DERIVATIVES OF ARYLALKYLAMINES.

XXIII. SYNTHESIS OF N-ARYLALKYL-SUBSTITUTED 3-[2,3 (OR 2,4)-DIHYDROXYPHENYL]-3-PHENYLPROPYLAMINES AND THEIR EFFECT ON THE UPTAKE OF CATECHOLAMINES

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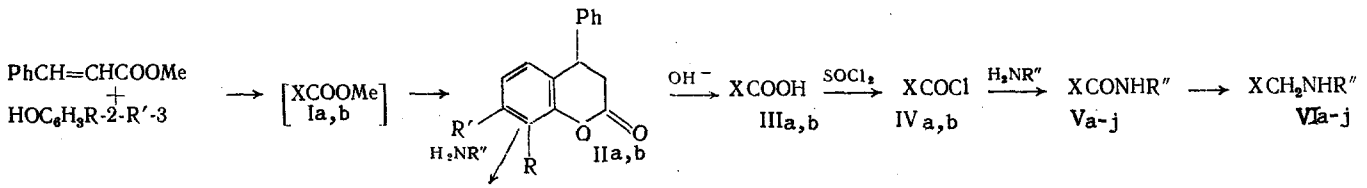
Certain derivatives of diphenylpropylamine have sympatho- and andrenolytic activity and block the uptake of catecholamines [2, 7, 9, 10]. This served as a basis for the synthesis of new compounds (VIa-j) containing two hydroxyl groups in one of the aromatic rings of the diphenyl fragment, and a study of their action on the uptake of catecholamines, liberation of a mediator from the sympathetic nerve extremities, and on α-adrenoreceptors. Compounds VIa-j were synthesized by the following scheme:



X = $CH_2CH(Ph)C_6H_2OH$-2-R-3-R′-4;
I—IVa, Va-d: R = OH, R′ = H; I—IVb, Vf-j, VIf-j: R = H,
R′ = OH; Va, f, VIa, f; R″ = $CHMeCH_2Ph$; Vb, g, VIb, g:
R″ = $(CH_2)_2C_6H_3(OMe)_2$; Vc, h, VIc, h: R″ = $CHMe(CH_2)_2Ph$:
Vc, i, VIi, i: R″ = $(CH_2)_2CHPh_2$; Vд, j, VIд, j: R″ = $CHMeCH_2CHPh_2$.

Alkylation of pyrocatechol or resorcinol by crotonic acid ester in the presence of $AlCl_3$ leads to coumarins IIa, b via the intermediate esters (Ia, b), which confirms the ortho-orientation of the phenolic hydroxyl in the addition of aryl to the conjugated unsaturated bond, found in [3, 4, 8].

Absorption bands were found in the 1750 (C=O lact.) and 3200-3500 cm^{-1} regions (OH assoc.) in the IR spectra of IIa, b, and the presence of a peak of a molecular ion was revealed in the mass spectrum.

Compounds IIa, b were converted by alkaline saponification into acids IIIa, b with absorption bands at 2500-2750 cm^{-1} region in the IR spectrum, characteristic of an intramolecular hydrogen bond in hydroxy acids [6], in addition to absorption in the 3200-3500 cm^{-1} region (OH assoc).

Amides Va-j were obtained by both condensation of coumarins IIa, b with arylalkylamines, and by the reaction of the latter with acid chlorides IVa, c. However, the first method is preferable. Reduction of amides Va-j by lithium aluminum hydride gave amines IVa-j, which were then converted into hydrochlorides.

In the IR spectra of Va-j there are absorption bands in the regions of 1625-1635 (C=O amide), 3200-3250 (NH amide), 3400-3500 cm^{-1} (OH phen.), while VIa-j have bands in the region of 3150-3400 cm^{-1} (NH, OH assoc.).

EXPERIMENTAL (CHEMICAL)

The IR spectra were run on a UR-20 spectrophotometer in mineral oil, and the mass spectra on a "MX-1303" mass spectrometer with direct introduction of the sample into the ionic

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TABLE 1. N-Arylalkyl 3-[2,3 (or 2,4)-Dihydroxyphenyl]-3-phenylpropionamides (Va-j)

Compound	Yield, %	mp, °C	Found, %			Empirical formula	Calc., %			R_f (A)
			C	H	N		C	H	N	
Va	83	132—4	76,40	6,45	4,0	$C_{24}H_{25}NO_3$	76,77	6,60	3,73	0,8
Vb	68	113—5	70,90	6,80	3,34	$C_{25}H_{27}NO_5$	71,19	6,45	3,32	0,7
Vc	63	103—5	77,25	7,29	3,97	$C_{25}H_{27}NO_3$	77,63	6,94	3,32	0,6
Vd	77	182—4	77,11	7,0	3,50	$C_{30}H_{29}NO_3$	77,40	6,65	3,10	0,7
Ve	79	135—7	79,74	6,37	3,41	$C_{31}H_{31}NO_3$	80,0	6,66	3,01	0,7
Vf	93	135—8	76,50	6,50	4,04	$C_{24}H_{25}NO_3$	76,77	6,60	3,73	0,7
Vg	69	80—3	71,31	6,20	3,62	$C_{25}H_{27}NO_5$	71,19	6,45	3,32	0,7
Vh	50	Oil-like	77,90	7,25	3,80	$C_{25}H_{27}NO_3$	77,63	6,94	3,59	0,6
Vi	70	82—3	77,50	6,70	3,36	$C_{30}H_{29}NO_3$	77,40	6,65	3,10	0,5
Vj	92	134—5	80,0	6,84	3,38	$C_{31}H_{31}NO_3$	80,0	6,66	3,01	0,7

TABLE 2. 3-[2,3 (or 2,4)-Dihydroxyphenyl]-3-phenyl-N-(arylalkyl)propylamine Hydrochlorides (VIa-j)

Compound	Yield, %	mp, °C	Found, %		Empirical formula	Calc., %		R_f (B)
			Cl	N		Cl	N	
VIa	46	202—4	9,01	3,85	$C_{24}H_{28}NO_2Cl$	8,91	3,51	0,7
VIb	53	100—2	8,25	2,95	$C_{25}H_{30}NO_4Cl$	7,98	3,15	0,6
VIc	51	125—6	88,8	3,01	$C_{25}H_{30}NO_2Cl$	8,62	3,40	0,6
VId	49	190—3	7,19	3,21	$C_{30}H_{32}NO_2Cl$	7,49	2,95	0,7
VIe	51	90—2	7,44	3,08	$C_{31}H_{34}NO_2Cl$	7,27	2,86	0,7
VIf	53	215—8	8,70	3,22	$C_{24}H_{28}NO_2Cl$	8,91	3,51	0,7
VIg	50	131—3	8,05	3,40	$C_{25}H_{30}NO_4Cl$	7,98	3,15	0,6
VIh	50	188—90	8,95	3,70	$C_{25}H_{30}NO_2Cl$	8,62	3,40	0,7
VIi	52	129—32	7,29	3,09	$C_{30}H_{32}NO_2Cl$	7,49	2,95	0,6
VIj	49	120—3	7,40	3,01	$C_{31}H_{34}NO_2Cl$	7,27	2,86	0,6

source. In TLC, Siluvol UV-254 plates in benzene—acetone (4:1) (A) and benzene—acetone (7:4) (B) systems, using iodine vapors as a developer.

4-Phenyl-8-hydroxy-3,4-dihydrocoumarin (IIa). A 13.6 g (0.12 mole) portion of pyrocatechol is added to 34.6 g (0.26 mole) of $AlCl_3$ in 200 ml of $PhNO_2$, and after 30 min, 20 g (0.12 mole) of methyl crotonate are added at 15-20°C. The mixture is then heated for 10-12 h at 70-75°C, then cooled and decomposed by 50 g of crushed ice. The mixture is stirred for 30 min, and approximately 150 ml of dilute HCl (1:1) are added in the course of 30 min until the precipitate is dissolved. The mixture is extracted by ether, the solvent is evaporated, and the residue is distilled in vacuo. Yield 17 g (59.2%) of IIa, bp 198-200°C (3-4 mm Hg). Found %: C 75.28; H 5.03. $C_{15}H_{12}O_3$. Calculated %: C 74.98; H 5.03. Rf 0.68 (A). M^+ 240.

4-Phenyl-7-hydroxy-3,4-dihydrocoumarin (IIb) is obtained in the same way as IIa. Yield 15 g (53.5%), bp 245-247°C (2 mm Hg). Found %: C 75.30; H 5.27. $C_{15}H_{12}O_3$. Calculated, %: C 74.98; H 5.03. Rf 0.8 (A). M^+ 240.

3-(2,3-Dihydroxyophenyl)-3-phenylpropionic Acid (IIIa). A solution of 2.5 g (0.062 mole) of NaOH in 20 ml of water is added to 5 g (0.027 mole) of coumarin IIa. The mixture is boiled for 5-6 h until a homogeneous mass is obtained, and then it is diluted with water and extracted by ether. From the aqueous layer acid IIa is precipitated by dilute HCl (1:1). The product is purified by recrystallization from an alcohol—water mixture. Yield 4.6 g (86.5%) of IIIa, mp 116-118°C. Found, %: C 70.02; H 5.86. $C_{15}H_{14}O_4$. Calculated, %: C 69.75; H 5.46. Rf 0.53 (A).

3-(2,4-Dihydroxyphenyl)-3-phenylpropionic acid (IIIb) is obtained in the same way as IIIa. Yield 4.5 g (84.4%), mp 130-133°C. Found, %: C 70.10; H 5.41. $C_{15}H_{14}O_4$. Calculated, %: C 69.75; H 5.46. Rf 0.74 (B).

N-Phenylisopropyl 3-(2,3-Dihydroxyphenyl)-3-phenylpropionamide (Va). a) A mixture of 4 g (0.016 mole) of acid IIIa and 3 ml of $SOCl_2$ in 150 ml of $SOCl_2$ in 150 ml of absolute benzene is boiled for 6 h. After distillation of the solvent and excess of $SoCl_2$, 100 ml of benzene, 0.016 mole of phenylisopropylamine and 0.016 mole of pyridine are added to the residual acid chloride IVa. The mixture is boiled for 5-6 h, and cooled, and water is added.

TABLE 3. Influence of Hydrochlorides VIa-j on Uptake of Catecholamines

Compound	Action of compounds in a concn. of 1 μmole on neuronal uptake of noradrenaline-^{3}H by rat's spermiduct				Action of compounds in a concn. of 10 μmoles on extraneuronal uptake of adrenaline-^{3}H by sections of ventricle wall of rat's heart			
	number of organs used	uptake of noradrenaline, disintegrations/min per 1 g of tissue (M ± m)	uptake of noradrenaline, % with respect to control	P	number of organs used	uptake of adrenaline, disintegrations/min per 1 g of tissue (M±m)	uptake of adrenaline, % with respect to control	P
Control	40	175 118±16 811	100		20	59 617±173	100	
VIa	20	92 819±3 527	53	<0,002				
VIb	20	64 794±2 657	37	<0,001	10	41 136±3702	69	<0,02
VIc	20	127 836±31 192	73	>0,5				
VId	20	92 815±4 177	53	<0,01				
VIe	20	141 846±6 950	81	>0,25				
VIf	20	54 287±5 157	31	<0,001	10	38 155±6219	64	<0,01
VIg	20	47 282±5 201	27	<0,001	10	34 578±3769	58	<0,01
VIh	20	96 315±1 445	55	<0,05				
VIi	20	141 846±9 646	81	>0,25				
VIj	20	119 080±6 192	68	>0,25				
Melipramine	10	92 812±4 266	53	<0,002				
Metanephrine	10	155 855±29 612	89	>0,5	10	37 857±3824	63	<0,01

TABLE 4. Influence of Hydrochlorides VIa-j on Liberation of Mediator from Sympathetic Nerve Extremities and on Adrenoreceptors in Experiments on Rat's Spermiduct

Compound	Decrease in number of duct constrictions caused by transmural irritation, % with respect to control (number of constrictions/60 min action), M ± m	Decrease in number of duct constrictions caused by adrenaline, % with respect to control (number of constrictions per 60 min action), M ± m
VIa	77±16	59±35
VIb	48±46	68±40,4
VIc	78±25,8	+91±124
VId	76±30,5	26±16
VIe	9±15	+91±139
VIf	96±8	93±10,7
VIg	80±7,9	30±11,1
VIh	95±5,4	89±20.7
VIi	40±38	9±52
VIj	60±33	+24±35
Melipramine	99±3,2	83±27
Desipramine	99±1	55±24
Octadine	84±8,3	+134±26,8
Prasosine	71±12,1	98,5±1,1

Note. + increase in number of duct constrictions, caused by adrenaline (in % with respect to control).

The benzene layer is separated, and washed, first with 6% HCl to an acid reaction, and then with water. After distillation of the solvent, the residue is crystallized from ether (Table 1).

b) A mixture of 0.01 mole of coumarin IIa and 0.01 mole of phenylisopropylamine is boiled in absolute benzene for 5-6 h, the solvent is distilled, and amide Va is precipitated from the residue by ether.

Amides Vb-j are obtained in the same way as Va (see Table 1).

3-(2,3-Dihydroxymethyl)-3-phenyl-N-(phenylisopropyl)propylamine Hydrochloride (VIa). A solution of 0.02 mole of amide Va in 100 ml of absolute ether is added to a solution of 0.03 mole of $LiAlH_4$ in 100 ml of absolute ether. The mixture is heated for 10-12 h, and decomposed, with cooling, by 10 ml of water. The precipitate on the filter is washed with ether. After distillation of the solvent, the residue is converted into hydrochloride, which is recrystallized from an alcohol–ether mixture (Table 2).

Hydrochlorides VIb-j are obtained in the same way as (VIa) (see Table 2).

EXPERIMENTAL (PHARMACOLOGICAL)

The influence was studied of hydrochlorides VIa-j on the uptake or noradrenaline-^{3}H and adrenaline-^{3}H from the firm "Amersham" (England). The radioactivity was measured on a liquid scintillation counter "Intertechnique CL-30" (France).

The influence of compounds VIa-j on the neuronal uptake of catecholamines was studied in experiments on spermiducts of rats, which were placed into 5 ml chambers containing an oxygen-saturated Tyrode solution, at 37°C for 30 min. The sperimiducts were then incubated with compounds VIa-j for 30 min. They were then incubated in a fresh Tyrode solution for 30 min in the presence of compounds VIa-j and noradrenaline-^{3}H at a concentration of 0.2 uCi/ml.

The influence of the most active compounds VIb, f, g on the extraneuronal uptake of catecholamines was studied on sections of left ventricle wall of the rat's heart under somewhat changed experimental conditions: 1) Instead of noradrenaline-^{3}H, adrenaline-^{3}H was used, since the affinity to the extraneutronal uptake sites is greater in adrenaline than in noradrenaline [11]; 2) the amount of adrenaline added to the incubation medium was increased by diluting adrenaline-^{3}H with a nonlabeled (cold) adrenaline to $2.5 \cdot 10^{6}$ mole; 3) the time of incubation with adrenaline-^{3}H was shortened to 5 min, since 2-3 min are sufficient for complete extraneuronal uptake of catecholamines in experiments with heart perfusion [11].

Our investigations showed that compounds VIa-j have a blocking action on the neuronal uptake of noradrenaline-^{3}H. Thus, at a concentration of 1 μmole, six of ten compounds reliably block the uptake of noradrenaline-^{3}H (Table 3). Statistical treatment of the results obtained also showed that in their blocking activity, compounds VIb, g reliably surpass melipramine ($P < 0.05$), while compounds VIa, d do not differ from the latter. The influence of metanephrine on the neuronal uptake of noradrenaline-^{3}H is statistically unreliable ($P > 0.05$). Compounds VIb, f, g, which most pronouncedly block the neuronal uptake of noradrenaline-^{3}H, at concentration of 10 μmole also reliably block the extraneuronal uptake of adrenaline-^{3}H to the extent of 31-42%, and with respect to this parameter do not differ from known blocker of the extraneuronal uptake of catecholamines, metanephrine ($P > 0.1$).

In experiments on an isolated rat's spermiduct we studied the influence of the compounds on the constriction of the organ, caused by transmural electric irritation and by adrenaline at a concentration of $1 \cdot 10^{-6}$ g/ml [1]. The compounds were tested at a final concentration of 0.05 μ mole/ml. The action of each of the compounds was verified on at least four ducts.

It was found that like melipramine and prasosine, compounds VIf, h induce a pronounced blocking of both the liberation of the mediator from the sympathetic nerve extremities, and of α-adrenoreceptors (Table 4). The action of compound VIc resembles that of octadine: a sympatholytic effect leads to increase in the sensitivity of the adrenoreceptors ("reaction to denervation").

The acute toxicity of the most active compounds was determined in experiments on white mice of both sexes weighing 18-23 g each. The compounds were administered intraperitoneally. Each dose was tested on 6 animals. The experimental results were recorded 24 h after administration. The mean lethal dose (LD_{50}) was calculated according to Leachfield and Wilkoxon [5]. The LD_{50} of compound VIf is equal to 128 (101.6-158.75) mg/kg, of compound VIg 165 (142-191.4) mg/kg, and of melipramine 91 (83.9-98.7) mg/kg. The difference between the toxicities of VIf, g and melipramine was statistically reliable ($P = 0.05$), they are less toxic than melipramine.

Our investigations thus showed that compounds VIb, f, g have a pronounced blocking action on the neuronal uptake of noradrenaline-^{3}H and extraneuronal uptake of adrenaline-^{3}H, while compound VIf, like melipramine blocks other adrenergic processes also: the process

of liberation of the mediator from the sympathetic nerve extremities, and on α-adrenoreceptors. Hence, hydrochlorides VIa-j are interesting as anti-adrenergic compounds with a considerable blocking action on several adrenergic processes, simultaneously.

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ANTIHYPOXIC ACTION OF DIOXINDOLE DERIVATIVES

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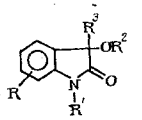
In a study of the antihypoxic activity of isatin and other compounds of the indolinone series [2, 5, 6], we and other authors have noted the presence of this activity under the condition that the 2-carbonyl group is retained. In particular, acetyloxindole, a compound in which the 3-keto group is completely reduced in comparison with isatin, exhibits pronounced protective action during hypobaric hypoxia [2]; this structural fragment is contained also in pyracetam, in which an antihypoxic activity has also been observed [4].

It was interesting to study the antihypoxic properties of derivatives of dioxindole, which occupies an intermediate position between compounds of the oxindole and isatin series.

We therefore synthesized 13 dioxindole derivatives of the general formula



I-XIII

I: $R = R^1 = R^2 = R^3 = H$; II: $R = Me$-5, $R^1 = R^1 = R^2 = R^3 = H$;
III: $R = Cl$-7, $R^1 = R^2 = R^3 = H$; IV: $R = R^2 = R^3 = H$,
$R^1 = Ac$; V: $R = R^1 = R^2 = H$, $R^3 = CH_2Ac$; VI: $R = Br$-5, $R^1 = R^2 = H$, $R^3 = CH_2Ac$;
VII: $R = Br$-5, $R^1 = R^2 = H$, $R^3 =$ pyridyl-2-methyl; VIII: $R = Br$-5,
$R^1 = R^3 = H$; $R^2 = Ac$; IX: $R = Cl$-7, $R^1 = R^3 = H$, $R^2 = Ac$; X: $R = R^3 = H$,
$R^1 = R^2 = COEt$; XI: $R = Me$-5, $R^1 = R^2 = COEt$, $R^3 = H$; XII: $R = Br$-5,
$R^1 = R^2 = COEt$, $R^3 = H$; XIII: $R = Br$-5, $R^1 = R^2 = COPr$, $R^3 = H$.

Dioxindoles containing substituents in the benzene ring and at the nitrogen atom only (II-IV), were obtained by reducing the corresponding isatins by sodium dithionite [8], and 3H-substituted compounds (V-VII) were obtained by condensing CH_2-active compounds with isatins [3].

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