RELATIONSHIP OF THE CHEMICAL STRUCTURE OF UREA DERIVATIVES TO ANTISPASMODIC ACTIVITY. ALKYL-, ARALKYL, AND DIARALKYL DERIVATIVES OF UREA

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Most of the known antispasmodic preparations are cyclic derivatives of urea. Noncyclic derivatives have been less studied along this line, although highly active compounds exist among them, for example, phenuron [1]. However, this preparation has not found wide use in clinical practice, chiefly on account of its toxic effects, arising during prolonged administration [2, 3]. Urea derivatives substituted in the N-position by aralkyl residues, and in the N'-position by acid residues with a branched structure [4], have practically the same antispasmodic effect as phenuron, but they are less toxic. The introduction of residues of acids of normal structure in the N-position does not lead to an intensification of antispasmodic properties.

Taking into consideration such a strong influence of the isostructure of the acid residues on the anticonvulsive action, we synthesized a series of new urea derivatives, possessing branched alkyl, diaralkyl, and aralkyl structures in the N-position.

Nitrourea and primary amines were used as the starting materials in the synthesis of N-substituted ureas. Nitrourea is the source of isocyanic acid when heated slightly in water or other polar solvents [7], and isocyanic acid is an active ingredient in this reaction.

$$NO_2NHCONH_2 \rightarrow HNCO + NH_2NO_2$$
$$HNCO + RNH_2 \rightarrow RNHCONH_2$$

The primary amines were produced from the corresponding ketones by hydroamination according to the Leuckart reaction [8].

The compounds obtained were investigated for antispasmodic activity according to the test of maximal electroshock [5] and the change in the threshold of corazol convulsions [6] on white mice. Data on those tests are cited in Table 1.

The results of the pharmacological investigations show that there is a definite relationship between the antispasmodic action and the chemical structure among the three groups of N-derivatives of urea studied (I, II, III).

$$(Alk)_2CHNHCONH_2,\ Alk(Ar)CHNHCONH_2\ (ArAlk)_2,\ CHNHCONH_2$$

Thus, monoalkyl derivatives of urea (I) manifest a rather weak antispasmodic action, both according to the test of maximum electroshock and according to the corazol test. However, among these compounds

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TABLE 1. Antispasmodic Activity of N-Substituted Derivatives of Urea $RNHCONH_2$

Compound	R	Melting point (in (in degrees)	Pharmacological activity	
			maximal electroshock (in %)	change in the threshold of corazol convulsions (in mg/kg)
I	$(CH_3)_2CH$	154	0	77±10,9[1]
II	$(CH_3)_2CHCH_2$	141—2	17	135±13,7
III	$CH_3(C_2H_5)CH$	167—8	17	146±7,9[1]
IV	$(CH_3)_2CH(CH_2)_2$	89—90	100	154±8,5[1]
V	CH_3(iso-C_3H_7)CH	200—1	17	144±11,2[1]
VI	$CH_3(C_4H_9)CH$	127—8	67	159±13,8[1]
VII	$CH_3(C_5H_{11})CH$	124	50	124±6,8
VIII	$CH_3(C_6H_{13})CH$	130—1	67	139±5,2[1]
IX	$CH_3CHC(CH_3)_3$	200—2	67	179±7,8[1]
X	$(C_2H_5)_2CH$	186	83	155±17,7[1]
XI	$(C_3H_7)_2CH$	171—2	33	154±10,9[1]
XII	$(C_4H_9)_2CH$	154—6	0	117±11,8
XIII	$(C_6H_{13})_2CH$	111—2	0	124±10,5
XIV	$C_6H_5(CH_3)CH$	137	100	157±8,2[1]
XV	$C_6H_5(C_2H_5)CH$	100—1	100	219±5,6[1]
XVI	$C_6H_5(C_3H_7)CH$	122	100	212±30,2[1]
XVII	C_6H_5(iso-C_3H_7)CH	142—3	100	241±25,6[1]
XVIII	$C_6H_5(C_4H_9)CH$	131—2	83	136±4,2[1]
XIX	C_6H_5(iso-C_4H_9)CH	102—3	100	146±9,1[1]
XX	$C_6H_5CH_2(CH_3)CH$	154	100	194±9,8[1]
XXI	$C_6H_5CH_2(C_2H_5)CH$	106	100	209±19,6[1]
XXII	$C_6H_5CH_2(C_6H_5)CH$	99—100	100	152±9,4[1]
XXIII	$(C_6H_5CH_2)_2CH$	135	All died	
XXIV	$C_6H_5CH_2CH_2(C_6H_5)CH$	115	100	139±4,8[1]
XXV	$(C_6H_5)_2CHCH_2(C_6H_5)CH$	203	0	112±15,2
XVI	$(C_6H_5)_3C$	240	0	134±2,8

[1]Significant changes with respect to the control group of animals, the spasmodic threshold for which was equal to 110 ± 9.4 mg/kg.

a certain dependence of the activity on the number of carbon atoms in the alkyl residue can be noted: pronounced activity is observed for a chain length of 5-6 carbon atoms (compounds IV, VI, IX, X). Further increasing the number of carbon atoms leads to a decrease or total disappearance of activity (compounds XII, XIII). The position of the urea residue in the alkyl chain, possessing the same number of carbon atoms, does not significantly influence the activity according to both tests (compounds II and III, IV and X, VII, and XI).

The supplementary introduction of a phenyl residue into the alkyl chain of N-substituted ureas, leading to compounds of the type II, increases the antispasmodic activity of the preparations according to both tests (compounds XIV-XXI). In this series all the preparations significantly increase the threshold of corazol convulsions and prevent tonic extension in mice in the presence of maximal electroshock. The introduction of two phenyl residues into the branched chain of N-alkylureas, leading to structures of the type of III, does not cause any appreciable intensification of the antispasmodic activity (compounds XXII-XXIV) in comparison with compounds II. N-Derivatives of urea, containing a triphenylalkyl group (compounds XXV, XXVI), are inactive according to both groups.

EXPERIMENTAL

N-Substituted Ureas. A 1.2-mole portion of nitrourea was dissolved in one liter of water, then 1 mole of the corresponding amine was added to the suspension obtained with mixing. The mixture was heated for 1 h at 70°, whereupon evolution of gas and complete dissolution of nitrourea was observed. After heating for 1 h, the N-substituted urea formed precipitated in the form of a colorless precipitate. The precipitate was filtered off and purified by recrystallization from the corresponding solvent.

All the compounds obtained were identified according to the analysis for nitrogen, carbon, and hydrogen. The IR spectra of the compounds were taken on a UR-10 instrument in liquid petrolatum and in a solution of chloroform (concentration 0.05 M). An intense absorption band $\nu C=O$ (1680-1690 cm^{-1}) and the bands of primary and secondary amino groups νNH (3520, 3450, 3420 cm^{-1}), as well as the characteristic absorption bands of the corresponding substituents at the nitrogen atom, were detected in the IR spectra in chloroform.

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