SYNTHESIS AND ANTICONVULSANT ACTIVITY OF BENZHYDRYLAMINES

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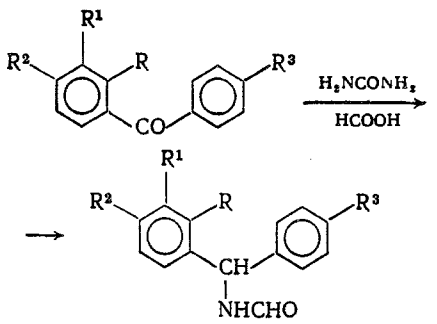
The benzhydryl group forms part of many biologically active compounds, which include benzhydrylamines with high anticonvulsant activity [7-9]. We have established [9] a quantitative relationship between the structures of benzhydrylureas and their anticonvulsant activity and ^{13}C NMR spectra. A limited amount of information on the anticonvulsant activity of benzhydrylamides is available in the literature [4, 6].

In order to compare the effects of substituents of the same type in the benzhydryl group in benzhydrylureas (reported in [9]) and benzhydrylformamides on pharmacological activity (compounds I-XVI) and also to study the anticonvulsant effects of various pharmacophoric amide groups in the benzhydryl moiety, we have synthesized and measured the anticonvulsant activity of compounds (I-XLVII).

The benzhydrylformamides (I-XVI) were obtained by a modified Leuckart reaction from the benzophenones in formic acid, using the more readily accessible urea in place of the formamide usually employed [2]:



I—XVI

R = H (I—XI, XIII), CH_3 (XII), Cl (XIV, XVI), OH (XV); R^1 = H (I—III, V, VI, X, XI, XIV), OH (IV), CH_3 (VII, XII), Cl (VIII, XIII, XV), NO_2 (IX, XVI); R^2 = H (I, VII—IX, XII, XV, XVI), CH_3 (II, X), CH_3O (III), OH (IV), F (V), Br (VI), Cl (XI, XIII, XIV); R^3 = H (I—IX, XII—XVI), CH_3 (X), Cl (XI).

Benzhydrylamine hydrochloride (XVII) was obtained by hydrolysis of benzhydrylformamide with hydrochloric acid, the free base (XVIII) being obtained by treatment of the hydrochloride with 20% NaOH solution.

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TABLE 1. Chemical Characteristics and Anticonvulsant Activity of N-Benzhydrylformamides

Compound	mp, °C	Yield, %	IR spectrum ν, cm⁻¹		¹H NMR spectrum, δ, ppm			Anticonvulsant activity				
								maximum electroshock			corazole convulsion threshold, mg/kg (M ± m)	ACI
			C=O	N—H	CH	NH	—C(=O)H	% prev. convulsion	% of animals surviving	ED_{50}, mg/kg		
I	132—133	94	1665	3212	6,43	8,44	9,34	100	100	160	284,1±52,6	2,5
II	91—92	81	1660	3225	6,36	8,37	9,26	50	0	—	133,9±8,3	1,2
III	92—93	69	1658	3240	6,37	8,40	9,27	83,3	0	—	137,3±42,1	1,3
IV	121—122	70	1670	3260	6,33	8,39	9,19	50	50	645	122,8±14,4	1,1
V	102—103	87	1648	3225	6,45	8,45	9,34	66,7	50	190	211,1±27,9	1,6
VI	126—127	86	1645	3210	6,43	8,44	9,36	33,3	50	210	205,5±26,9	1,8
VII	74—75	79	1650	3262	6,40	8,42	9,30	16,7	16,7	250	123,2±17,0	1,1
VIII	88—89	92	1660	3215	6,45	8,44	9,39	66,7	100	110	144,5±18,6	1,3
IX	102—104	74	1662	3315	6,61	8,47	9,52	83,3	50	180	188,8±12,3	1,4
X	113—114	83	1656	3290	6,34	8,40	9,23	33,3	0	375	138,3±14,2	1,2
XI	125—126	88	1652	3305	6,46	8,44	9,36	100	16,7	160	248,0±30,3	2,0
XII	106—107	59	1662	3286	6,55	8,39	9,19	50	0	—	118,8±17,9	1,1
XIII	74—75	89	1664	3304	6,47	8,44	9,38	50	16,7	270	151,9±18,6	1,4
XIV	144—145	74	1670	3310	6,86	8,39	9,36	50	0	—	145,6±9,8	1,2
XV	202—204	48	1654	3270	6,32	8,62	8,97	83,3	50	190	145,5±8,0	1,2
XVI	103—105	53	1646	3290	6,77	8,65	9,68	66,7	16,7	325	169,9±22,5	1,5

Note. The elemental analyses for compounds (I-XVI) were in agreement with the calculated values. Here and in Tables 2 and 3, with maximum electroshock effect obtained from an internal dose of 200 mg/kg; ACI is the anticorazole index.

TABLE 2. Chemical Characteristics and Anticonvulsant Activity of Benzhydrylamides $Ph_2CHNHC(O)R$

Compound	mp., °C	Yield, %	Empirical formula	Anticonvulsant activity				
				maximum electroshock			corazole convulsion threshold, mg/kg(M ± m)	ACI
				% prevention of convulsion	% of animals surviving	ED_{50}, mg/kg		
XIX	144—145	69	$C_{15}H_{15}NO$	83,3	83,3	96	191,4±34,2	1,8
XX	127—129	53	$C_{16}H_{17}NO$	50,0	66,7	200	136,3±25,9	1,3
XXI	122—123	47	$C_{17}H_{19}NO$	33,3	50,0	—	123,9±17,1	1,2
XXII	143—144	45	$C_{17}H_{19}NO$	50,0	66,7	180	121,6±10,4	1,2
XXIII	115—117	50	$C_{18}H_{21}NO$	0	83,3	—	104,3±5,1	1,0
XXIV	138—140	37	$C_{18}H_{21}NO$	16,7	33,3	—	77,4±9,4	0,7
XXV	105—107	39	$C_{19}H_{23}NO$	0	66,7	—	119,9±26,2	1,1
XXVI	104—105	45	$C_{20}H_{25}NO$	0	66,7	—	134,7±6,6	1,3
XXVII	244—246	48	$C_{24}H_{27}NO$	83,3	100	145	126,7±9,9	1,1
XXVIII	173—174	59	$C_{20}H_{17}NO$	0	66,7	—	113,4±8,4	1,0
XXIX	201—202	55	$C_{22}H_{21}NO_3$	16,7	16,7	335	116,9±18,2	1,0
XXX	202—203	57	$C_{23}H_{23}NO_4$	50,0	83,3	200	140,6±10,8	1,2
XXXI	156—158	33	$C_{20}H_{16}FNO$	33,3	50,0	—	125,9±15,9	1,1
XXXII	165—166	50	$C_{20}H_{16}FNO$	33,3	100	250	93,0±10,5	0,8
XXXIII	215—217	46	$C_{20}H_{16}FNO$	50,0	50,0	170	119,9±11,6	1,0
XXXIV	161—162	44	$C_{20}H_{16}ClNO$	16,7	50,0	—	135,6±4,9	1,4
XXXV	153—154	45	$C_{20}H_{16}ClNO$	16,7	33,3	—	128,4±12,5	1,1
XXXVI	215—216	42	$C_{20}H_{16}ClNO$	33,3	66,7	290	145,4±12,5	1,2
XXXVII	191—192	49	$C_{20}H_{16}NOI$	0	33,3	—	99,7±10,6	1,0
XXXVIII	166—168	48	$C_{20}H_{16}NOI$	0	50,0	—	102,6±13,0	1,0
XXXIX	201—203	39	$C_{20}H_{16}N_2O_3$	0	16,7	—	123,3±10,0	1,2
XL	170—172	32	$C_{20}H_{16}N_2O_3$	0	83,3	—	143,4±14,3	1,4
XLI	218—219	40	$C_{20}H_{16}N_2O_3$	0	0	—	143,3±4,4	1,4
XLII	154—156	44	$C_{18}H_{15}NO_2$	0	16,7	—	111,1±43,7	1,0
XLIII	103—105	32	$C_{19}H_{16}N_2O$	66,7	66,7	175	157,9±29,5	1,4
XLIV	180—181	41	$C_{19}H_{16}N_2O$	100	83,3	80	131,4±10,8	1,2
XLV	213—214	39	$C_{19}H_{16}N_2O$	50,0	83,3	170	119,1±16,4	1,0
Chloracon	—	—	—	50,0	83,3	240	132,4±11,4	1,3

Note. The IR spectra of the benzhydrylamides (XIX-XLV) showed strong absorption for stretching vibrations of the carbonyl (1640-1690 cm^{-1}) and NH= (3170-3400 cm^{-1}) groups.

TABLE 3. Chemical Characteristics and Anticonvulsant Activity of Benzhydrylamine and Its Derivatives

Compound	Yield, %	mp., °C	Empirical formula	Anticonvulsant activity			
				maximum electroshock		corazole convulsion threshold, mg/kg (M ± m)	ACI
				% prevention of convulsions	ED_{50}, mg/kg		
XVIII	90	bp 178° at 23 mm Hg	$C_{13}H_{13}N$	66,7	72	219,7±17,5	2,5
XVII	74	274—275	$C_{13}H_{14}ClN$	100	72	193,8±7,3	1,7
XLVI	78	167—168	$C_{14}H_{13}NO$	100	100	286,2±63,6	2,8
XLVII	69	169—170	$C_{15}H_{15}N_3O_2$	33,3	305	202,2±29,1	1,9
Diphenine sodium	—	—	—	100	12,2	243,5±54,8	2,3

Acylation of benzhydrylamine (XVIII) with the appropriate acid chlorides gave the benzhydrylamides [9]:

$Ph_2CHNHC(O)R$

XIX—XLV

where R = CH_3 (XIX), C_2H_5 (XX), C_3H_7 (XXI), i-C_3H_7 (XXII), C_4H_9 (XXIII), i-C_4H_9 (XXIV) C_5H_{11} (XXV), C_6H_{13} (XXVI), 1-adamantyl (XXVII), C_6H_5 (XXVIII), 3,4-$(CH_3O)_2C_6H_3$ (XXIX) 3,4,5-$(CH_3O)_3C_6H_2$ (XXX), 2-FC_6H_4 (XXXI), 3-FC_6H_4 (XXXII), 4-FC_6H_4 (XXXIII), 2-ClC_6H_4 (XXXIV), 3-ClC_6H_4 (XXXV), 4-ClC_6H_4 (XXXVI), 2-IC_6H_4 (XXXVII), 3-IC_6H_4 (XXXVIII), 2-$NO_2C_6H_4$ (XXXIX), 3-$NO_2C_6H_4$ (XL), 4-$NO_2C_6H_4$ (XLI), 2-furyl (XLII), 2-pyridyl (XLIII), 3-pyridyl (XLIV), 4-pyridyl (XLV).

Compounds $Ph_2CHCONH_2$ (XLVI) and $Ph_2CHNHCONHCONH_2$ (XLVII) were synthesized in the usual way [3] from diphenylacetic acid and benzhydrylurea respectively.

The chemical properties of the products together with data on their anticonvulsant activity in the maximum electroshock test and corazole "titration" are given in Tables 1-3.

Examination of the biological activity of the benzhydrylformamides (I-XVI, see Table 1) showed them to possess varying degrees of anticonvulsant activity. High activity was shown by the benzhdrylformamides (V, VI, VIII, IX, XI, XVI), which contain electron-acceptor substituents (F, Br, Cl, NO_2), but they were all less active than the unsubstituted benzhydrylformamide (I). The benzhydrylformamides (II-IV, VII, X, XII), which contain electron-donor substituents, were less active. Comparison of the anticonvulsant activity of the benzhydrylformamides (I-XVI) with that of the similarly-substituted benzhydrylureas [7-9] failed to reveal any general correlations, suggesting that the mechanisms of their anticonvulsant activity are different. In these series of compounds, having the benzhydryl group in common, preference is given to the carbamoyl pharmacophoric group rather than the formamide group, since the benzhydrylureas were more active as anticonvulsants [7-9].

The benzhydrylamides (XIX-XLV) included compounds which showed high anticonvulsant activity, and those which failed to show any anticonvulsant effects. To judge from the results shown in Table 2, the anticonvulsant activity of the benzhydrylamides (I, XIX-XXVI) decreases as the length and degree of branching of the alkyl radicals R is increased. A linear relationship has been found between the anticorazole indices of the amides (I, XIX-XXVI) and the Charton steric constants ν [10] of the appropriate alkyl groups (equation (1), see Fig. 1).

$$A = 2.56 - 2.00\nu;\ r = 0.954,\ S_0 = 0.17. \quad (1)$$

The range of benzhydrylamides examined here considerably extends the data previously available [9], and shows unambiguously that there is a linear relationship between the steric characteristics of the acylamides (I, XIX-XXVI) and their anticorazole index, rather than an exponential one.

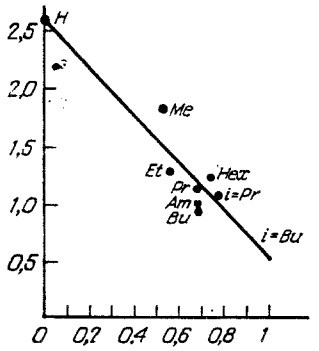

Fig. 1. Plot of the biological activity of benzhydrylamides against the steric constants of the substituent R. The horizontal axis shows the steric constant ν for the substituent (arb. units), and the vertical axis the biological activity A in terms of the anticorazole index (arb. units).

The clear structural relationships found for the acylamides (I, XIX-XXVI) are not apparent with the benzhydrylbenzamides (XXVIII-XLI) or the benzhydrylhetarylacylamides (XLII-XLV). These series of compounds include compounds with very low (XXVIII, XXXVII-XXXIX, XLII) or quite high anticonvulsant properties. No clear relationships have been found in these series between activity and the electronic or steric properties of the aromatic or heterocyclic substituents in the amide group. Some partial qualitative generalizations may however be discerned. For instance, the anticonvulsant activity in terms of the anticorazole index for the pyridyl compounds (XLIII-XLV) varies directly with the inductive constants of the pyridyl substituents [11]; for (XLIII) $\sigma_j = 0.11$, for (XLIV) $\sigma_j = 0.22$, and for (XLV) $\sigma_j = 0.25$. However, the amide with a 2-furyl substituent (XLII) ($\sigma_j = 0.15$) [11] has anticonvulsant activity which is anomalously low for the above series. In the series of fluoro- and chlorobenzhydrylbenzamides (XXXI-XXXVI), anticonvulsant activity varies undirectionally depending on the position of the substituent: para > ortho > meta. The two iodoamides (XXXVII and XXXVIII), however, have very similar, low activity. In general, for the compounds (XXVIII-XLV) it may be concluded that acylation of benzhydrylamine (XVIII) with aromatic and heterocyclic acids reduces anticonvulsant activity to a greater extent than does acylation with aliphatic and cycloaliphatic acids (XIX-XXVII).

It may also be noted that assessment of anticonvulsant properties by the corazole convulsion threshold reveals the effects of smaller changes in the structures of the test compounds than when the maximum electroshock test is used. It is also noteworthy that using the latter test, most of the compounds examined (XIX-XLV), especially the amides (XIX, XXVII-XLIV), had substantially greater ED_{50} values than Chloracon (β-chloropropionamide) (Table 2), which is used clinically.

Examination of the results presented in Table 1-3 shows that the greatest anticonvulsant activity is found in benzhydryl derivatives with a primary amino-group (XVII, XVIII, XLVI, XLVII). this group of compounds includes benzhydrylurea [7-9]. Benzhydrylamine (XVIII) and its hydrochloride (XVII) exhibit high anticonvulsant activity in both of the tests used (Table 3). Diphenylacetamide (XLVI) raises the corazole convulsion threshold to a greater extent than Diphenine. Extension of benzhydrylurea by a carbamoyl group (XLVII) reduces its anticonvulsant activity in the corazole test as compared with benzhydrylurea itself by a factor of nearly 2 [9], although the high anticonvulsant activity of the biuret (XLVII) is maintained.

To summarize these studies, it may be concluded that the large number of results obtained (for compounds I-XLVII), in conjunction with previously-obtained information [7-9], provide the basis for a more rational search for anticonvulsant drugs in nitrogen-containing benzhydryl compounds, and the identification of novel relationships in these series of organic compounds.

EXPERIMENTAL (CHEMISTRY)

^1H NMR spectra were obtained on a BS-497 spectrometer (100 MHz, internal standard HMDSO), and IR spectra on a UR-20 instrument (in vaseline grease). The purities of the products were established by TLC on Silufol UV-254 plates, eluent benzene—ethanol (8:2), visualization in UV light.

N-Benzhydrylformamides (I-XVI) (general method). In a one-necked flask fitted with combined reflux and distillation condensers were placed 0.01 mole of the ketone, 0.08 mole of urea, and 20-30 ml of 99.7% formic acid. The mixture was heated to 120°C (in a bath), kept at this temperature for 2 h, then the temperature of the bath was raised to 180°C over one hour, and this temperature maintained for 5-6 h. The mixture was then cooled, poured into water with stirring, and the resulting granular solid filtered off, washed with warm water, and recrystallized from aqueous ethanol (water—ethanol, 3:4) to give the products (I-XVI) in yields of 53-94%.

Benzhydrylamides (XIX-XLV). A mixture of benzhydrylamine (XVIII), the appropriate acid chloride, and pyridine (2.5 mmole of each) in 30 ml of benzene was boiled for one hour. The benzene was then distilled off, and the residue washed with aqueous sodium bicarbonate and water. Compounds (XX-XXIII) and (XXXVIII) were recrystallized from aqueous propan-2-ol, (XIX) and (XXIV-XXVI) from aqueous ethanol, (XXVIIII), (XXXI), (XXXII), (XXXIV), and (XLI-XLV) from ethanol, (XXXIII) from benzene, and (XXXVIII) from toluene. The benzhydrylamides (XIX-XLV) were obtained in 32-69% yields.

EXPERIMENTAL (PHARMACOLOGY)

The pharmacological studies were carried out with mongrel white mice of both sexes, weighing 18-25 g. The test compounds were administered internally as suspensions, prepared in 1% starch mucilage 1.5-2 h before treatment with the convulsant agents. Anticonvulsant activity was assessed on convulsions induced by a supramaximum current (maximum electroshock method), by prevention of the phase of tonic extension of the rear limbs [13], and by corazole "titration" [12], from the increase in the convulsion threshold as compared with the controls, using the indirect difference method of calculation [5]. The Litchfield and Wilcoxon probit analysis method was used to calculate the 50% effective doses (ED_{50}) in the maximum electroshock test [1].

LITERATURE CITED

1. M. L. Belen'kii, Fundamentals of the Quantitative Measurement of Pharmacological Activity [in Russian], 2nd edition, Leningrad (1963), pp. 81-117.
2. B. M. Bogoslovskii, Reactions and Methods of Study of Organic Compounds [in Russian], Moscow (1954), Vol. 3, p. 253.
3. K. Weygand and G. Hilgetag, Experimental Methods in Organic Chemistry [Russian translation from the German], Moscow (1969).
4. N. K. Kochetkov and N. V. Dubykina, Zh. Obshch. Khim., 27, No. 5, 1399-1402 (1957).
5. E. V. Montsevichyute-Eringene, Pat. Fiziol., No. 4, 71-78 (1964).
6. P. A. Petyunin and M. S. Khodyreva, All-Russian Conference of Pharmacists, No. 1. Proceedings [in Russian], Moscow (1964), pp. 310-314.
7. A. G. Pechenkin, L. G. Tignibidina, V. K. Gorshkova, et al., Khim.-farm. Zh., No. 6, 63-65 (1974).
8. A. G. Pechenkin, L. G. Tignibidina, V. K. Gorshkova, et al., ibid., No. 5, 57-59 (1979).
9. V. D. Filimonov, A. A. Bakibaev, A. V. Pustovoitov, et al., ibid., No. 5, 540-545 (1988).
10. O. Exner, Correlation Analysis in Chemistry: Recent Advances (L. B. Champan and J. Shorter, eds.), New York (1978), pp. 929-937.
11. R. Knorr, Tetrahedron, 37, No. 3, 929-937 (1981).
12. M. J. Orloff, H. L. Williams, and C. C. Pfeiffer, Proc. Soc. Exp. Biol. (N.Y.), 70, 254-257 (1949).
13. E. A. Swineyard, W. C. Brown, and L. S. Goodman, J. Pharmacol. Exp. Ther., 106, No. 3, 319-330 (1952).