SYNTHESIS AND PHARMACOLOGICAL INVESTIGATION OF ACYL DERIVATIVES OF IMINODIBENZYL

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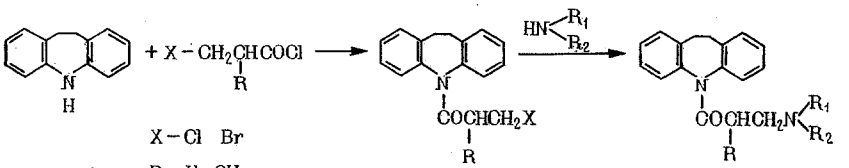
Aminopropyl derivatives of iminodibenzyl are physiologically active [1] and some of them, for example, N-(3-dimethylaminopropyl)iminodibenzyl, find wide application in medicinal practice as antidepressants [1]. It appeared of interest to synthesize a series of aminoacyl derivatives of iminodibenzyl with the purpose of studying the physiological activity. The pharmacological reason for the synthesis of these derivatives was reported earlier [2].

β-Aminopropionyl and β-amino-α-methylpropionyl derivatives of iminodibenzyl were selected. Some of these compounds, particularly N-(β-diethylamino- and β-dimethylaminopropionyl)iminodibenzyl, were synthesized earlier [3], but the results of their pharmacological examination were not published.

The aminoacyl derivatives of iminodibenzyl were obtained by condensation of the acid chlorides of the corresponding halogen-containing carboxylic acid with iminodibenzyl with subsequent substitution of the chlorine atom in the obtained haloacyl derivatives of iminodibenzyl by primary or secondary amines.

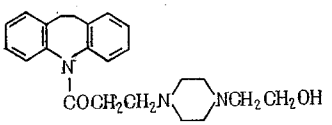


where R = H, CH_3

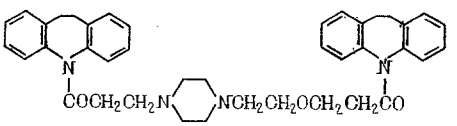
R_1 R_2 = Alk, Ar (see Table 1)

A 2-6 fold excess of amine was used in the substitution of the chlorine atom for the amino group. The acyl derivatives of iminodibenzyl are, in the majority of cases, oily materials which were characterized in the form of salts with mineral or organic acids. Yields, certain physicochemical constants, and elemental analysis data obtained for the aminoacyl derivatives of iminodibenzyl are presented in Table 1.

Upon reaction of N-(β-chloropropionyl)iminodibenzyl with N-hydroxyethylpiperazine, depending on the ratio of reagents (1:6 and 1:1), 2 compounds, (X) and (XVI), respectively, were obtained.

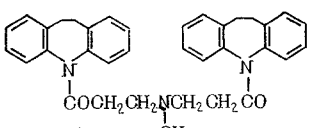


(X)



(XVI)

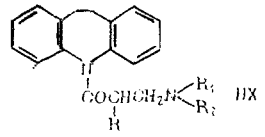
Reaction with a benzene solution of methylamine also proceeds with the formation of a product containing 2 residues of iminodibenzyl. Here, compound (XVII) is formed in addition to the secondary amine (I).



(XVII)

Lensovet Leningrad Technological Institute. Translated from Khimiko-Farmatsevticheskii Zhurnal, No. 12, pp. 21-26, December, 1967. Original article submitted July 10, 1967.

TABLE 1. Characteristics of the Obtained N-(β-Aminopropionyl- and β-Amino-α-methylpropionyl)iminodibenzyls



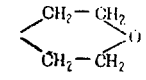
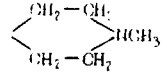
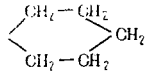
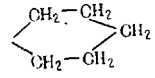
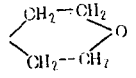
Compound	R	R_1	R_2	HX	Melting temperature (in degrees)	Crystallization solvent	Yield (in %)	Found (in %)		Empirical formula	Calculated (in %)	
								N	Cl		N	Cl
I	H	H	CH_3	HCl	167 dec.	Ethyl alcohol	20	8,53 8,59		$C_{18}H_{21}N_2OCl$	8,85	
II	H	CH_3	CH_3	HCl	165—167	Ethyl alcohol-ether	87	8,46 8,30		$C_{19}H_{23}N_2OCl$	8,48	
III	H	C_2H_5	C_2H_5	HCl	168—170	Ethyl alcohol-ether	40	7,84 7,71		$C_{21}H_{27}N_2OCl$	7,8	
IV	H	$(CH_3)_2CH$	$(CH_3)_2CH$	HCl	187—188	Isopropyl alcohol	43,7		9,34 9,35	$C_{23}H_{32}N_2OCl$		9,18
V	H	C_4H_9	C_4H_9	$(COOH)_2$	126—127	Ethyl alcohol-ether	54,5	6,48 6,57		$C_{27}H_{36}N_2O_5$	6,39	
VI	H	CH_3	C_6H_5	HCl	172—174	Isopropyl alcohol	33	7,77 8,03	9,15 8,83	$C_{24}H_{25}N_2OCl$	7,86	9,04
VII	H	C_2H_5OH	$C_6H_5CH_2$	$(COOH)_2$	170—172[1]	Ethyl alcohol-ether	75	5,75 5,78		$C_{28}H_{30}N_2O_6$	5,71	
VIII	H			HCl	205—206	Ethyl alcohol-ether	54,6	7,48 7,62	10,16 10,24	$C_{21}H_{25}N_2O_2Cl$	7,51	9,8
IX	H			HCl	227—232[2]	Ethyl alcohol-ether	83	10,99 11,18		$C_{22}H_{28}N_2OCl$	10,90	

TABLE 1 (continued)

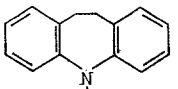
Compound	R	R_1	R_2	HX	Melting temperature (in degrees)	Crystallization solvent	Yield (in %)	Found (in %) N	Found (in %) Cl	Empirical formula	Calculated (in %) N	Calculated (in %) Cl
X	H	$(-CH_2CH_2)_2NC_2H_5OH$		2HCl	130[3]	Isopropyl alcohol	51	9,26 9,31	15,30 15,29	$C_{23}H_{29}O_2N_3Cl_2$	9,3	15,7
XI	H			HCl	158—159	Isopropyl alcohol	67,5	7,30 7,44	9,48 9,52	$C_{22}H_{27}N_2OCl$	7,55	9,58
XII	CH_3	CH_3	CH_3	HCl	240—241		43	8,31 8,34	10,22 10,16	$C_{20}H_{25}N_2OCl$	8,08	10,25
XIII	CH_3	C_2H_5	C_2H_5	HCl	230—231	Methyl alcohol	52	7,79	9,85 9,87	$C_{20}H_{29}N_2OCl$	7,50	9,55
XIV	CH_3			HCl	248	Methyl alcohol	50	7,07 7,33	9,45 9,44	$C_{23}H_{29}N_2OCl$	7,24	9,44
XV	CH_3			HCl	250—251	Methyl alcohol	39	7,30 7,42	9,46 9,48	$C_{22}H_{27}N_2O_2Cl$	7,24	9,18

*N-(β-benzylhydroxylethylaminopropionyl)iminodibenzyl has mp 101-103°. Found, %: N 7.09; 7.096. $C_{26}H_{28}N_2O_2$. Calculated, %: N 7.00.

† Found, %: C 68.70; H 7.14. $C_{22}H_{28}N_3OCl$. Calculated, %: C 68.48; H 7.26.

‡ N-{β-[4-(β-hydroxyethyl)piperazinyl]propionyl} iminodibenzyl fumarate mp 170-175° (dec.), W. Schindler, F. Haefliger, Swiss 368,496. Chem. Abstr. 60, 8046 (1964).

An attempt was made to condense N-methylpyridonimine with N-(β-chloropropionyl)iminodibenzyl. As a result of the reaction, instead of the expected N-[β-(N-methylpyridonimino)propionyl]iminodibenzyl was obtained N-(acrylyl)iminodibenzyl, the structure of which was confirmed by qualitative reactions and elemental analysis data. Evidently, in the



(XVIII) $COCH=CH_2$

reaction of the strongly basic N-methylpyridonimine (pKa-13) [4] with N-(β-chloropropionyl)iminodibenzyl, hydrogen chloride is cleaved from the latter which reacts with N-methylpyridonimine. In addition to compound (XVIII) and N-methylpyridonimine hydrochloride, the initial N-(β-chloropropionyl)iminodibenzyl was isolated from the reaction mixture in 30% yield.

The pharmacological examination of the aminopropionyl derivatives of iminodibenzyl was carried out on mice and rats in comparison with the known antidepressants: N-(β-dimethylaminopropyl)iminodibenzyl (imipramine), N-(β-methylaminopropyl)iminodibenzyl (desipramine), and N-(diethylaminopropionyl) chlorophenothiazine (chloroacizine). Tests were used which made the pharmacological activity of the antidepressants apparent.

Of the synthesized aminopropionyl derivatives of iminodibenzyl, N-(β-methylamino-, β-dimethylamino-, and β-diethylaminopropionyl)iminodibenzyls [compounds (I-III)] give the most expressed adrenopositive, cholinonegative, and antireserpine effects. The first 2 effects are stronger in them than in imipramine, and the third is weaker or equal to the effect in imipramine. The mentioned compounds differ from imipramine and desipramine by the absence of a distinct tranquilizing effect.

In the spectrum of pharmacological activity, these compounds, and also other aminopropionyl derivatives of iminodibenzyl, are similar to chloroacizine and other aminopropionyl derivatives of phenothiazine and chlorophenothiazine (which were also examined by us in comparison with the derivatives of iminodibenzyl), and occupy an intermediate position between them and propyl derivatives of iminodibenzyl.

Among the derivatives of iminodibenzyl, the change from aminopropyl to aminopropionyl derivatives is accompanied qualitatively by the same changes in pharmacological effects as going from aminopropyl to aminopropionyl derivatives of phenothiazine and namely, the sharp increase of adrenosensitizing and cholinolytic effects and weakening of the tranquilizing effect.

Demethylation of the terminal amino group in the dimethylaminopropionyl derivative [going from compound (II) to (I)] in the same way as in imipramine (its conversion into the monomethylimipramine) or even to a greater degree, is combined with weakening of the total depressant effect, but in contrast to imipramine and desipramine, is not accompanied by strengthening of the antagonism with reserpine.

The aminopropionyl derivatives containing the piperazine residue in the side chain [compounds (IX) and (X)], which strengthens the psychopharmacological activity in the neuroleptics, the aminopropyl derivatives of phenothiazine, and also the morpholinic residue (VIII), are low-activity. In these compounds, among them also is N-(β-morpholino-α-methylpropionyl)iminodibenzyl (XV), antagonism with reserpine is absolutely absent, which is the most typical effect of propyl and propionyl derivatives of iminodibenzyl. This paradoxical fact was subjected to a special pharmacological analysis [5].

β-Amino-α-methylpropionyl derivatives of iminodibenzyl (XII-XV) differ from the corresponding β-aminopropionyl derivatives (II, III, VIII, XI) by slightly weakened adrenopositive and cholinonegative effects. The antireserpine effect of (II) and (XII) is approximately the same, and compound (XIII) is stronger than (III). Since the adrenopositive and cholinonegative effects of (XIII) are weaker than of (III), the more selective antireserpine effect is most characteristic for antidepressents [1]. Introduction of a methyl group into the acyl residue was not accompanied by a noticeable increase of tranquilizing effect of the aminopropionyl derivatives, as in the propyl derivatives of iminodibenzyl and phenothiazine. It is possible that this is associated with the depressent effect being expressed minimally in compounds (I)-(III).

The toxicity of the aminopropionyl derivatives of iminodibenzyl is slightly less than that of the aminopropyl derivatives of phenothiazine.

Compounds (IV)-(VI) were not subjected to pharmacological examination because of poor solubility.

EXPERIMENTAL SECTION

N-(β-Chloropropionyl)iminodibenzyl was obtained upon reaction of 2 g (0.01 mole) of iminodibenzyl and 1.3 g (0.01 mole) of the freshly-distilled acid chloride of β-chloropropionic acid in dry benzene. Yield 2.37 g (81% of theoretical). After crystallization from ethyl alcohol, the mp was 105-106°C. Found, %: N 5.02, 5.08. $C_{17}H_{16}NOCl$. Calculated, %: N 4.93.

N-(β-Bromo-α-methylpropionyl)iminodibenzyl was obtained upon reaction of 7.5 g (0.04 mole) of iminodibenzyl and 7.4 g (0.04 mole) of the acid chloride of β-bromo-α-methylpropionic acid [6]. Yield 11.8 g (89.5% of theoretical), after crystallization from cyclohexane, mp 118.5°. Found, %: N 3.98, 3.96; Br 23.15, 22.94. $C_{18}H_{18}NOBr$. Calculated, %: N 4.05; Br 23.12.

N-(β-Diisopropylaminopropionyl)iminodibenzyl Hydrochloride. To a solution of 2.85 g (0.01 mole) of N-(β-chloropropionyl)iminodibenzyl in 70 ml of anhydrous toluene was added 2.02 g (0.02 mole) of diisopropylamine. The reaction mixture was boiled for 18 h, then the precipitated diisopropylamine hydrochloride was filtered. The filtrate was washed with water, dried over magnesium sulfate, and evaporated. The obtained oil was dissolved in anhydrous ether and was treated with ether saturated with hydrogen chloride. The separated precipitate of the hydrochloride salt after crystallization from isopropanol has mp 187-188°. Yield 1.7 g (43.7% of theoretical). Found, %: Cl 9.34, 9.35. $C_{23}H_{32}N_2OCl$. Calculated, %: Cl 9.18.

Analogously to the synthesis described above were obtained compounds (I-XV) (see Table 1).

Compound (XVI) was obtained by the same method upon reaction of 2.85 g (0.01 mole) of N-(β-chloropropionyl)iminodibenzyl and 1.7 g (0.013 mole) of N-hydroxyethylpiperazine. Yield 1.7 g (40% of theoretical), after crystallization from methanol, mp 238-238.5°. Found, %: N 8.12, 8.13; Cl 10.01, 10.09 $C_{40}H_{42}O_3N_4Cl_2$. Calculated, %: N 8.09; Cl 10.1.

Compound (XVII). Bis-β-(N-propionyliminodibenzyl)methylamine. To a solution of 0.85 g (0.003 mole) of N-(β-chloropropionyl)iminodibenzyl in 15 ml of anhydrous benzene was added 0.75 g (0.012 mole) of methylamine in 5 ml of benzene. The mixture was maintained for 7 days at room temperature, then boiled for 2 h. The precipitated methylamine hydrochloride was filtered. The filtrate was washed with water, dried over sodium sulfate, and evaporated. The obtained oil was dissolved in anhydrous ether and treated with ether saturated with hydrogen chloride. The separated oil after two reprecipitations from anhydrous alcohol with petroleum ether crystallized. Yield 0.5 g (55% of theoretical), mp 137° (dec.). Found, %: C 74.61, 74.40; H 6.50, 6.30; N 7.23, 7.50. $C_{35}H_{36}O_2N_3Cl$. Calculated, %: C 74.10; H 6.36; N 7.41.

From alcohol-petroleum ether mother solution upon standing was separated N-(β-methylaminopropionyl)iminodibenzyl hydrochloride.

Compound (XVIII). 5-(Acrylyl)iminodibenzyl was obtained by the method described above for obtaining the aminopropionyl derivatives of iminodibenzyl from 2.85 g (0.01 mole) of N-(β-chloropropionyl)iminodibenzyl and 2.67 g (0.025 mole) of N-methylpiridonimine [7]. Yield 1.25 g (50% of theoretical), after crystallization from isopropanol, mp 97-98°. Found, %: N 5.74, 5.90. $C_{17}H_{16}NO$. Calculated, %: N 5.6.

CONCLUSIONS

1. The reaction of β-haloacyl derivatives of iminodibenzyl with different amines leads to the formation of β-aminoacyl derivatives of iminodibenzyl.

2. Of the synthesized compounds, N-(β-methylamino-, β-dimethylamino-, β-diethylaminopropionyl)- and (β-diethylamino-α-methylpropionyl)iminodibenzyls can be regarded as prospective antidepressants and deserve clinical examination.

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