THE CONNECTION BETWEEN THE CHEMICAL STRUCTURE OF UREA DERIVATIVES AND THEIR ANTISPASMODIC ACTIVITY

II. N'-ACYL-N-ALKYL (ARALKYL) DERIVATIVES OF UREA

A. G. Pechenkin, L. G. Tignibidina,
A. P. Gulev, V. K. Gorshkova,
and V. M. Kurilenko

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It is known that the acylation of amino and hydroxyl groups in medicinal compounds leads to new and less toxic products. In some cases acylation increases the activity of the preparations as well as lowering the toxicity. It has already been established that benzoylation of Luminal and Barbamyl considerably increases the antispasmodic activity of the original compounds and decreases their soporific side effect and toxicity [1, 2]. A similar effect is observed in the acylation of N-substituted ureas [3].

We have carried out aculation of a series of N-substituted ureas. The N-alkyl(aralkyl)-N'-acylated ureas obtained were investigated for antispasmodic activity by the maximum electric shock test [4] and the change in Corazol spasm threshold [5]. The pharmacological data from both tests are shown in Table 1.

In the investigation of antispasmodic activity it was seen that the introduction of normal and branched fatty acid groups and also of benzoic and phenylacetic acid groups into active N-substituted ureas has a considerable influence in lowering their activity as measured in the maximum electric shock test (compounds I-VII, XV, XVI, XX, and XXV). Only some of the acyl derivatives significantly increase the Corazol spasm threshold, a positive effect being observed with increase in length of the carbon chain in the acyl group up to C_4. Further increase in the length of the carbon chain of the acyl group leads to a drop in activity. The literature evidence of increase in antispasmodic properties of butylurea on benzoylation [6] is not repeated in our investigations in the case of inactive isopropylurea (compounds IX, X).

We have attempted to explain the unexpected decrease in the antispasmodic properties of active N-substituted ureas after acylation on the basis of the mechanism proposed for their activity in the organism. It is known that the physiological activity of acylated produces often depends on their rate of hydrolysis [7]. However, many compounds only exhibit activity in the form of the acyl derivatives (phenurons).

It was of interest to find out whether or not in our case the activity of N'-acyl-N-aralkylureas depends on the rate of their hydrolysis to N-aralkylureas. The hydrolysis was carried out in 0.1 N aqueous-alcoholic sodium carbonate solution at 70° for 3 h. The hydrolysis rate constants were calculated from a first-order equation since the solvent is present in considerable excess and its concentration does not change significantly during the reaction. The calculated hydrolysis rate constants are shown in Table 1.

Comparison of the resistance to hydrolysis with the pharmacological activity shows that there is a clear correlation between the rate of hydrolysis and the antispasmodic activity of the acylated N-alkyl(aralkyl)ureas: the more rapidly the product is hydrolyzed, the greater is its antispasmodic activity (compounds VI, VII, XI, XIV, XVII, and XIX), while, on the other hand, acyl derivatives with a low hydrolysis rate are less active or completely inactive (compounds I, II, IV, XV, XX, XXI, and XXIII).

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TABLE 1. N'-acyl-N-alkyl(aralkyl)ureas

Compound*	R'	M_p (deg)	Hydrolysis rate constant $K \cdot 10\ min^{-1}$	Pharmacological activity	
				max. electric shock †	change in Corazol spasm threshold, mg/kg
I	CH_3	102—3	2,30	0	150±8,1‡
II	C_2H_5	95—6	3,56	16,6	136±10,8
III	C_3H_7	107—9		16,6	165±8,9‡
IV	n-C_4H_9	94—5	3,56	0	134±10,7
V	iso-C_4H_9	83—4		50,0	127±12,5
VI	C_6H_5	108	10,50	33,3	125±20,0
VII	$C_6H_5CH_2$	85—6	7,98	33,3	—
VIII	C_2H_5	47—8		0	—
IX	C_6H_5	113		0	136±11,6
X	$C_6H_5CH_2$	105—7		0	—
XI	CH_3	76—7	6,93	83,3	172,5±14,8‡
XII	C_2H_5	99—100	7,56	100,0	220±12,5‡
XIII	C_3H_7	33—5	5,25	100,0	234±19,6‡
XIV	C_4H_9	37—9	5,88	83,3	206±25,7‡
XV	C_6H_5	135	3,30	0	116±7,9
XVI	$C_6H_5CH_2$	135—6		0	131±5,1
XVII	CH_3	79	3,8	83,3	124±13,6
XVIII	C_2H_5	63—4	4,62	66,6	157±9,26‡
XIX	n-C_3H_7	50—1	3,99	83,3	214±10,7‡
XX	iso-C_3H_7	51—3	1,89	16,6	203±21,7‡
XXI	iso-C_4H_9	55—6	2,10	0	119±12,1
XXII	C_6H_5	127		0	121±10,5
XXIII	$C_6H_5CH_2$	99—100	1,47	0	—
XXIV	C_2H_5	58—9		0	135±2,5
XXV	$C_6H_5CH_2$	66—7		0	130±6,9

* For compounds I-VII R=iso-C_5H_{11}, VIII, IX, and X R=iso-C_3H_7, XI-XVI R=$C_6H_5(CH_3)CH$, XVII-XXIII R=$C_6H_5CH_2(CH_3)CH$, XXIV, XXV R=$C_6H_5(C_3H_7)CH$.

†Antispasmodic activity expressed in %.

‡ Significant changes in relation to a control group of animals for which the Corazol spasm threshold is 110 ± 9.4 mg/kg.

Thus, it may be assumed that some N'-acyl-N-alkyl(aralkyl)ureas have weak antispasmodic properties since their rate of hydrolysis in the organism is insufficient to give the concentration of original active N-substituted ureas required to ensure antispasmodic properties.

Despite the fact that acylation of N-substituted ureas leads (in our case) to a decrease in activity, it is possible to suppose that active antispasmodic compounds may also be found among these derivatives. Above all, these compounds should be easily hydrolyzed since both components formed in the hydrolysis (N-substituted urea and acid) must have antispasmodic properties. Some amino acids are known to be active anticonvulsants [8] and acylation of N-substituted ureas with these may give favorable results.

EXPERIMENTAL

N'-acyl-N-alkyl(aralkyl)-substituted ureas. To 0.05 mole N-substituted urea in 150 ml benzene were added 0.15 mole pyridine and 0.06 mole acid chloride. The reaction mixture was held at 90° for 1 h with agitation, then poured into a porcelain dish and allowed to stand until the solvent had completely evaporated. The residue was washed with water and 10% sodium bicarbonate solution, washed and crystallized from a mixture of ethanol and water (2:1). The yield of purified N'-acyl-derivative is in the range 60-70%. The compounds prepared and their melting points are shown in Table 1. The compounds were identified by C, H, N analysis and by infrared spectroscopy. Acylation in the N' and not in the N position was confirmed by reverse synthesis of similar compounds by the Hofmann reaction. A mixture of samples obtained by the different methods gave no melting point depression.

Hydrolysis of N'-acyl-N-aralkylureas. Forty milliliters of a 0.1 N sodium carbonate solution (0.002 mole) were added to a solution of 0.002 mole N'-acyl-N-aralkylurea in 40 ml of 95% ethanol and the mixture held at 70°. The hydrolysis was carried out for 3 h and the reaction mixture analyzed every hour. The remaining sodium carbonate was potentiometrically titrated with a 0.1 N solution of hydrochloric acid ("by halves" to pH 8.35) and the quantity of hydrolyzed product calculated.

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