5. V. A. Yakovlev, Kinetics of Enzyme Catalysis [in Russian], Moscow (1965), p. 113-125.
6. E. Bülbring, Br. J. Pharmacol., 1, 38-61 (1946).
7. A. W. Liley, J. Physiol. (London), 142, 650-666 (1956).
8. I. Litchfield and F. Wilcoxon, J. Phamacol. Exp. Ther., 96, 99-113 (1949).

QUANTITATIVE RELATIONSHIP BETWEEN ANTICONVULSANT ACTIVITY IN N-BENZHYDRYLAMIDES AND N-BENZHYDRYL-UREAS, THEIR STRUCTURES, AND ^{13}C NMR SPECTRA

V. D. Filimonov, A. A. Bakibaev, A. V. Pustovoitov, L. G. Tignibidina, A. G. Pechenkin, V. K. Gorshkova, and A. S. Saratikov

UDC 615.213.074

The benzhydryl group is found in numerous biologically active compounds [3, 4, 9]. In particular, N-benzhydrylurea is known to display quite high anticonvulsant activity [3, 4]. There have, however, been no literature reports on quantitative relationships between structure and activity in these compounds.

In order to establish quantitative relationships between anticonvulsant activity and the structures of compounds containing the common amide grouping $Ph_2CHNHCOR$, we have synthesized the N-benzhydrylamides (I-V) and N-benzhydrylureas (VI-XX), and measured their ^{13}C NMR chemical shifts and anticonvulsant activity as expressed by the anticorazole index.

$Ph_2CHNHCOR$ $RC_6H_4CH(Ph)NHCONH_2$

I—VI VII—XX

R=H (I), Me (II), Et (III), Pr (IV), *i*-Pr (V), NH_2 (VI). o-F (VII), m-F (VIII), p-F (IX), o-Cl (X), m-Cl (XI), p-Cl (XII), o-Br (XIII), m-Br (XIV), p-Br (XV), o-I (XVI), m-I (XVII), o-Me (XVIII), m-Me (XIX), p-Me (XX).

The synthesis of benzhydrylformamide (I) was effected by a modified Leuckart reaction from benzophenone and formic acid, using the more readily available urea in place of the more usual formamide [5]. Compounds (II-V) were obtained by acylating benzyhydrylamine with the appropriate acid chlorides. The N-benzhydrylureas were obtained by standard methods from the appropriate benzhydrylamines and urea [1]. The constants of the products (I-XX) are given in Tables 1 and 2.

The anticonvulsant activity of (I-VI) is shown in Table 1, from which it will be seen that the activity of the N-benzhydrylamides decreases with increasing length and branching of the alkyl radical R. A linear relationship is evident between the value of the exponent of the anticorazole index for compounds (I-V) and the Charton steric constant ν [6] [Fig. 1, equation (1)].

$$e^A = 13.01 - 14.28\,\nu;\ r = 0.980,\ S_0 = 0.24. \quad (1)$$

The introduction of other steric constants for the alkyl substituents (E_S, E_S^0 [6]) gives a somewhat less satisfactory correlation. N-benzhydrylurea (VI) is the most active compound in the series (I-VI). Although there is at present no strictly unified scale of steric constants for various types of functional groups, and it is not possible from the steric constants available to make comparisons between the amino-group and alkyl radicals, it is nevertheless clear that (VI) basically does not comply with the relationship (1), since the van der Waals or covalent radii of the NH_2 group are at the very least greater than those of hydrogen. The much higher than expected activity of the urea (VI) as compared with amides (I-V) suggests that there is no similarity between the mechanisms of anticonvulsant activity of the benzhydrylureas (VI-XX) and the amides (I-V).

Since the high activity of the benzhydrylurea (VI) suggests the possible practical value of this type of compound as an anticonvulsant drug, we have examined the influence of

S. M. Kirov Tomsk Polytechnic Institute, and the Research Institute for Pharmacology, Academy of Medical Sciences of the USSR, Tomsk. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 22, No. 5, pp. 540-545, May, 1988. Original article submitted December 2, 1986.

 0091-150X/88/2205-0358 $12.50

TABLE 1. N-Benzydrylamides

Compound	Yield, %	mp, °C	Calculated, %			Empirical formula	Found, %			ν	e^A	Threshold for corazole convulsions, mg/kg	
			C	H	N		C	H	N			$M \pm m$	anticorazole index
I	88	131—2	79,53	6,15	6,63	$C_{14}H_{13}NO$	79,73	6,17	6,21	0	13,20	284,1±52,6	2,58
II	69	144—5	79,91	6,66	6,22	$C_{15}H_{15}NO$	80,17	6,74	6,19	0,52	6,23	191,4±34,2	1,83
III	53	127—9	80,25	7,11	5,85	$C_{16}H_{17}NO$	80,21	7,20	5,52	0,56	3,60	136,3±25,9	1,28
IV	47	122—3	80,55	7,50	5,53	$C_{17}H_{19}NO$	80,36	7,69	5,98	0,68	3,16	123,9±17,1	1,15
V	45	143—4	80,55	7,50	5,53	$C_{17}H_{19}NO$	80,91	7,55	5,80	0,76	2,87	121,6±10,4	1,06

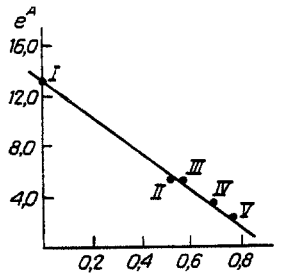

Fig. 1. Plot of the exponential of the anticorazole index for N-benzhydrylamines (I-VI) versus the steric constants for the substituent R; x-axis, ν; y-axis, e^A.

TABLE 2. N-Benzhydrylureas

Compound	Yield, %	mp, °C	Calculated, %			Empirical formula	Found, %		
			C	H	N		C	H	N
IV	78	143—4	74,33	6,19	12,38	$C_{14}H_{14}N_2O$	74,19	6,19	12,04
VII	64	153—4	68,85	5,32	11,47	$C_{14}H_{13}N_2OF$	68,52	5,44	11,21
VIII	67	136—7	68,85	5,32	11,47	$C_{14}H_{13}N_2OF$	68,43	5,51	11,62
IX	71	163—4	68,85	5,32	11,47	$C_{14}H_{13}N_2OF$	69,11	5,09	11,71
X	70	155—6	64,61	5,00	10,76	$C_{14}H_{13}N_2OCl$	64,91	5,15	10,85
XI	76	135—6	64,61	5,00	10,76	$C_{14}H_{13}N_2OCl$	64,38	5,12	10,81
XII	72	153—4	64,61	5,00	10,76	$C_{14}H_{13}N_2OCl$	64,52	5,07	10,49
XIII	62	165—6	55,79	4,47	9,53	$C_{14}H_{13}N_2OBr$	55,38	4,59	9,86
XIV	59	133—4	55,79	4,47	9,53	$C_{14}H_{13}N_2OBr$	55,49	4,78	9,57
XV	67	167—9	55,79	4,47	9,53	$C_{14}H_{13}N_2OBr$	55,52	4,29	9,21
XVI	57	184—5	44,72	3,58	7,95	$C_{14}H_{13}N_2OI$	47,98	3,72	8,17
XVII	55	165—6	44,72	3,58	7,95	$C_{14}H_{13}N_2OI$	44,69	3,67	7,75
XVIII	59	134—5	75,00	6,66	11,66	$C_{15}H_{16}N_2O$	74,68	6,60	11,86
XIX	70	99—100	75,00	6,66	11,66	$C_{15}H_{16}N_2O$	74,88	6,73	11,41
XX	63	160—2	75,00	6,66	11,66	$C_{15}H_{16}N_2O$	75,26	6,97	11,82

the substituents in the benzene ring in N-benzhydrylureas (VII-XX) on their anticonvulsant activity. The values of the anticorazole index for (VI-XX), together with the steric and electronic constants of the substituents R and the chemical shifts of the methine and carbonyl carbon atoms in the ^{13}C NMR spectra, are given in Table 3. The ^{13}C NMR chemical shifts for (XIX) and (XX) are not given in Table 3, since it was difficult to find a common solvent for all the benzhydrylureas.

Examination of the data presented in Table 3 leads to the following qualitative conclusions: 1) for all types of substituent R, the activity decreases in the sequence o > m > p (VI > VIII > IX, X ≳ XI > XII, XIII ≳ XIV > XV, XVI > XVII, XVIII > XIX > XX); and 2) in the halo-substituted benzhydrylureas, irrespective of the position of the substituent, the activity falls smoothly in the sequence F > Cl > Br > I compounds (VII > X > XIII > XVI, XII > XI > XIV > XVII, IX ≳ XII > XV).

Comparison of the activity of o-substituted ureas (VII), (X), (XIII), (XVI), and (XVIII) with the electronic and steric constants of the substituents shows a regular change in parameters A, ν, and δ_R^0 (Table 3). The best correlation is found between the values A (but not e^A, as in the benzhydrylamides) and the steric constants ν (Fig. 2). The greatest departure from the regression plot is shown by the o-methyl compound (XVIII); taking into account all five points on the regression plot the correlation coefficient is 0.901, whereas without (XVIII), this coefficient is considerably improved, and the relationship between the values of A and ν is given by the following equation:

$$A = 5.32 - 4.40\nu; \; r = 0.986, \; S_0 = 0.20. \qquad (2)$$

The correlation of anticonvulsant activity with the resonance constants (σ_R^0) and of halogen substituents (VII, X, XIII, XVI) is somewhat inferior than with the steric constants (r = 0.962), but the inclusion in this relationship of (XVIII) results in almost random changes in the values of parameters A and δ_R^0 (r = 0.647).

TABLE 3. Constants for N-Benzhydrylureas

Compound	δ_{CO}	δ_{CH}	δ_j	δ_R^0	ν	Corazole convulsion threshold, mg/kg	
						$M \pm m$	anticorazole index
VI	157,52	56,45	0,0	0,0	0,0	406,0±31,2	3,7
VII	159,83	51,08	0,52	—0,32	0,27	470,4±12,2	4,14
VIII	157,77	56,23				349,4±35,2	3,10
IX	157,44	55,86				249,0±2,2	2,50
X	157,44	53,91	0,37	—0,18	0,55	340,4±32,1	3,00
XI	157,52	56,08				326,4±26,8	2,90
XII	157,52	55,78				280,0±17,1	2,50
XIII	157,29	56,01	0,44	—0,16	0,65	246,0±46,2	2,22
XIV	157,52	56,23				247,6±42,0	2,20
XV	158,21	56,17				166,0±12,1	1,50
XVI	157,22	58,02	0,42	—0,14	0,78	227,5±4,9	2,00
XVII	157,52	56,08				197,7±25,6	1,60
XVIII	157,52	53,24	—0,08	—0,15	0,52	406,2±63,6	3,91
XIX						172,8±4,3	1,74
XX						121,6±1,4	1,07

Hence, in correlations with constants ν and δ_R^0 also, good and satisfactory linear relationships are obtained only for the series of o-halogenated ureas, but the benzhydrylurea (VI) and its o-methyl derivative (XVIII) depart considerably from the regression plot. In order to establish whether it is possible in principle to describe the anticonvulsant activity of o-substituted benzhydrylueas using a set of known electronic and steric constants for the substituents, or whether this is possible only with halo-substituted compounds, we carried out a multifactor evaluation, comparing the values of A with the constants δ_j, δ_R^0, and ν. It was found that the anticonvulsant activity of the benzhydrylureas VI, VII, X, XIII, XVI, and XVIII is well described by the multifactor regression equation (3):

$$A = 3.70 - 2.64\delta_j - 7.52\delta_R^0 - 2.16\nu; \quad R = 0.996, \; S_0 = 0.17. \tag{3}$$

It should be emphasized that only by a combination of the electronic (inductive and resonance) and steric effects of the substituents is it possible to arrive at a single correlational equation relating the activity of benzhydrylureas with substituents of different types (hydrogen, halogens, and methyl), so that it follows that equation (3) is of practical predictive value.

For p- and m-substituted benzhydrylureas, multifactor regression equations such as (3) show low values for the correlation coefficients (0.944 and 0.723 respectively), so that they are of little practical value.

Examination of the ^{13}C NMR chemical shifts (δ, ppm) of the methine and carbonyl carbon atoms in the benzhydrylureas (Table 3) shows that the greatest amount of screening is found in the o-substituted compounds (VII, X, XIII, XVI, and XVIII). In this series, the differences in the chemical shifts between the most and least screened atoms are $\Delta\delta_{CH} = 8.71$ and $\Delta\delta_{C=O} = 2.61$ ppm. The differences in the chemical shifts in the m- and p-substituted benzhydrylureas are smaller by approximately an order of magnitude, making it difficult to interpret them in a statistically reliable way.

The activities of the o-substituted compounds (VII, X, XIII, XVI, XVIII), and the benzhydrylurea (VI) vary directly with the changes in the chemical shifts in the ^{13}C NMR spectra, increased activity being accompanied by screening (Table 3). If the point for the benzhydrylurea (VI) is excluded from the A–δ_{CH} plot, a satisfactory correlation coefficient is obtained (r = 0.948), and the correlation equation for the o-substituted series (VII, X, XIII, XVIII) takes the following form:

$$A = 21.78 - 0.34\delta_{CH}; \; r = 0.948, \; S_0 = 0.35. \tag{4}$$

It is known that in diphenylmethanes a substituent in the o-position has a considerable screening effect on the methylene carbon in the ^{13}C NMR spectra as a result of steric effects [2] (the steric compression effect). Doubtless, the introduction into the diphenylmethane molecule of a carbamide group (like any other bulky group) should give rise to even greater steric strain than in diphenylmethanes. It is thus easy to understand the screening of the methine atom by the o-substituents F, Cl, Br, and CH_3 as compared with the benzhydrylurea (VI) (Table 3). The screening effect is, however, reduced as the volume of the substituent is increased, and with the largest substituent, iodine (XVI), the signal for the

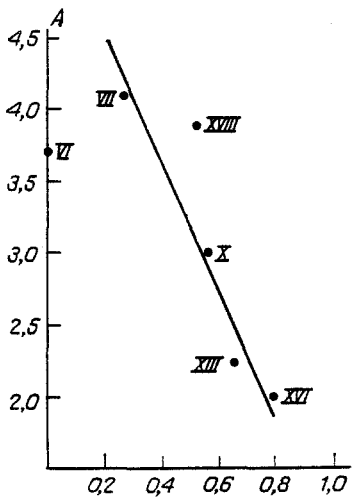

Fig. 2. Plot of anticorazole indices for o-substituted N-benzhydrylureas (VI, VII, X, XIII, XVI, and XVIII) versus the steric constants R for the substituents; x-axis, ν; y-axis, A.

methine carbon is shifted to an even lower field than in the case of the benzhydrylurea (VI). The most likely explanation for this apparent anomaly is as follows. The diphenylmethane system is conformationally labile, and an increase in the volume of the substituent in the o-position of the benzhydrylurea results in an increase in the angle of rotation of the substituted ring around the Ar—CH bond, resulting in progressive elimination of the steric compression effect and corresponding descreening of the methine carbon. Bearing in mind this interpretation and the relationship between the activity of benzhydrylureas and the extent of screening of the methine carbon [equation (4)], it must be accepted that activity in this group of compounds is related to the geometry of the diphenylmethane fragment, primarily to the value of the Ar—CH torsion angle, so that the most compact and at the same time most sterically strained structures (VI, VII, and XVIII) have the greatest anticonvulsant activity.

It is reasonable to suppose that apart from the steric effects of the o-substituents on activity, their electronic effects will also play a definite part, as shown by the correlation equation (3). However, the relatively small effects of m- and p-substituents both on the activity of the benzhydrylureas and on the spectral parameters (Table 3) show that the electronic effects of these substituents play a secondary part.

It is noteworthy that the changes in the ^{13}C NMR chemical shifts of the methine and carbonyl carbon atoms in the o-substituted compounds (VI, VII, X, XIII, XVI, and XVIII) are well described by multifactor equations (5) and (6), which incorporate both the electronic and steric constants of the parameters.

$$\delta_{CH} = 56.43 + 4.68\delta_j + 26.36\delta_R^0 + 2.03\nu;\ r = 0.985,\ S_0 = 0.22. \quad (5)$$

$$\delta_{C=O} = 157.51 - 0.12\delta_j + 9.76\delta_R^0 - 2.87\nu;\ r = 0.993,\ S_0 = 0.16. \quad (6)$$

The empirical relationships found for benzhydrylamides and benzhydrylureas (particularly o-substituted derivatives of the latter) enable an a priori evaluation to be carried out of the anticonvulsant activity of new derivatives from the electronic and steric constants of the substituents [equations (1) and (3)], and to use ^{13}C NMR spectroscopy of benzhydrylureas as an experimental method for the approximate assessment of anticonvulsant activity.

EXPERIMENTAL (CHEMISTRY)

^{13}C NMR spectra were obtained on a BS-567A spectrometer with an operating frequency of 25.14 mHz, in DMF solution with the addition of DMSO-d_6 with full spin decoupling from protons. The chemical shifts are given from TMS to an accuracy of ±0.05 ppm.

Benzhydrylformamide (I). A mixture of 0.01 mole of benzophenone, 0.08 mole of urea, and 0.08 mole of formic acid was heated to 120°C and kept at this temperature for 2 h, then the temperature was raised over 1 h to 185°C, and kept at this temperature for 3 h. The hot reaction mixture was poured into water, and the (I) which separated was filtered off, dried, and recrystallized from aqueous ethanol to give 88% of (I).

Benzhydrylamides (II-V). A mixture of benzhydrylamine, the appropriate acid chloride, and pyridine (2.5 mmole of each) in 30 ml of benzene was boiled for 1 h. The benzene was removed, and the residue washed with sodium bicarbonate solution and water. Recrystallization from aqueous ethanol gave (II-V) in yields of 45-69%.

Benzhydrylureas (VI-XX). A mixture of 0.01 mole of the appropriate benzhydrylamine, 0.06 mole of urea, and 50 ml of water acidified with 5 ml of conc. HCl was heated to 140-145°C, kept for 3 h, cooled, and the solid filtered off and dried. Recrystallization from aqueous ethanol (1:1, 2:1) gave (VI-XX) in yields of 55-78%.

EXPERIMENTAL (PHARMACOLOGY)

The pharmacological studies were carried out using mongrel white mice of both sexes weighing 18-25 g. The test compounds were administered internally as suspensions in 1% starch mucilage, 1.5-2 h before treatment with the convulsant agent corazole, to animals both in the control and test groups. The control animals received starch mucilage in an amount corresponding to their mass (0.1 ml per 10 g body weight). A 1% solution of corazole was given intravenously via the caudal vein at a rate of 0.02 ml every 10 sec, until tonic extensions of the rear extremities were observed [8]. Anticonvulsant activity was assessed by calculating the convulsion threshold (CT) in the control and test groups using the indirect difference method [7], and by the anticorazole index of the compound (CT_{exp}/CT_{cont}). The results were evaluated statistically, and are shown in Tables 1 and 3.

LITERATURE CITED

1. T. P. Vishnyakova, I. A. Golubeva, and E. V. Glebova, Usp. Khim., 54, No. 3, 429-449 (1985).
2. G. Levy and G. Nelson, Carbon-13 Nuclear Magnetic Resonance for Organic Chemists, Wiley, New York (1972).
3. A. G. Pechenkin, V. K. Gorshkova, and L. G. Tignibidina, Khim.-farm. Zh., No. 6, 63-65 (1974).
4. A. G. Pechenkin, L. G. Tignibidina, V. K. Gorshkova, and L. A. Tikhonova, ibid., No. 5, 57-59 (1979).
5. G. R. Clemo et al., J. Chem. Soc., 1958-1960 (1939).
6. O. Exner, in: Correlation Analysis in Chemistry: Recent Advances, (N. B. Chapman and J. Shorter (eds.), Plenum, New York (1978), p. 541.
7. M. J. Orloff, J. L. Williams, and C. C. Pfeiffer, Proc. Soc. Exp. Biol., N. Y., 70, 254-257 (1949).
8. E. A. Swinyard, W. C. Brown, and L. S. Goodman, J. Pharmacol. Exp. Theor., 32, 513-540 (1952).
9. V. Zotta, M. Popescu, and A. Serper, Farmacia (Buc.), 11, 449-464 (1963).