CONNECTION OF THE CHEMICAL STRUCTURE OF UREA DERIVATIVES WITH THEIR ANTICONVULSIVE ACTIVITY.

III. N-ACYL-N'-BENZHYDRYLUREAS

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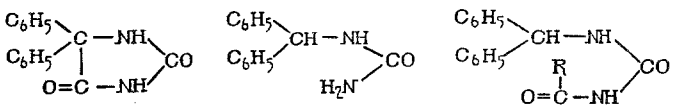
Continuing investigations on the relationship between structure and anticonvulsive activity in a series of N- and N,N'-substituted ureas [1, 2] we have synthesized and studied a series of N-acyl-N'-benzhydrylureas, which may be considered as structural noncyclic analogs of diphenine and, in view of this, are of interest for a comparison of their anticonvulsive properties. It is also possible to answer the question of the influence of the introduction of various acyl groups into the benzhydrylurea molecule on its anticonvulsive activity.



Diphenene Benzhydrylurea N-Acyl-N'-benzhydrylurea

The N-acyl-N'-benzhydrylureas were obtained by acylating benzhydrylurea with carboxylic acids in benzene in the presence of thionyl chloride.

The compounds synthesized (I-XVI) are shown in Table 1. It must be mentioned that some of them (I-III, V, and XI) have been synthesized previously [3], but for the systematic evaluation of the whole series we synthesized them again and studied their anticonvulsive activity.

In experiments on white mice (screening test) it was found that the anticonvulsive activity of the N-acyl-N'-benzhydrylurea derivatives is feeble or completely absent, regardless of the nature of the acyl residue, while benzhydrylurea itself possesses a high anticonvulsive action: ED_{50} according to the maximum electric shock test is 47 mg/kg, and according to the corazole test (in similar doses) it is twice as great as the ED_{50} of diphenine.

The half-effective dose according to the maximum electric shock test for the acyl derivatives of benzylurea is 30-50 times greater than for diphenine (ED_{50} for diphenine is 12.2 mg/kg), and, unlike the latter, it causes insignificant changes in the threshold of corazole convulsions (Table 2).

Thus, in spite of the structural similarity of diphenine, benzhydrylurea, and its acyl derivatives, they differ considerably in anticonvulsive properties. The absence of anticonvulsive activity close to that of diphenine and benzhydrylurea in the acylated benzhydrylureas can be explained by the fact that they hydrolyze in the organism, liberating the active principal, benzhydrylurea, only slowly.

In order to determine whether an interrelationship exists between the rate of hydrolysis and the anticonvulsive activity of the compounds investigated, we studied their hydrolysis in 0.1 N aqueous ethanolic sodium bicarbonate at 70°C for 1, 2, and 3 h. In this medium, the acylated benzhydrylureas hydrolyze to benzhydrylurea and the sodium salt of the corresponding carboxylic acid.

It was found that the acyl derivatives of benzhydrylurea are difficultly hydrolyzable compounds. The acetyl- and propionyl benzhydrylureas (I and III) hydrolyzed fastest, while

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TABLE 1. N-Acyl-N'-benzhydrylureas

Compound	R	Yield (in %)	mp (in %)	Found (in %)			Empirical formula	Calculated (in %)		
				C	H	N		C	H	N
I	CH_3	54	155—6*	—	—	—	—	—	—	—
II	$ClCH_2$	62	120—2†	—	—	—	—	—	—	—
III	C_2H_5	49	130—2‡	—	—	—	—	—	—	—
IV	β-ClC_2H_4	58	120—1	64,78	5,14	9,29	$C_{17}H_{17}ClN_2O_2$	64,55	5,38	8,86
V	C_3H_7	67	135—7**	—	—	—	—	—	—	—
VI	α-BrC_3H_6	52	124—5	57,90	4,96	8,00	$C_{18}H_{20}BrN_2O_2$	57,44	5,32	7,45
VII	C_4H_9	64	130—1	74,16	7,19	9,30	$C_{19}H_{22}N_2O_2$	73,64	7,09	9,03
VIII	iso-C_4H_9	51	155—6	73,17	7,15	9,21	$C_{19}H_{22}N_2O_2$	73,64	7,09	9,03
IX	C_5H_{11}	65	101—2	74,5	8,9	8,52	$C_{20}H_{24}N_2O_2$	74,04	8,64	8,64
X	$C_{17}H_{33}$	64	80—2	78,33	9,98	6,02	$C_{32}H_{46}N_2O_2$	78,04	9,75	5,68
XI	C_6H_5	58	208—9††	—	—	—	—	—	—	—
XII	$C_6H_5CH_2$	53	180—3	76,28	5,69	8,61	$C_{22}H_{20}N_2O_2$	76,75	5,83	8,14
XIII	$C_6H_5OCH_2$	52	190—2	72,95	5,32	8,23	$C_{22}H_{20}N_2O_3$	73,33	5,55	7,77
XIV	$(C_6H_5)_2CH$	68	244—6	79,64	6,07	7,38	$C_{28}H_{24}N_2O_2$	80,00	5,71	6,66
XV	Quinolin-2-yl	50	166—7	75,81	5,03	11,32	$C_{24}H_{19}N_3O_2$	75,59	4,97	11,02
Benzhydrylurea		80	144—6‡‡	—	—	—	—	—	—	—

*mp 154-5°C [3].
†mp 120-1°C [3].
‡mp 130-1°C [3].
**mp 135-6°C [3].
††mp 208-10°C [3].
‡‡mp 143°C [4].

compounds such as benzoylbenzhydrylurea (XI) and diphenylacetylbenzhydrylurea (XIV) did not hydrolyze at all under the conditions mentioned. The hydrolysis rate constants were calculated by means of the first-order equation and are given in Table 2. As can be seen, the nature of the acyl residue has no fundamental influence on the antitumoral activity of the compounds synthesized, and the factor determining the anticonvulsive action of the N-acyl-N'-benzhydrylureas is the hydrolytic stability of the compounds: The faster they hydrolyze the higher is their anticonvulsive activity.

EXPERIMENTAL

Benzhydrylurea. This was obtained by the method described previously [1].

N-Acyl-N'-benzhydrylureas. A solution of 22.6 g (0.1 mole) of benzhydrylurea in 100 ml of dry benzene was treated with 0.12 mole of a carboxylic acid and 0.12 mole of thionyl chloride. The reaction mixture was kept at 90°C with stirring for 3 h, after which it was poured into a porcelain dish and left to stand until the solvent had evaporated completely. The residue was washed with a 10% solution of sodium bicarbonate, dried, and crystallized from ethanol—water (2:1). The yields of purified N-acyl-N'-benzhydrylureas were between 50 and 70%. The compounds obtained and their yields and melting points are given in Table 1. They are crystalline substances soluble in the majority of organic solvents and practically insoluble in water. The individuality of the N-acyl-N'-benzhydrylureas was confirmed by the results of elementary analysis and by IR spectroscopy.

The IR spectrum of benzhydrylurea has the absorption bands of the stretching vibrations of a C=O group at 1660 cm^{-1} and of NH_2 and NH groups at 3450, 3330, and 3215 cm^{-1}. The IR spectra of the N-acyl-N'-benzhydrylureas are characterized by the disappearance of the absorption bands of the stretching vibrations of an NH_2 group, and in the region of the stretching vibrations of NH groups there are bands at 3280, 3223, and 3100 cm^{-1}. The absorption bands of the C=O stretching vibrations of these compounds are located at 1690 cm^{-1}.

Hydrolysis of the N-Acyl-N'-benzhydrylureas. The procedure for hydrolysis was similar to that which we have described previously [2]. Compounds (XI) and (XIV) did not hydrolyze at all in 3 h under the selected conditions. The hydrolysis of compound (XIII) did not give reproducible results. Compounds (II, IV, and VI) were not studied for hydrolytic stability,

TABLE 2. Comparative Information on the Pharmacological Activity and Hydrolysis of the N-Acyl-N'-benzhydryl Derivatives of Urea

Compound	Dose (in mg/kg)	Pharmacological activity			Hydrolysis constant (in min^{-1})
		maximum electric shock		threshold of corazole convulsions (in mg/kg)	
		% prevention of convulsions	ED_{50} (in mg/kg)		
Control	—	0	—	110,0±9,4	—
I	400	33,3	360 (300÷432)	—	1:4
	200	16,7		166,0±20,6	
II	200	0	—	145,0±11,2	—
III	500	83,3	420 (331÷533)	—	1,25
	200	0		175,0±20,4	
IV	500	33,3	614 (479,3÷750)	—	—
	200	0		142,1±15,5	—
V	500	33,3	—	—	0,90
	200			154,0±11,1	
VI	500	16,7	684 (589,6÷793)	—	—
	200	0		101,2±2,1	
VII	500	0	—	—	—
	200	0		126,0±6,1	
VIII	500	0	—	—	0,44
	200	0	—	134,0±8,2	
IX	500	33,3	526 (305,8÷810)	—	0,70
	200	16,7		111,5±4,6	
X	500	33,3	640 (556,5÷736)	—	0,42
	200	0		109,7±6,98	
XI	200	0	—	121,0±1,7	0
XII	200	0	—	99,5±14,5	0,79
XIII	500	50,0	430 (296,5÷623,5)	—	—
	200	16,7		125,9±15,5	
XIV	500	50,0	388 (250,3÷601,4)	—	0
	200	33,3		99,1±14,5	
XV	500	33,3	526 (305,8÷810)	—	—
	200	16,7		101,4±8,6	
Benzhydrylurea	200	100	47 (37÷72)	406,0±81,2	—
Diphenine	200	100	12,2	243,5±58,2	—

since in these compounds the hydrolytic splitting out of halogen is possible in addition to the hydrolysis of the acyl group.

LITERATURE CITED

1. A. G. Pechenkin, L. G. Tignibidina, A. P. Gilev, et al., Khim. Farmats. Zh., No. 7, 29 (1972).
2. A. G. Pechenkin, L. G. Tignibidina, A. P. Gilev, et al., Khim. Farmats. Zh., No. 1, 16 (1973).
3. US Patent No. 2,560,522 (1951); Chem. Abstr., 46, 3568 (1952).
4. R. Leuckart and E. Bach, Ber. Dtsch. Chem. Ges., 19, 2130 (1886).