1,4-BENZODIAZEPINES AND THEIR CYCLIC HOMOLOGS AND ANALOGS

XII.* INFLUENCE OF EFFECTS OF ELECTRONIC DISPLACEMENTS ON THE PROPERTIES OF DERIVATIVES OF 1,2-DIHYDRO-3H-1,4-BENZODIAZEPINE

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The physicochemical and pharmacological properties of compounds of eight series of derivatives of 1,2-dihydro-3H-1,4-benzodiazepine have been considered. A marked relationship between the half-neutralization potentials, half-wave potentials of polarographic reduction, and the dipole moments of the compounds with Hammett's σ constants of the substituents in position 7 has been found. In all the series studied, a tendency is observed to an increase in the physiological activity of the compounds with an increase in the electron-accepting nature of the substituents in position 7.

1,2-Dihydro-3H-1,4-benzodiazepines are the most interesting derivatives of benzodiazepine from the practical point of view in view of the wide use of some of them in medicine as minor tranquilizers [2, 3]. In investigations that we performed previously [4-7] it was established that in a series of 1,2-dihydro-3H-1,4-benzodiazepin-2-ones (A), the nature of the substituent in position 7 has a fundamental importance in the determination of the antispasmodic activity: a tendency was observed for the appearance of a correlation between the activity of compounds of series A and the values of the Hammett σ constants of these substituents. Although too much significance must not be attached to such correlations, it was of interest to determine the range of this law or, more correctly, tendency. In view of this, we performed the present investigation, setting ourselves the aim of determining the role of the effects of electronic displacements in the cyclic system of 1,4-benzodiazepine on the appearance of the pharmacological activity of these substances.

With this aim, in homologous series of eight different types of 1,4-benzodiazepine derivatives (A-H) we have compared, on the one hand, the tabular values of the Hammett σ constants of the substituents in position 7 of the ring and the experimental values of a number of magnitudes characterizing the effects of electronic displacements (dipole moments, half-neutralization potentials, half-wave potentials of polarographic reduction) with, on the other hand, the indices for individual types of psychopharmacological activity.

*For Communication XI, see [1].

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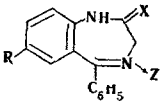
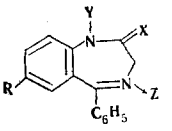
TABLE 1. Basicities of Some 1,2-Dihydro-3H-1,4-benzodiazepin-2-ones and the Corresponding Thiones

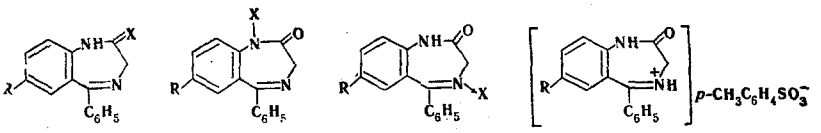


Compound	R	X	$E_{1/2}$, mV	$\Delta E_{1/2}$, mV	pK_{BH^+}
I	CH_3	O	−117	−364	3,95
II	H	O	−130	−377	3,73
III	Cl	O	−173	−420	3,00
IV	Br	O	−175	−422	2,97
V	NO_2	O	−215	−462	2,29
VI	CH_3	S	−140	−387	3,56
VII	H	S	−153	−400	3,34
VIII	Cl	S	−195	−442	2,63
IX	Br	S	−190	−437	2,72

TABLE 2. Dipole Moments of Compounds of Series A, B, and F



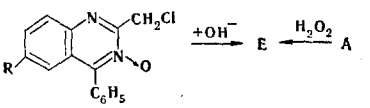
Compound	R	Z	X	α	μ, D
I	CH_3	—	O	41,45	5,44
II	H	—	O	42,02	5,50
III	Cl	—	O	31,68	4,78
IV	Br	—	O	26,22	4,36
V	NO_2	—	O	12,31	3,30
VI	CH_3	—	S	53,14	6,35
VII	H	—	S	45,05	5,85
VIII	Cl	—	S	38,20	5,36
IX	Br	—	S	32,21	4,95
XXII	CH_3	O	O	59,12	6,70
XXIII	H	O	O	31,89	4,91
XXIV	Cl	O	O	28,18	4,62
XXV	Br	O	O	38,69	5,40



A, B C–E F, H G

A X=O; B X=S; C X=CH_3; D X=CH_3CO; E X=  F X=O; H X=SiF_4

The synthesis and properties of the substances of series A-D, H have been described previously [5, 7]. The compounds of series E were obtained by the reaction of the sodium salts of the lactams A with 2-(β-bromoethyl)-4-methyl-1,3-dioxane in DMFA [8]. The 4-oxides F were synthesized by known methods employing the action of alkali on 2-halogenomethyl-4-phenylquinazoline 3-oxides [9] or by the oxidation of substances A with hydrogen peroxide [10]. The tosylates of the substances of series A – compounds G – were formed quantitatively when solutions of substances of series A in benzene (or toluene) were boiled with p-toluenesulfonic acid previously carefully dehydrated by the azeotropic distillation of water.



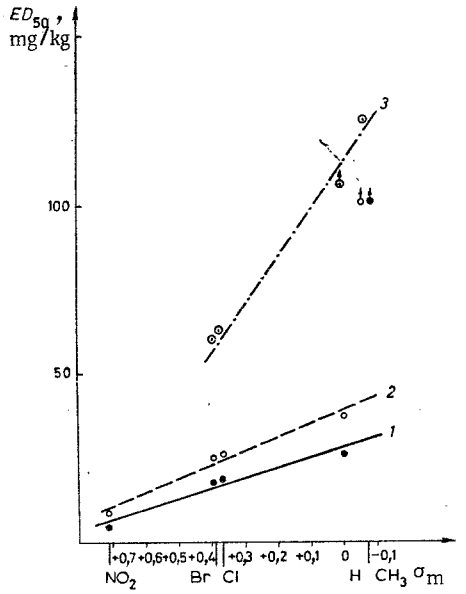


Fig. 1

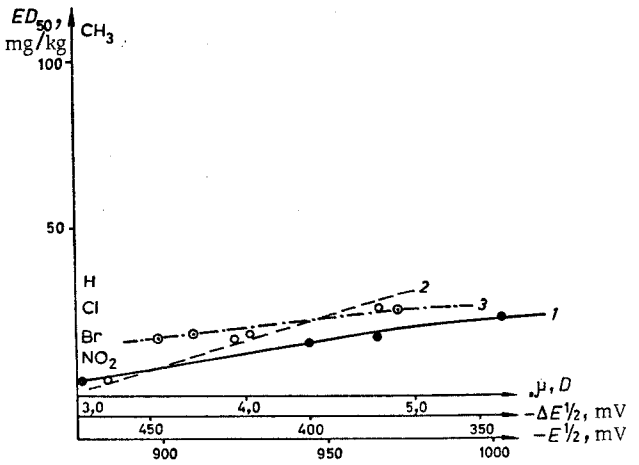


Fig. 2

Fig. 1. Comparison of the effective doses in the test of antagonism to the spasmodic action of a maximum electric shock for the compounds of series A (1), G (2), and F (3) with the Hammett σ_m constants of the substituents R.

Fig. 2. Comparison of the effective doses in the test for antagonism to the spasmodic action of a maximum electric shock with the dipole moments (1), the relative half-neutralization potentials (2), and the half-wave potentials of polarographic reduction (3) of the compounds of series A.

TABLE 3. Half-Wave Potentials of the Polarographic Reduction of the Compounds of Series E

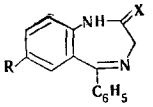
Compound	R	$-E_{1/2}$, mV
XIX	CH_3	1,12
XX	Cl	1,05
XXI	Br	1,06

A comparison of the basicities of the individual compounds in series A-C shows that an increase in basicity is observed with a decrease in the electron-accepting nature of the substituent R. Since in the titration of the compounds of series A with acid the nitrogen atom in position 4 is protonated, this fact agrees well with the observed law describing the connection between the nature of the substituent R and the ease of polarographic reduction of individual compounds of the series [7]. Consequently, both the basicity and the ease of polarographic reduction obviously depend on the electron density in the region of the C=N bond. The half-neutralization potentials of the substances of series A and B are given in Table 1.

In series A, B, and F we determined the values of the dipole moments (DMs) on the basis of the corresponding values of the dielectric permeabilities by means of Higashi's formula [11]. In all these series, a regular decrease in the values of the DMs is observed with an increase in the electron-accepting properties of the substituent R (Table 2), which can be explained from the point of view of general ideas on the influence of donor and acceptor substituents. In actual fact, electron-accepting substituents, by drawing off electrons from the heterocyclic ring of the condensed system, lead to a more uniform distribution of the electron density over the whole system. Electron-donating substituents, conversely, increase the electron density in the region of the azomethine and carbonyl groups. These displacements of the electron density can be traced fairly clearly by spectral methods [4], by polarography [7], and also by determining pK_{BH^+} values [12].

We may also note that in the polarographic reduction of the substances of series E an increase in the half-wave potential of polarographic reduction of approximately 100 mV is observed in comparison with the substances of series A (see Table 3). This fact can be explained by the electron-donating influence of the β-(1,3-dioxanyl)ethyl residue in the cyclic system, and also the shielding of the azomethine group by the voluminous substituent on the N_1 atom of the ring, which is well observed in Stuart–Briegleb models.

TABLE 4. Pharmacological Properties of Some Derivatives of 1,2-Dihydro-3H-1,4-benzodiazepine



Compound	R	X	Y	Z	Potentiation of hexenal sleep, ED_{50}, mg/kg	Antagonism to spasmodic action of a max. electric shock, ED_{50}, mg/kg	Disturbance of orienting reactions, ED_{50}, mg/kg	Disturbance of motor coordination, ED_{50}, mg/kg	Antagonism to corazole, ED_{50}, mg/kg
I	CH_3	O	H	—	40,0 (29,6—54,0)	>100	26,0 (16,7—40,5)	60—20%	16,0 (8,0—32,0)
II	H	O	H	—	1,55 (0,86—2,8)	26,0 (15,3—44,2)	8,0 (5,5—11,8)	20—20%	0,42 (0,16—1,05)
III	Cl	O	H	—	0,9 (0,57—1,41)	18,0 (17,0—19,1)	3.7 (2,46—5,5)	14,0 (9,6—20,3)	0,35 (0,23—0,53)
IV	Br	O	H	—	0,1 (0,06—0,15)	17,0 (11,7—24,6)	4,5 (3,9—5,0)	4,6 (3,2—6,7)	0,11 (0,05—0,29)
V	NO_2	O	H	—	0,09 (0,06—0,12)	4,5 (1,8—11,2)	1,5 (1,15—1,95)	2,5 (1,56—4,0)	0,27 (0,15—0,48)
VI	CH_3	S	H	—	25,0 (18,9—33,0)	>100	>200	>200	15,0 (11,2—15,3)
VIII	Cl	S	H	—	10,0 (6,7—15,0)	100—33%	100—33%	100—16%	30,0 (23,4—37,2)
IX	Br	S	H	—	5,2 (3,9—6,9)	60—33%	21,0 (15,9—27,7)	16,0 (10,0—25,6)	2,0 (1,65—2,38)
XIII	Cl	O	CH_3	—	0,66 (0,53—0,8)	3,5 (1,75—7,0)	2,8 (2,3—3,2)	2,75 (1,37—5,5)	0,51 (0,39—0,67)
XIV	Br	O	CH_3	—	0,42 (0,28—0,63)	13,5 (8,4—21,6)	42,0 (22,1—79,8)	2,4 (1,4—4,1)	0,03 (0,014—0,063)
XV	CH_3	O	$COCH_3$	—	39,0 (30,0—50,7)	200—16%	200—16%	200—33%	—
XVI	H	O	$COCH_3$	—	31,5 (18,4—53,5)	100—16%	100—16%	100—33%	—
XVII	Cl	O	$COCH_3$	—	7,8 (6,14—9,91)	100—33%	150 (100,0—225,0)	>200	0,64 (0,4—1,02)
XIX	CH_3	O	$CH_2CH_2C_5H_9O_2$*	—	31,0 (12,9—74,4)	200—10%	105,0 (84,0—131,0)	>100	>80
XX	Cl	O	$CH_2CH_2C_5H_9O_2$*	—	5,4 (4,0—7,2)	105,0 (77,3—143,6)	27,0 (23,2—31,3)	56,0 (46,6—67,2)	2,6 (2,2—3,04)
XXI	Br	O	$CH_2CH_2C_5H_9O_2$*	—	5,0 (3,1—8,3)	—	16,0 (12,1—21,1)	12,5 (8,93—17,5)	1,75 (1,32—1,98)
XXII	CH_3	O	H	O	10,5 (8,4—13,1)	125,0 (107,7—145,0)	290,0 (184,0—322,0)	320,0 (232,0—441,0)	>40
XXIII	H	O	H	O	15,0 (6,0—37,2)	>100	>400	>400	>20
XXIV	Cl	O	H	O	1,2 (1,16—1,24)	62,0 (42,8—89,9)	>60	5,4 (3,9—7,6)	4,8 (3,2—7,2)
XXV	Br	O	H	O	1,3 (0,65—2,6)	60,0 (46,1—78,0)	31,0 (23,9—40,3)	2,1 (1,4—3,0)	7,8 (6,0—10,1)
XXVII	CH_3	O	H	p-$CH_3C_6H_4SO_3H$	>40	>100	38,1 (24,6—57,1)	>80	20,0 (15,2—24,8)
XXVIII	Cl	O	H	p-$CH_3C_6H_4SO_3H$	2.5 (1,58—4,2)	37,0 (24,6—55,1)	15,0 (11,6—19,5)	—	2.3 (1,64—4,31)
XXIX	Br	O	H	p-$CH_3C_6H_4SO_3H$	1,7 (1,17—2,46)	25,5 (22,2—29,4)	10,5 (4,9—16,8)	>20	1,5 (1,13—2,1)
XXX	H	O	H	p-$CH_3C_6H_4SO_3H$	1,5 (0,8—2,7)	24,0 (18,1—28,2)	8,2 (3,6—16,4)	8,0 (5,5—11,6)	1.55 (1,1—1,8)
XXXI	NO_2	O	H	p-$CH_3C_6H_4SO_3H$	0,5 (3,2—6,7)	8,1 (3,6—16,8)	2,1 (1,51—2,68)	5	1,1 (0,5—2,4)
XXXII	CH_3	O	H	SiF_4	18,5 (10,2—33,4)	100—20%	31,0 (26,8—35,6)	46,0 (39,3—53,8)	21,0 (15,4—28,5)
XXXIII	Cl	O	H	SiF_4	0,96 (0,66—1,39)	16,0 (12,2—20,1)	6,2 (4,7—8,2)	9,4 (6,6—13,3)	0,3 (0,21—0,38)
XXXIV	NO_2	O	H	SiF_4	0,6 (0,41—0,87)	58,0 (50,9—66,1)	5,2 (2,4—10,9)	5,0 (3,2—7,7)	0,33 (0,25—0,43)

*$C_5H_9O_2$ is 4-methyl-1,3-dioxan-2-yl.

TABLE 5. Tosylates of the 1,2-Dihydro-3H-1,4-benzodiazepin-2-ones G

Compound	R	mp, °C	Empirical formula	Found, %		Calc., %		Yield, %
				N	S	N	S	
XXVIII	H	240—241	$C_{22}H_{20}N_2O_4S$	7,0	7,7	6,9	7,8	99
XXVII	CH_3	233—235	$C_{23}H_{22}N_2O_4S$	6,7	7,5	6,6	7,6	98
XXIX	Cl	280—281	$C_{22}H_{19}ClN_2O_4S$	6,5	7,3	6,3	7,2	99
XXX	Br	268—269	$C_{22}H_{19}BrN_2O_4S$	5,8	6,4	5,7	6,6	98
XXXI	NO_2	250—251	$C_{22}H_{19}N_3O_6S$	6,3	7,0	6,2	7,0	95

The study of the pharmacological activity of the compounds of series A-H was performed in experiments on mice (weight 18-22 g) making use of the procedure generally employed for evaluationg substances with a similar type of action [13]: a test with the subcutaneous administration of corazole to evaluate the anticorazole action; the maximum-electric-shock test to evaluate the antispasmodic activity; the "rotating rod" method for characterizing disturbances of motor coordination; the "grid-climbing" method for evaluating disturbances in orientation reactions; and the test of the potentiation of the soporific action of hexenal for judging the hypnosedative effect. The activity of the compounds studied was expressed in terms of the doses in which the substance caused an effect in 50% of the animals (ED_{50}) (Table 4).

A comparison of the activities of the compounds of series A-H by means of the maximum-electric-shock test, the depression of orienting reactions, the potentiation of hexenal sleep, and the disturbances of motor coordination with their structures showed a definite tendency to an increase in the activity of the preparations with the introduction of electron-accepting substituents (NO_2 > Br > Cl) into position 7 and to a lowering of activity when the hydrogen atom in position 7 was replaced by the electron-donating substituent CH_3. It is characteristic that this tendency appears in all the series of 1,4-benzodiazepine derivatives that have been studied.

It is extremely interesting that this qualitative pattern is found in agreement with quantitative correlations. In actual fact, Fig. 1 shows the relationship between the values of ED found experimentally and tabular values of the Hammett σ_m constants. A gradual decrease in the activity of the preparations is observed with a decrease in the positive values of the constant from +0.71 to 0.0 and a further decrease down to the negative value of −0.07. The relationship found has a stable nature throughout series A-H and is consequently retained for all compounds including substituents in position 1. A similar relationship is observed on comparing the Hammett constants with the values of ED for the tests of the disturbance of orienting reactions, the disturbance of motor coordination, and of the potentiation of hexenal sleep. In the case of antagonism to corazole, this relationship is less pronounced and no clear correlations exist. The latter confirms the hypothesis put forward previously [13] of two possible mechanisms of the action of minor tranquilizers.

The substantial role of the magnitude of the electron density on the azomethine nitrogen atom as a nucleophilic center for the appearance of psychopharmacological activity is shown by the similar correlations of the ED values (Fig. 2) with the experimentally found values of the DM, the half-neutralization potentials, and the half-wave potentials of polarographic reduction. Naturally, all these magnitudes correlate satisfactorily with the Hammett σ constants. The approach to this type of correlation with ED values must be extremely circumspect. However, the information discussed is interesting, since it relates to eight groups of compounds and shows a definite tendency in the characteristics of the influence of the structure of substances of types A-H on their psychopharmacological activity.

EXPERIMENTAL

The polarographic reduction of substances (XIX-XXI) was performed with the aid of a PÉ-312 polarograph in the cell described elsewhere [15] with a dropping mercury electrode using a saturated calomel electrode as the reference electrode. The characteristics of the capillary were τ 2.45 sec, m 2.1 mg/sec. The concentration of depolarizer was $(3\text{-}5) \cdot 10^{-5}$ M.

The dielectric constants of solutions of substances (I-IX, XXII-XXV) in 1,4-dioxane were determined in a "Tangens" dielcometer.

The half-neutralization potentials were determined with the aid of an LPM-60M pH meter at a temperature of 25°C. The measuring electrode was an ÉSL-411-05 and the comparison electrode a silver chlo-

ride electrode with a saturated solution of KCl. The error in the determination of the half-neutralization potentials was 2-5 mV.

7-Chloro-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one Tosylate. A mixture of 0.2 g (0.0012 mole) of p-toluenesulfonic acid and 25 ml of benzene was boiled with a Dean-Stark trap until the evolution of water ceased. Then a solution of 0.2 g (0.7 mmoles) of 7-chloro-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one in 10 ml of benzene was added and the mixture was boiled for 3 h. After this, the benzene was poured off from the colorless crystalline precipitate, and the latter was washed with absolute benzene (3 × 10 ml) to eliminate the excess of p-toluenesulfonic acid. Yield 0.32 g (99%); mp 280-281°C.

Substances (XXVII, XXVIII, XXX, and XXXI) were obtained similarly (Table 5).

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