.1-0.25 mg/kg spasm of the bronchial musculature and a lowering of arterial pressure were observed. However, these effects are associated not with tryptaminergic structures but possibly caused by released histamine or by stimulation of histaminergic receptors since they are significantly reduced on introducing antihistamine substances. The remaining compounds did not only not exert spasmogenic action on the musculature of the bronchi and peripheral vessels but gave rise to a spasmolytic effect. At concentrations of 10^{-4} to $2 \cdot 10^{-4}$ they reduce the tone and peristalsis of rabbit intestine.

According to a number of properties characterizing action on the central nervous system the dihydrochloride of 1-phenyl-4-methyl-7-azatryptamine (IV g) displayed very pronounced activity. In mice, beginning with a dose of 25 mg/kg, the compound reduces the tone of the skeletal musculature, retards motor activity, causes hypothermia, weakens the stimulating action of phenamine, strengthens analgesia produced by Promedol or morphine, and exerts an antispasmodic effect. Substitution of the phenyl by a butyl group (compound IVf) or the introduction of a methoxy group into the para position of the phenyl ring (compound IVj) is accompanied by a reduction in pharmacological activity.

The activity displayed by the dihydrochloride of 1-benzyl-4-methyl-7-azatryptamine (IVl) is characteristic of antidepressants: starting at a dose of 25 mg/kg the compound enhances re-

flex excitability, increases the group toxicity of phenamine, reduces ptosis and hypothermia produced by tetrabenazine, and inhibits the development of experimental catalepsy.

Substitution of both hydrogen atoms of the primary amino group in the aminoalkyl side chain by methyl groups is accompanied by the emergence of hypotensive action. The dihydrochloride of 1-phenyl-4-methyl-7-azagramine (XIc) reduces the arterial pressure in narcotized animals even starting with a dose of 1-2 mg/kg. The 3-(β-aminobutyl)-derivatives of 1-phenyl-4-methyl-7-azaindole (IVh and IVi) also produce pronounced hypotension. The introduction of a methoxy group into the para position of the phenyl ring (compound IVk) and also substitution of the phenyl group by hydrogen (compounds IVa-d) lead to a reduction in hypotensive activity.

Since the action of tryptamine and certain other 3-aminoalkyl derivatives of indole is intensified during inactivation of monoamine oxidase (MAO), we studied the effect of MAO inhibition on the action of azaindole derivatives. During this in experiments on mice using iprazide (200 mg/kg intraperitoneally 4 h before introducing the compound under test) as MAO inhibitor it was established that the activity of the dihydrochloride is intensified somewhat on inactivation of MAO. The action of the other 3-aminoalkyl derivatives of azaindoles studied did not change.

Thus, substitution of a methine group in the benzene portion of the indole ring by a nitrogen atom, i.e., transformation into azaindoles, led as a rule to a change of the properties characteristic of the action of 3-aminoalkylindole compounds. The investigation carried out has shown that the pharmacological activity of 3-aminoalkylazaindole compounds is determined to a considerable degree by the nature of the 3-aminoalkyl chain and the substituents in position 1 of the azaindole ring. As a result of this work on a number of 3-aminoalkyl derivatives of azaindoles pharmacologically active compounds with a different type of action have been obtained.

EXPERIMENTAL

3-Formylazaindoles (II). To 60 ml of distilled dimethylformamide cooled to 10°C was added dropwise 20 ml of phosphorus oxychloride maintaining the temperature at 10°. The reaction mixture was warmed to room temperature and 0.2 mole of I in 60 ml of dimethylformamide was added to it. After keeping at 35° for 45 min the reaction mixture was poured onto ice (~500 g) and basified with a solution of 38.5 g of sodium hydroxide in 200 ml of water. The obtained suspension was heated to boiling, rapidly cooled, and extracted with benzene. The benzene extract was dried with magnesium sulfate, evaporated, and the residue recrystallized. The yields, constants, and analyses of the obtained substances II are given in Table 1.

3-(β-Nitrovinyl)azaindoles (III). A mixture of equimolecular quantities of II and ammonium acetate in 15 times the volume of the appropriate nitroalkane was heated for 1 h at 100°. The precipitate of III which separated on cooling was filtered off and where necessary recrystallized. The yields, constants, and analyses of the obtained substances III are given in Table 2.

3-(β-Aminoalkyl)azaindoles (IV). Compounds III were reduced with 6 g-eq of lithium aluminium hydride in boiling tetrahydrofurna for 5-6 h at a dilution of 1:40. The base of IV was extracted with ether, the solvent was distilled off, and the hydrochloride salt of IV was precipitated from an alcoholic solution of the base by hydrogen chloride. The yields, constants, and analyses of the obtained salts are given in Table 3.

3-Aminomethylazaindoles (IX). To a solution or suspension of X in 50 times the volume of 17% hydrochloric acid twice the quantity by weight of zinc dust was added with stirring in portions at room temperature. The reaction mixture was stirred at room temperature for a further 1 h, treated with an excess of a 50% solution of potassium hydroxide, and IX was extracted with ether. The solvent was evaporated and IX was converted into the hydrochloride salt by treatment with hydrogen chloride in alcohol solution. The yields, constants, and analyses of the compounds IX obtained are given in Table 3.

3-Dimethylaminomethylazaindoles (XI). A mixture of I, dimethylamine hydrochloride, and paraform in the molar ratio 5:6:6 was boiled for 30 min in 20 times the volume of n-butyl alcohol and evaporated under vacuum. The residue was dissolved in 5% hydrochloric acid, impurities of a nonbasic character were separated by extraction with ether, and the aqueous was basified with 50% potassium hydroxide solution. Compound XI was extracted with ether and converted into the hydrochloride salt by treatment with hydrogen chloride in alcohol solution. The yields, constants, and analyses of the compounds XI obtained are given in Table 3.

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