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SYNTHETIC ANTICONVULSANTS, ANTIHYPOXICS, AND INDUCERS OF THE LIVER MONOOXYGENASE SYSTEM BASED ON AMIDES AND UREAS. XVII.* SYNTHESIS OF N-BENZHYDRYL-N′-(HETEROYL)UREAS AND STUDIES OF THEIR ANTICONVULSIVE ACTIVITY

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Previous studies [2, 3] have shown that benzhydrylureas have high anticonvulsive activity, and another report [4] showed that the introduction of aliphatic or aryl carboxyl radicals at the free nitrogen atom of monosubstituted ureas leads to a reduction in the biological activity of the original compound.

With the aim of gaining further understanding of these relationships in benzhydrylurea derivatives substituted with heteroyl radicals, and to find new biologically active compounds, we have synthesized N-benzhydryl-N′-(heteroyl)ureas (I-VII and hydrochlorides VIII-X) and studied their anticonvulsive activity in maximum electric shock and corasole "titration" tests (Table 1).

Benzhydrylurea was acylated with chloranhydrides in benzene in the presence of catalytic quantities of hydrochloric acid or pyridine. Benzhydrylurea was not acylated by picolinic chloranhydride in the presence of hydrochloric acid (method A), probably because of the known tendency of picolinic acid to undergo decarboxylation in strong acids [5]. However, this difficulty was overcome by using pyridine as the catalyst for acylation of benzhydrylurea with picolinic chloranhydride (method B).

$$(Ph)_2CHNHCONH_2 \xrightarrow{RCOCl} (Ph)_2CHNHCONHCOR \qquad I—X$$

R: Furyl-2 (I), pyridyl-4 (II), pyridyl-3 (III), pyridyl-2 (IV), quinolyl-2 (V), 2-phenylquinolyl-4 (VI), 2-hydroxyquinolyl-4 (VII); hydrochlorides of II (VIII), III (IX), and V (X).

Hydrochlorides VIII-X were prepared by passing dry hydrogen chloride through hot ethanolic solutions of the corresponding ureas II, III, and V.

Compounds I-X were of low toxicity, with LD_{50} values exceeding 2000 mg/kg.

Ureas I-VII and hydrochlorides VIII-X had no anticonvulsive activity in the corasole titration test. Compounds I and III-X had low activity in the maximum electric shock test, though N-benzhydryl-N′-(isonicotinoyl) urea II had higher anticonvulsive activity than benzhydrylurea itself (ED_{50} = 47 mg/kg [2]). Comparison of the anticonvulsive activities of heteroylbenzhydrylureas I-VII and their hydrochlorides VIII-X showed that the heteroyl radicals at the N′-position of benzhydrylurea produced greater reductions in activity than aliphatic and aroyl radicals at the N′-position of benzhydrylurea [4].

*See [1] for communication XVI.

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TABLE 1. Anticonvulsive Activities of Compounds I-X

Compound	Dose, mg/kg	Maximum electric shock test			Convulsive threshold of corasole, mg/kg	
		% prevention of convulsions	% of animals surviving	ED_{50}, mg/kg	$M \pm m$, p	ACI
I	200	0	16,7	—	105,5±15,1 0,442	0,9
II	200	100	100	33,2	122,4±2,38 0,087	1,1
	50	66,7	100			
	20	33,3	83,3			
III	200	16,7	83,3	—	119,1±24,0 1,000	1,0
IV	200	33,3	66,7	350	129,4±11,0 0,341	1,2
V	200	16,7	66,7	526	104,4±8,6 0,102	0,8
	500	33,3	50			
VI	200	0	83,3	—	109,1±18,8 0,628	0,9
	500	0	33,3			
VII	200	0	66,7	—	77,4±18,5 0,062	0,6
VIII	200	0	16,7	682	131,8±8,3 0,298	1,1
	500	16,7	50,0			
	700	50,0	66,7			
IX	200	16,7	66,7	576	105,9±12,7 1,000	1,0
	600	16,7	50,0			
X	200	16,7	33,3	344	107,0±19,4 0,922	1,0
	300	33,3	33,3			

Notes. ACI = anticorasole index (ratio of experimental to control anticorasole indexes).

TABLE 2. Yields and Properties of Compounds I-X

Compound	Yield, %		Melting point, °C	Atomic formula	IR spectrum, ν_{max}, cm^{-1}			
	method A	method B			NH	C=O	CONHCO	COR
I	17	16	177—8	$C_{19}H_{16}N_2O_3$	3340	1670	3220	1710
II	18	15	197—8	$C_{20}H_{17}N_3O_2$	3345	1666	3220	1710
III	16	18	202—4	$C_{20}H_{17}N_3O_2$	3330	1670	3215	1715
IV	15	17	122—3	$C_{20}H_{17}N_3O_2$	3350	1670	3220	1710
V	17	16	166—7	$C_{24}H_{17}N_3O_2$	3335	1665	3235	1715
VI	18	18	178—80	$C_{30}H_{23}N_3O_2$	3340	1660	3230	1710
VII	16	17	179—81	$C_{30}H_{19}N_3O_3$	3345	1665	3235	1720
VIII	45	35	205—7	$C_{20}H_{18}ClN_3O_2$	3355	1660	3210	1715
IX	49	40	194—6	$C_{20}H_{18}ClN_3O_2$	3360	1660	3215	1710
X	60	42	169—71	$C_{24}H_{20}ClN_3O_2$	3355	1665	3110	1720

CHEMICAL METHODS

N-Benzhydryl-N'-(heteroyl)ureas (I-VII). Method A: Chloranhydrides of the appropriate heterocarbonic acids (0.25 mole) were mixed vigorously with 0.24 mole of benzhydrylurea in 75 ml of anhydrous benzene, and the mixtures were heated to boiling point, after which 10 drops of 57% hydrochloric acid were added and reactions were incubated for 6-8 h (until HCl liberation ceased). Benzene was then evaporated off and the residue treated with a saturated solution of sodium bicarbonate, filtered, and washed with water. The precipitate was recrystallized three times from ethanol to produce compound I with a yield of 15-18%.

N-Benzhydryl-N'-(heteroyl)ureas (I-VII). Method B: The method used for acylation of benzhydrylurea with the chloranhydrides of heterocarbonic acids in the presence of pyridine and extraction of the desired products I-VIII was analogous to method A.

The properties of compounds I-X are shown in Table 2. The results of elemental analyses agreed with predicted values.

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