SYNTHESIS AND STUDY OF THE PHARMACOLOGICAL ACTIVITY OF 1-(INDOLYL-3')-2-ALKYLAMINOETHANOLS

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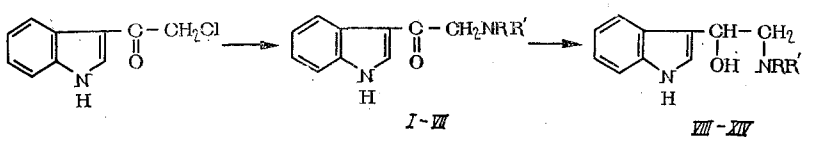
UDC 615.31:547.751]012.1

In view of the high and varied pharmacological activity of adrenalin and its derivatives, we were interested in studying the chemical and pharmacological properties of adrenalin analogs, in which the pyrocatechol ring is replaced by indole. On the other hand, 1-(indolyl-3')-2-alkylaminoethanols can be considered as β-hydroxytryptamines.

Earlier we described a method of synthesis and studied the pharmacological activity of indole analogs of ephedrine and ψ-ephedrine — 1-(indolyl-3')-2-alkylaminopropanols, produced by the reduction of substituted 3-α-aminopropionylindoles [1, 2]. Among the 1-(indolyl-3')-2-alkylaminoethanols, only the production of 1-(indolyl-3')-2-dimethylaminoethanol has been described (by the action of sodium borohydride on 3-methylaminoacetylindole [3]).

We used 3-alkylaminoacetylindoles (I-VII, Table 1), produced by the interaction of 3-chloroacetylindole (or 3-bromoacetylindole [4]) with primary or secondary amines, as the starting materials in the synthesis of 1-(indolyl-3')-2-alkylaminoethanols.



I-VII VIII-XIV

We studied the effects of various reducing agents on 3-alkylaminoacetylindoles: sodium borohydride in methanol, lithium aluminum hydride in tetrahydrofuran, and hydrogenation over Raney nickel in alcohol at 60 atm and 30°. It was found earlier that under the action of lithium aluminum hydride on 3-acetylindoles containing no substituent in the 1-position of the indole ring, the carbonyl group conjugated with the indole ring is reduced to a methylene group. Thus, the production of N,N-disubstituted tryptamines under the action of lithium aluminum hydride on 3-alkylaminoacetylindoles has been described [5]. However, it has been found that in the case when there are voluminous substituents at the nitrogen atom of the side chain, the reduction by lithium aluminum hydride stops at the corresponding amino alcohol, and practically no formation of N-substituted tryptamines is observed. Thus, 3-(N-morpholyl)-acetylindole (VI) and 3-(N-piperidyl)acetylindole (V) were successfully reduced with lithium aluminum hydride with good yields to the corresponding amino alcohols (XIII and XII, Table 2). Probably in this case the reduction stops at the step of the amino alcohol as a result of steric shielding of the hydroxy group by the neighboring voluminous piperidine or morpholine group.

Under the action of sodium borohydride on N-substituted 3-aminoacetylindoles (on I and VII), the corresponding amino alcohols are formed with good yields (VIII and XIV, see Table 2). Evidently in certain cases, in the presence of large substituents at the nitrogen atom of the side chain, there is no reduction, which may be explained by steric shielding of the carbonyl group and by the comparatively large effective radius of the reducing agent.

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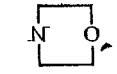
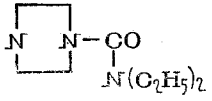
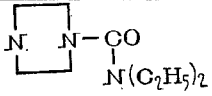
TABLE 1. 3-Alkylaminoacetylindoles

Compound	NRR′	Yield (in %)	Melting point (in degrees)	Found (in %)			Gross formula	Calculated (in %)		
				C	H	N		C	H	N
I	$NHCH_3$	85	197—8 From ethanol	70,27	6,24	15,03	$C_{11}H_{12}N_2O$	70,18	6,42	14,8
II	NHC_2H_5	72	151—3 From acetone	71,62	6,96	13,96	$C_{12}H_{14}N_2O$	71,25	6,97	13,84
III	$NHCH(CH_3)_2$	68	139—41 From acetone	72,10	7,39	12,87	$C_{13}H_{16}N_2O$	72,19	7,45	12,95
IV	$N(CH_3)_2$	77	208—9 From ethanol				$C_{12}H_{14}N_2O$			
V		78	161—163,5 From acetone	74,59	7,33	11,66	$C_{15}H_{18}N_2O$	74,38	7,49	11,56
VI		64	163,5—164,5 From acetone	68,35	6,70	11,38	$C_{14}H_{16}N_2O_2$	68,38	6,60	11,47
VII		82,5	165—6 From methanol	66,64	7,65	16,36	$C_{19}H_{26}N_4O_2$	66,40	7,50	16,30

Note: According to the literature data [5], mp of I 197-198°, mp of IV 208-209°, mp of V 169-170°, mp of VI 167°.

TABLE 2. 1-(Indolyl-3')-2-alkylaminoethanols

Compound	NRR'	Yield (in %)	Melting point (in degrees)	Found (in %)			Gross formula	Calculated (in %)		
				C	H	N		C	H	N
VIII	$NHCH_3$	82,7	123—5 (From ethyl acetate)	69,51	7,38	14,83	$C_{11}H_{14}N_2O$	69,44	7,41	14,73
IX	NHC_2H_5	59,5	145,5—146,5 (From ethyl acetate)	70,87	7,91	13,76	$C_{12}H_{16}N_2O$	70,55	7,89	13,71
X	$NHCH(CH_3)_2$	64,7	127,5—128,5 (From ethyl acetate, benzene)	71,25	8,30	12,79	$C_{13}H_{18}N_2O$	71,52	8,31	12,83
XI	$N(CH_3)_2$	61,5	118—20 (From ethyl) acetate)	70,59	7,61	13,68	$C_{12}H_{16}N_2O$	70,55	7,89	13,71
XII		73,2	140,5—141,5 (From benzene)	73,48	8,08	11,13	$C_{15}H_{20}N_2O$	73,73	8,25	11,47
XIII		53,5	146—147,5 (From benzene)	68,49	7,50	11,07	$C_{14}H_{18}N_2O_2$	68,27	7,37	11,37
XIV		60,5	144—6 (From ethyl acetate)	66,42	8,11	16,00	$C_{16}H_{28}N_{42}O$	66,24	8,19	16,27

Note: According to the literature data [3], mp. of XI 118-120°.

TABLE 3. Salts of 1-(Indolyl-3')-2-alkylaminoethanols

Compound	Melting point (in degrees)	Found (in %)			Gross formula	Calculated (in %)		
		C	H	N		C	H	N
VIII, adipate	126—7 (dec.)	63,65	7,23	10,71	$C_{11}H_{14}N_2O \cdot {}^1/_2C_6H_{10}O_4$	63,85	7,26	10,64
IX, adipate	120—21 (dec.)	65,13	7,39	9,98	$C_{12}H_{16}N_2O \cdot {}^1/_2C_6H_{10}O_4$	64,96	7,79	9,92
XII, adipate	130—31 (dec.)	68,56	8,10	9,10	$C_{15}H_{20}N_2O \cdot {}^1/_2C_6H_{10}O_4$	68,11	7,94	8,83
XIII, hydrochloride	102—3 (dec.)	59,34	6,48	9,56 (Cl 12,43)	$C_{14}H_{18}N_2O_2 \cdot HCl$	59,46	6,77	9,91 (Cl 12,53)
XIV, hydrochloride	116—8 (dec.)	60,22	7,55	14,25 (Cl 8,83)	$C_{19}H_{28}N_4O_2 \cdot HCl$	59,91	7,67	14,71 (Cl 9,31)

The most convenient method for converting from N-substituted 3-amino-acetylindoles to the corresponding amino alcohols is hydrogenation over Raney nickel. Amino alcohols (VIII-XI, see Table 2) were produced by this method. All the amino alcohols obtained were converted to salts (hydrochlorides or adipates, Table 3, which were also studied pharmacologically).

In a pharmacological study of indole analogs of adrenalin, attention was paid mainly to their influence on the peripheral adrenoreactive systems of the organism. The change in the level of arterial pressure, the tonus of the peripheral vessels, and the ability to induce contraction of the nictitating membrane were used as indices of activity. It was established that all the preparations containing a secondary amino group (VIII, IX, X) possess sympathomimetic properties: they induce an increase in the arterial pressure in narcotized rats and cats, contraction of the nictitating membrane, and the constriction of the vessels, which is evidently associated with an excitation of α-adrenoreactive systems, since the α-adrenoblocker tropaphen prevents and removes the indicated effects.

The most active with respect to all the enumerated indices is 1-(indolyl-3')-2-methylaminoethanol (VIII). Its activity is only 10-20 times weaker than that of adrenalin, but it exerts a more prolonged action. VIII is considerably less toxic than adrenalin: when it is injected subcutaneously in white mice, LD_{50} is equal to 265 mg/kg, while for adrenalin it is 23.5 mg/kg. In contrast to adrenalin, it is also active in the case of internal administration.

Amino alcohols containing a tertiary amino group (XI, XII, XIII, XIV) induce a decrease in the arterial pressure, lower the tonus of the peripheral vessels, and do not increase the tonus of the nictitating membrane, i.e., are devoid of adrenomimetic activity.

EXPERIMENTAL

3-Methylaminoacetylindole (I). To a suspension of 3 g 3-chloroacetylindole in 20 ml of methanol we added with boiling 20 ml of a 25% aqueous solution of methylamine. The mixture was boiled for an hour, then cooled, the crystalline precipitate filtered off and recrystallized from alcohol. All the amino ketones obtained analogously are presented in Table 1.

1-(Indolyl-3')-2-methylaminoethanol (VIII). A. To a solution of 2 g I in 50 ml absolute methanol we added in portions 1.78 g sodium borohydride, mixed for 2 h at room temperature, and distilled off the solvent under vacuum. The residue crystallized after the addition of cold water. The amino alcohols VIII and XIV obtained in this way are presented in Table 2.

B. A 7-g portion of I was dissolved in 200 ml of alcohol and hydrogenated over 10.5 g Raney nickel at 30° and 60 atm for 20 h. The catalyst was filtered off, the solvent evaporated, and the residue recrystallized from 50 ml ethyl acetate. We obtained 5.04 g VIII, which was recrystallized once again from 45 ml of ethyl acetate with an addition of activated charcoal. The amino alcohols IX-XI, produced analogously, are presented in Table 2.

1-(Indolyl-3')-2-(N-piperidyl)-ethanol (XII). To a suspension of 1 g lithium aluminum hydride in 50 ml absolute tetrahydrofuran we added in portions 1 g of 3-(N-piperidyl)-acetylindole (V) and mixed for 2 h at room temperature. Then 1 ml of water, 1 ml of a 15% solution of sodium hydroxide, and 3 ml of water were

added successively. The precipitate was filtered off and washed with tetrahydrofuran. The filtrate was dried with potash, evaporated, and the residue recrystallized from benzene. The amino alcohols XII and XIII thus obtained are presented in Table 2.

Adipate of 1-(Indolyl-3')-2-methylaminoethanol. To a solution of 0.95 g VIII in 25 ml of absolute acetone we added a hot solution of 0.36 g adipic acid in 20 ml absolute acetone. We obtained 1.1 g (88%) of the neutral salt in the form of a colorless crystalline precipitate, and recrystallized from acetone. All the adipates obtained in this way are presented in Table 3.

Hydrochloride of 1-(Indolyl-3')-2-(N-morpholino)-ethanol. To a solution of 0.48 g XIII in 6 ml of methanol with cooling we added 2 ml of methanol saturated with hydrogen chloride. Then ether was added. A colorless crystalline precipitate of the hydrochloride was formed. We obtained 0.47 g (84%). The hydrochlorides of amino alcohols obtained are presented in Table 3.

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