SYNTHETIC ANTICONVULSANTS, ANTIHYPOXICS, AND LIVER MONOOXYGENASE SYSTEM INDUCERS BASED ON AMIDES AND UREA. XI.* SYNTHESIS OF ALKYL- AND ARYLALKYLUREAS AND THEIR EFFECTS ON THE LIVER MONOOXYGENASE SYSTEM

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During studies on the search for and synthesis of new compounds able to induce the liver cytochrome—P-450-dependent monooxygenase system, we have produced a series of urea derivatives (I-XVIII) and we have evaluated their enzyme-inducing activities using the hexobarbital sleep test. Alkyl- and arylalkylureas I-XVIII were prepared by combining the corresponding alkyl- and arylalkylamines with nitrourea in aqueous solution as described in [1]. The yields, physicochemical properties, and spectral characteristics (IR, ^1H, and ^{13}C NMR) of compounds I-XVIII are given in Tables 1-3, and their enzyme-inducing activities are shown in Table 4.

$$RR'CHNHCONH_2,$$
I—XVIII

where

I—V, XVIII: R=R′=Et(I), Pr(II), Bu(III), Am(IV), Hex(V), CH_2Ph(XVIII);
V—VIII: R=Me(VI—VIII); R′=Pr(VI), Bu(VII), Hex(VIII);
IX—XVII; R=Ph(IX—XVII); R′=H(IX), Me(X), Et(XI), Pr(XII), *i*-Pr(XIII), Bu(XIV), *i*-Bu(XV), CH_2Ph(XVI), Ph(XVII).

Studies of the biological activity of these substances showed that compounds III, IV, VII, and XVI-XVIII had pronounced effects on the liver monooxygenase system of experimental animals. A group of symmetrical alkylureas, compounds I-V, had activity levels that increased with the length of the R and R′ radicals, as far as dihexylmethylurea V, where activity was close to the control level. The enzyme-inducing activity of the nonsymmetrical alkylureas, compounds VI-VIII, changed with increases in the length of the R′ radical in an irregular way; the hexyl radical (compound VIII), as in the case of symmetrical alkylureas, produced a reduction in activity. In both series of compounds, I-V and VI-VIII, there were weak correlations between activity and the steric constants of the E-substituent R′, though there was no correlation with the Charton steric constant (ν) [5].

$$A=15{,}38+137{,}44E_s;\ r=0{,}7682,\ s=13{,}98. \quad (1)$$

In addition, the series of urea derivatives I-V showed symbatic changes in activity and the extent of screening of the carbamide carbon atom in the ^{13}C NMR spectrum [Eq. (2)]: activity increased with increasing screening of this atom.

$$A=-16397+101\delta_{C=O},\ r=0{,}9854,\ s=3{,}719. \quad (2)$$

*For Communication X, see [3].

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TABLE 1. Properties of Alkylureas I-VIII and Arylalkylureas IX-XVIII

Compound	Yield, %	Melting point, °C	Atomic formula
I	75	186—187	$C_6H_{14}N_2O$
II	70	171—172	$C_6H_{18}N_2O$
III	66	154—156	$C_{10}H_{22}N_2O$
IV	63	122—123	$C_{12}H_{26}N_2O$
V	60	111—112	$C_{14}H_{30}N_2O$
VI	48	200—201	$C_5H_{13}N_2O$
VII	59	127—128	$C_6H_{15}N_2O$
VIII	68	130—131	$C_8H_{15}N_2O$
IX	79	148—149	$C_8H_{10}N_2O$
X	75	136—137	$C_9H_{12}N_2O$
XI	52	100—101	$C_{10}H_{14}N_2O$
XII	57	121—122	$C_{11}H_{15}N_2O$
XIII	68	142—143	$C_{11}H_{15}N_2O$
XIV	63	131—132	$C_{12}H_{15}N_2O$
XV	52	103—103	$C_{12}H_{15}N_2O$
XVI	53	99—100	$C_{15}H_{16}N_2O$
XVII	78	143—144	$C_{14}H_{14}N_2O$
XVIII	43	125—126	$C_{15}H_{16}N_2O$

TABLE 2. IR Spectra of Ureas I-XVIII (M ± m)

Characteristic absorption bands, cm^{-1}		Identification
compounds I-VIII	compounds IX-XVIII	
3426±16	3426±16	$\nu_{a,s}$ NH_2
3334±15	3328±18	ν_s NH
3214±5	3210±10	ν_s NH
3100±0	3080±10	
	3025±5	ν_s CH(aromatic)
1655±5	1655±5	ν_s C=O

TABLE 3. ^1H and ^{13}C NMR Spectra of Alkylureas I-VIII and Arylalkylureas IX-XVIII

Compound Compound	^{13}C NMR spectrum, δ, DMSO-d_6, ppm		^1H NMR spectrum, δ, ppm		
	CH	C=O	CH	NH	NH_2
I	54,48	161,89	3,68	5,99	5,56
II	50,97	161,67	3,67	5,92	5,51
III	51,49	161,40	3,69	5,93	5,47
IV	55,83	161,30	3,70	5,98	5,49
V	51,48	161,67	3,72	5,88	5,45
VI	48,03	161,33	3,70	5,95	5,54
VII	47,61	161,37	3,71	5,98	5,56
VIII	47,20	161,40	3,70	5,96	5,52
IX	46,04	161,12	4,41	6,79	5,86
X	51,57	161,15	4,94	6,47	5,68
XI	57,62	161,37	4,72	6,66	5,65
XII	55,75	161,22	4,82	6,68	5,68
XIII	61,58	161,45	4,67	6,71	5,71
XIV	56,12	161,30	4,79	6,67	5,66
XV	54,33	161,30	4,89	6,69	5,70
XVI	57,77	161,07	5,12	6,81	5,71
XVII	56,45	157,52			
XVIII			4,34		5,07

TABLE 4. Effects of Compounds I-XVIII on the Duration of Hexobarbital Sleep in Mice (means of 6-8 experiments) (M ± m)

Compound	Duration of hexobarbitial sleep, min		% of control
	expt.	calc.	
I	70,0±3,6	70,0±2,8	100
II	57,6±2,0*	70,0±2,8	85
III	38,5±4,0*	70,0±2,8	57
IV	28,6±3,0*	70,0±2,8	40
V	61,3±2,3*	70,0±2,8	86
VI	68,0±4,0	70,0±2,8	100
VII	35,1±5,1*	70,0±2,8	50
VIII	71,2±3,2	70,0±2,8	100
IX	60,0±4,0	60,0±3,1	100
X	61,0±3,6	60,0±3,1	100
XI	59,7±3,8	60,0±3,1	100
XII	61,5±3,1	60,0±3,1	100
XIII	62,1±4,2	60,0±3,1	100
XIV	64,2±3,2	65,0±2,9	100
XV	66,7±2,6	65,0±2,9	100
XVI	32,4±3,3*	65,0±2,9	50
XVII	21,5±2,8*	65,0±2,9	33
XVIII	21,3±2,5*	65,0±2,9	35

*Differences from control significant at $p < 0.05$.

According to previous studies [4, 6], changes in the chemical shift of the C=O atom in urea derivatives depend on conformational changes in the carbamide fragment. Thus, it follows that Eqs. (1) and (2) reflect a definite relationship between the enzyme-inducing activities of alkylureas I-V and conformational changes in the $NHCONH_2$ radical.

Replacement of one alkyl radical R in compounds I-VIII with a phenyl radical (i.e., to make phenylalkylureas, compounds IX-XV) led to virtually complete loss of enzyme-inducing activity, independently of the structure of the alkyl radical R. Only the introduction of a second phenyl nucleus (to make compounds XVI-XVIII) sharply increased enzyme-inducing activity on the mouse liver cytochrome—P450-dependent monooxygenase system. It is interesting to note that, as in the case of alkylureas I-V, increases in the level of screening of the carbonyl carbon atom in the ^{13}C NMR spectra were accompanied by increases in activity (see Table 3). The results obtained with phenylalkylureas IX-XVIII support our earlier conclusion [2] that high levels of enzyme-inducing activity in linear and cyclic ureas require their structure to contain two phenyl rings in combination with the Ph—C—N fragment. Phenylalkylureas IX-XV are structurally similar to amino acids, i.e., the endogenous substrates of the cell. It is possible that introduction of an additional phenyl nucleus (in compounds XV-XVIII) gives them substrate noncorrespondence for the systems involved in the metabolism of natural cellular substrates, i.e., these compounds are xenobiotics.

EXPERIMENTAL (PHARMACOLOGICAL)

Experiments were carried out using 400 mongrel male mice (18-22 g). Compounds I-XVIII were given at doses equivalent to a dose of benzhydrylurea XVII of 100 mg/kg: I at 58, II at 69, III at 82, IV at 94, V at 100, VI at 59, VII at 63, VIII at 76, IX at 66, X at 71, XI at 77, XII at 83, XIII at 83, XIV at 91, XV at 91, XVI at 105, and XVIII at 105 mg/kg. Doses were po and were given three times daily, as suspensions in 1% starch paste. Hexobarbital was injected ip at a dose of 80 mg/kg 24 h after the last dose of test compounds I-XVIII. The duration of hexobarbital sleep was measured in terms of the absence of the turning-over reflex. Results were analyzed statistically using Student's t test.

EXPERIMENTAL (CHEMICAL)

^1H NMR spectra were recorded on a Tesla BS-497 spectrometer (100 MHz, using HMDS as the internal standard). ^{14}C NMR spectra were recorded using a Tesla BS-567 A spectrometer (25.142 MHz, using TMS as the internal standard). IR

spectra were taken on a UR-20 spectrometer in Vaseline. Control of compound purity and monitoring of reactions were carried out using TLC analysis on Silufol UV-254 plates, using benzene:ethanol (8:2) as the eluant; spots were detected in UV light.

Alkylureas (I-VIII) and Phenylalkylureas (IX-XVIII). Nitroureas (0.15 mole) were dissolved in 150 ml of water, and 0.1 mole of the corresponding amine was added with constant mixing. The reaction mixes were heated to 70°C for 1 h until the nitrourea had completely dissolved. The resulting white precipitate was collected by filtration, washed with water, and recrystallized from aqueous ethanol. The yields and properties of the synthesized ureas (I-XVIII) are shown in Tables 1-3. Measured elemental compositions agreed with predicted values.

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