SYNTHESIS OF 2,4,4,6-TETRASUBSTITUTED 2,3-DIHYDRO-4H-1,3-BENZOTHIAZINES AND STUDY OF THEIR PSYCHOTROPIC ACTIVITY

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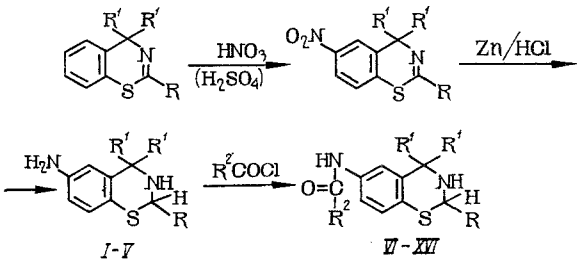
Some derivatives of 4H-1,3-benzothiazines, including 2,4,4-trisubstituted derivatives [1] possess psychotropic activity [1-3]. In order to trace the change in the pharmacological action as a function of the nature of the substituents in the 2,4,4 positions and on the introduction of an amino or alkylamino group into position 6, we have synthesized the 6-amino-2,4,4-trialkyl-2,3-dihydro-4H-1,3-benzothiazines (I-V) and the 6-acylamino-2,4,4-trialkyl derivatives (VI-XVI) (Table 1).



I-V VI-XVI

R = R^1 = CH_3; II R = CH_3, R^1 = C_2H_5; III R = C_4H_9, R^1 = CH_3; IV R = iso-C_4H_9, R^1 = CH_3; V R = C_4H_9, R^1 = C_2H_5; VI R = R^1 = R^2 = CH_3; VII R = C_4H_9, R^1 = R^2 = CH_3; VIII R^1 = C_2H_5, R = R^2 = CH_3; IX R = R^1 = CH_3, R^2 = C_6H_5; X R = C_4H_9, R^1 = CH^3, R^2 = C_6H_5; XI R = iso-C_4H_9, R^1 = CH_3, R^2 = C_6H_5; XII R = CH_3, R^1 = C_2H_5, R_2 = C_6H_5; XIII R = C_4H_9, R^1 = C_2H_5, R^2 = C_6H_5; XIV R = R^1 = CH_3, R^2 = OC_2H_5; XV R = iso-C_4H_9, R^1 = CH_3, R^2 = OC_2H_5; XVI R = CH_3, R^1 = C_2H_5, R^2 = OC_2H_5.

The nitration of 2,4,4-trialkyl-4H-1,3-benzo[1,4]thiazines with nitric acid in sulfuric acid gave the corresponding 6-nitrobenzothiazines which, without special purification, were reduced with zinc and hydrochloric acid to the dihydrobenzothiazines (I-V), the amines (II) and (V) being isolated and identified in the form of the dihydrochlorides and (III) and (IV) being used for further syntheses without isolation in the individual state. The structure of the amino derivatives (I, II, and V) was confirmed by IR and PMR spectroscopy. Thus, the IR spectrum of the dihydrochloride (II) lacked the $\nu_{C=N}$ vibrations in the 1645-1660 cm^{-1} range that are observed in the 4H-1,3-benzothiazine system [4] and contain broad bands in the 2580 and 3350 cm^{-1} region (ν_{+NH_2} and ν_{+NH_3}) [5]. PMR spectrum (in trifluoroacetic acid) of the amine (II), ppm*: 1.2 (6H, two with similar values of the chemical shifts; two 4-C$-CH_3$ groups), 2.1 (d, J = 7 Hz, 2-CH_3), 2.4 (4H, two q with similar values of the chemical shifts, the two 4-CH_2 groups), 5.1 (1H, unresolved m, 2-H), 7.3 and 8.3 (5H, broad s signals, $^+NH_2$ and $^+NH_3$), 7.6 (2H, 7-H and 8-H with almost the same values of the chemical shifts), 7.73 (1H, broadened s, 5H); on the addition of heavy water, the 2-H signal became a quadruplet with ^3J = 7 Hz.

The action of acetic anhydride on the amines (I-III) led to the acetamido derivatives (VI-VIII). The IR spectrum (tablets with potassium bromide) of, for example, the amide (VII) is characterized by intense absorption bands at, cm^{-1}; 3460 (ν_{NH} of an amide group), 1684 (amide (I)), 1513 (amide (II)). The PMR spectrum

*Abbreviations adopted: s) singlet; d) doublet; t) triplet; q) quadruplet; m) multiplet.

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TABLE 1. 2,4,4,6-Tetrasubstituted 2,3-Dihydro-4H-1,3-benzothiazines

Compound	Yield, %	mp, °C	Found, %			Molecular formula	Calculated, %		
			Cl	N	S		Cl	N	S
I	68	115—6*	—	13,40	15,39	$C_{11}H_{16}N_2S$	—	13,45	15,53
II·2HCl	71	218—20 (decomp.)	22,85	9,13	10,35	$C_{13}H_{20}N_2S \cdot 2HCl$	22,93	9,06	10,36
V·2HCl	77	198—200 (decomp.)	20,08	8,24	9,10	$C_{16}H_{26}N_2S \cdot 2HCl$	10,18	7,98	9,12
VI	68	209—9†	—	11,14	12,41	$C_{13}H_{18}N_2OS$	—	11,19	12,80
VI·HCl	—	270—1 (decomp.)	12,02	9,46	11,44	$C_{13}H_{18}N_2OS \cdot HCl$	12,37	9,76	11,21
VII	76	160—1‡	—	9,57	11,04	$C_{16}H_{24}N_2OS$	—	9,58	10,97
VII·HCl	—	243,5—4,0 (decomp.)	10,75	8,75	9,81	$C_{16}H_{25}N_2OS \cdot HCl$	10,77	8,52	9,75
VIII	85	138,5—40,0‡	—	10,03	11,65	$C_{15}H_{22}N_2O$	—	10,07	11,52
IX	98	199,0—200,5‡	—	8,84	10,13	$C_{18}H_{20}N_2OS$	—	8,97	10,26
X	50	168—9‡	—	7,70	9,16	$C_{21}H_{26}N_2OS$	—	7,91	9,04
X·HCl	—	274—5 (decomp.)	9,11	7,10	8,23	$C_{21}H_{26}N_2OS \cdot HCl$	9,07	7,17	8,20
XI	75	155—6‡	—	8,00	9,09	$C_{21}H_{26}N_2OS$	—	7,91	9,04
XI·HCl	—	212—4 (decomp.)	9,10	7,05	8,19	$C_{21}H_{26}N_2OS \cdot HCl$	9,07	7,17	8,20
XII	82	141,0—2,5‡	—	8,12	9,27	$C_{20}H_{24}N_2OS$	—	8,23	9,42
XII·HCl	—	246—7 (decomp.)	9,43	7,33	8,71	$C_{20}H_{24}N_2OS \cdot HCl$	9,40	7,43	8,50
XIII	68	108—9*	—	7,17	8,32	$C_{23}H_{30}N_2OS$	—	7,33	8,39
XIV	68	111,5—3,0‡	—	9,99	11,42	$C_{14}H_{20}N_2O_2S$	—	10,00	11,43
XIV·HCl	—	228—30 (decomp.)	11,29	9,04	10,08	$C_{14}H_{20}N_2O_2S \cdot HCl$	11,21	8,85	10,12
XV	81	113—4*	—	8,68	9,69	$C_{17}H_{26}N_2O_2S$	—	8,69	9,94
XV·HCl	—	246—7 (decomp.)	9,89	7,80	8,94	$C_{17}H_{26}N_2O_2S \cdot HCl$	9,87	7,80	8,93
XVI	78	97—8*	—	8,95	10,70	$C_{16}H_{24}N_2O_2S$	—	9,09	10,40
XVI·HCl	—	197—9 (decomp.)	10,28	8,24	9,28	$C_{16}H_{24}N_2O_2S \cdot HCl$	10,28	8,13	9,29

*From heptane.
†From acetone.
‡From benzene.

(in deuterochloroform) of the amide (VII), ppm: 0.9 (3H, distorted t, CH_2 in C_4H_9), 1.35 and 1.5 (two s, two 4-CH_3 groups; the signals overlap with the group of signals of the 2-CH_3 and 3-H protons), 2.12 (2H, s, $COCH_3$), 4.7 (1H, unresolved signal of 2-H), 7.1 (1H, d, J = 9 Hz, 8-H), 7.42 (1H, q, J_1 = 9 Hz, J_2 = 2 Hz, 7-H), 7.81 (1H, d, J = 2 Hz) 5-H), 8.32 (1H, broadened s, NHCO). Reaction of the amines (I-V) with benzoyl chloride led to the formation of the benzamido derivatives (IX-XIII). The IR spectra (tablets with potassium bromide) of the secondary amides are characterized by, in addition to bands in the 3280-3450 cm^{-1} region (ν_{NH}), strong absorption at 1637-1650 cm^{-1} (amide I), 1518-1530 cm^{-1} (amide II), and 3300-3320 cm^{-1} (ν_{NH} of an amide). The ethoxycarbonylamino derivatives (XIV-XVI) were obtained by the reaction of the amines (I, II, and IV) with ethyl chloroformate. The IR spectrum (tablet with potassium bromide) of the substituted urethane (XIV) showed absorption bands with the frequencies (cm^{-1}): 3280 (amide NH), 1730 (amide I), and 1532 (amide II).

The assignment of the amide II vibrations in the compounds studied was confirmed by the deuteration of samples in chloroform solution (0.1 M) in the case of the amides (VIII, XII, and XVI): In addition to the complete or partial disappearance of the narrow bands at 3435 cm^{-1} (free NH groups in amides) and the broad bands at 3300 cm^{-1} (bound NH groups in amides; the ν_{NH} vibrations of the aliphatic part of such dihydrobenzothiazines are of low intensity and are observed with difficulty), the amide II bands (1510, 1510, and 1513 cm^{-1}, respectively) disappeared or were greatly weakened. Acylation in the aromatic, and not the heterocyclic, amino group was also confirmed by the PMR spectrum of the free amide (VII): In $CDCl_3$ solution at 4.7 ppm the signal from C-H appears in the form of an unresolved multiplet which, after the addition of CD_3OD and the replacement of 3-H by 3-D is converted into a triplet signal with J = 5.2 Hz. By means of deuteration it is also possible to identify the signal from the NHCO group at 8.5 ppm. Such selective acylation is explained by steric hindrance to the amino group of the heterocyclic moiety of the dihydrobenzothiazines.

The study of the pharmacological activities of the compounds synthesized was performed on mice by the methods used for the primary evaluation of drugs with an antidepressive, neuroleptic, and tranquilizing action. The greatest interest is presented by the substances (V-VII, X-XII, XIV, and XVI) (Table 2). The effect of some of the compounds investigated has individual features of similarity with the tricyclic antidepressants (capacity for potentiating picrotoxin spasms and phenocoll stereotypy). However, the activity of the compounds investigated is inferior to that of the well-known antidepressants.

EXPERIMENTAL

Chemical

The IR spectra were taken on DS-301 and IR-10 instruments, and the PMR spectra on a Varian T-60 instrument (δ scale). The molecular weights of the bases (VI-XIV) and (XVI) were determined mass-spectro-

metrically on a Varian MAT-112 with the direct introduction of the sample into the ion source at an ionizing voltage of 80 V, and they corresponded to the calculated figures.

Dihydrochloride of 6-Amino-4,4-diethyl-2-methyl-2,3-dihydro-4H-1,3-benzothiazine (II). With cooling, 6 ml of nitric acid (sp. gr. 1.5) was added in portions to a solution of 10.6 g of 4,4-diethyl-2-methyl-4H-1,3-benzothiazine [1] in 100 ml of concentrated sulfuric acid, and the reaction mixture was left for 48 h and was then poured onto ice and the resulting solution was made alkaline with caustic soda and was extracted with benzene. The benzene solution was washed with water and distilled to give 11.7 g of unpurified 4,4-diethyl-2-methyl-6-nitro-4H-1,3-benzothiazine. A solution of 6.6 g of this compound in 40 ml of ethanol was heated to 60-70°C and 15 g of zinc and 40 ml of hydrochloric acid were added in small portions over 12 h, the temperature of the mixture being maintained at 70-80°C. After cooling, it was poured into a saturated solution of potassium carbonate (about 200 ml) and the product was extracted with toluene. The toluene solution was partially evaporated and the dihydrochloride of (II) was precipitated by the addition of an ethereal solution of hydrogen chloride; yield 5.5 g.

The amino derivatives (I) and (V) (see Table 1) were obtained similarly.

6-Acetylamino-2,4,4-trimethyl-2,3-dihydro-4H-1,3-benzothiazine (VI). A solution of 2.4 g of the amine (I) in 20 ml of chloroform was treated with 1.22 g of acetic anhydrate and 1.21 g of triethylamine, the mixture was boiled for 3 h, cooled, diluted with chloroform and washed with water, the chloroform was distilled off, and the residue was crystallized from acetone to give 2.1 g of the amide (VI). To obtain the hydrochloride, an ethereal solution of hydrogen chloride was added to a solution of (VI) in a mixture of benzene and ethanol.

The amides (VII) and (VIII) were obtained similarly (see Table 1).

6-Benzolyamino-4,4-diethyl-2-methyl-2,3-dihydro-4H-1,3-benzothiazine (XII). A solution of 2.16 g of the amine (II) in 25 ml of absolute toluene was treated with 0.9 g of benzoyl chloride and 4 ml of triethylamine and the mixture was kept at 20°C for 3 days, diluted with water, and extracted with toluene and chloroform. The solvents were distilled off, and crystallization from benzene yielded 1.95 g of the amide (XII). To obtain the hydrochloride, the base (XII) was dissolved in ethanol and an ethereal solution of hydrogen chloride was added.

The amides (IX-XI and XIII) were obtained similarly (see Table 1).

6-Ethoxycarbonylamino-4,4-diethyl-2-methyl-2,3-dihydro-4H-1,3-benzothiazine (XVI). At 5-7°C, 2.5 g of ethyl chloroformate and an aqueous solution of sodium bicarbonate, maintaining the pH at 7.0-8.0, were added in portions to a solution of 2.7 g of the amine (II) in 30 ml of ethanol. The reaction mixture was kept at 20°C for 1 h, diluted with water, and extracted with benzene, the benzene was distilled off, and the residue was crystallized from heptane to give 2.1 g of the urethane (XVI). The hydrochloride of (XVI) was obtained in ether by the action of an ethereal solution of hydrogen chloride.

The substituted urethanes (XIV) and (XV) were obtained similarly (see Table 1).

Dihydrochloride of 6-Amino-4,4-diethyl-2-methyl-4H-1,3-benzothiazine (XVII). The Raney nickel (2 g) was added to a solution of 2 g of unpurified 4,4-diethyl-2-methyl-6-nitro-4H-1,3-benzothiazine in 30 ml of methanol and hydrogenation was carried out under the usual conditions until the absorption hydrogen ceased. The catalyst was filtered off, the methanol was distilled off and the residue, consisting of the base (XVII), was purified by passage through a layer of alumina [activity grade IV; benzene–chloroform (1:1]. The dihydrochloride of (XVII) was obtained in dibutyl ether by the addition of an ethereal solution of hydrogen chloride, with a yield of 1.4 g (60%), mp 263-265°C (from aqueous ethanol). Found, %: Cl 22.80; N 8.92; S 10.60. $C_{13}H_{18}N_2S \cdot 2HCl$. Calculated, %: Cl 23.08; N 9.12; S 10.43. IR spectrum of the dihydrochloride (in oil), cm^{-1}: 1590 (benzene ring), broad band at 1610-1630 ($\nu_{C=N}$ and $\delta_{+}NH_3$), 1800-3300 (series of broad bands, ν_{+NH} and ν_{+NH_3}. The IR spectrum (carbon tetrachloride) of the base (XVII) has bands at 1624 and 1648 cm^{-1} (δ_{NH_2} and $\nu_{C=N}$) and 3395 and 3480 cm^{-1} (νNH_2). The PMR spectrum of the dihydrochloride of (XVII) of trifluoroacetic acid has no signals other than those of the protons of the 4-CH_3CH_2 group (t, δ 0.9 ppm, and q, 2.3 ppm, J = 7 Hz), of the 2-CH_3 group (s, δ 3 ppm) and of three aromatic protons at 7.7-8.3 ppm.

Pharmacological

The sedative action of the substances was investigated in respect to their influence on the orienting reactions (climbing up netting from an illuminated compartment of a chamber into a dark one). The coordination of the movements on a rotating rod was determined. To investigate the neuroleptic properties we studied the capacity of the substances for causing catalepsy and for preventing the development of phenocoll stereotypy.

TABLE 2. Pharmacological Properties of the 1,3-Benzothiazine Derivatives (ED_{50}, in mg/kg, and confidence interval)

Compound	Suppression of orienting reactions	Potentiation of picrotoxin atoms	Potentiation of phenocoll stereotypy†	Tremor effect
V·2HCl	*	24,0 (16,0—36,0)%	50,0 — 50%	100,0 — 33%
VI·HCl	*	18,0 (10,6÷30,6)%	50,0 — 40%	*
VII·HCl	62,0 (53,0—72,6)	10,0 — 50%†	50,0 — 25%	*
X·HCl	29,0 (23,2—36,3)	20,0 — 50%†	30,0 — 25%	*
XI·HCl	35,5 (28,1÷44,7)	20,0 — 42%†	40,0 — 38%	*
XII·HCl	81,0 (69,8—93,9)	30,0 — 50%†	50,0 — 38%	*
XIV·HCl	75,0 (65,2—86,3)	—	—	*
XVI·HCl	89,0 (77,0—102,4)	—	—	*
XVII·2HCl	*	5,6 (3,5—8,8)%	10,0 — 50%†	33,5 (29,6÷37,9)

*Effect absent.

† The doses causing the maximum effect are given; a further increase in the dose is accompanied by a reduction in the effect.

We also determined the capacity of the substances for potentiating phenocoll stereotypy and picrotoxin spasms. The analgesic properties were evaluated from the reduction in the pain reaction of the animal on applying a clamp closed with a force of 0.5 kg to its tail. To investigate their tranquilizing effect we studied the capacity of the compounds for preventing the spasms caused by the subcutaneous injection of pentylenetetrazole. The substances were administered intraperitoneally in suspensions of Tween-80, 30-40 min before the recording of activity. The effective doses were calculated by the method of Litchfield and Wilcoxon [6].

Compounds (VII, X-XII, and XVI) cause a disturbance of the orienting reactions with suppression of the action of climbing up netting (see Table 2), which may indicate the presence of a sedative effect on the animals. In doses causing a pronounced sedative effect, the compounds investigated exhibited no cataleptogenic action and did not interfere with the coordination of the movements of the animals on a rotating rod.

The majority of the substances potentiated picrotoxin spasms (see Table 2) and almost all the compounds studied possessed the capacity for potentiating phenocoll stereotypy. However, the potentiation had no great breadth: When the doses were increased the effect did not reach 100% but was replaced by antagonism. Not one of the compounds investigated was capable of preventing pentylenetetrazole spasms. Compound (V) caused tremors in the animals which is possibly due to the presence of the amino group in position 6. The 6-amino-4,4-diethyl-2-methyl-4H-1,3-benzothiazine (XVII) synthesized for comparison possessed a still more pronounced capacity for causing tremor.

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