INVESTIGATION OF HETEROCYCLIC SYSTEMS BASED ON BENZIMIDAZOLE.

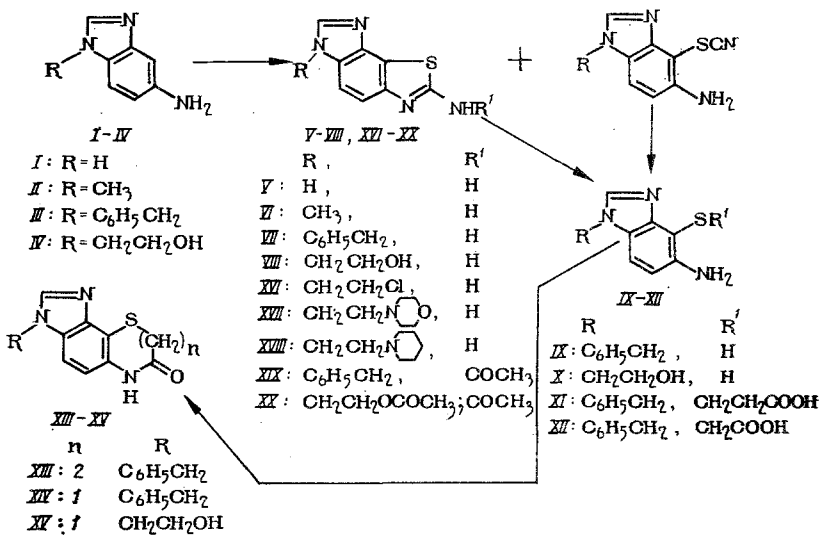
1. SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF DERIVATIVES OF 2-AMINOIMIDAZO[4,5-g]BENZTHIAZOLES AND SOME OF THEIR TRANSFORMATION PRODUCTS

E. A. Kuznetsova, N. T. Pryanishnikova,
L. I. Gaidukova, I. V. Fedina, and S. V. Zhuravlev*

UDC 615.31:547.789.6].012.1+615.31:547.789.6].015.4

The synthesis and properties of certain derivatives of benzthiazole [1] and benzimidazole [2] have been described by us previously. A series of substituted imidazo[4,5-g]benzthiazoles has been synthesized by a literature method [3] in the present work with the aim of studying pharmacologically certain nitrogen and sulfur containing heterocyclic systems.

Substances (V-VIII) were obtained by the rhodanation of amines (I-IV). The structures depicted below were assigned on the basis of the study [3], where the synthesis was achieved in the opposite way, and in which rhodanation of 1,2-dimethyl-5-aminobenzimidazole took place at the 4 position of the benzimidazole ring.



Fission of the aminothiazoles (V-VIII) to o-aminothiophenols of the benzimidazole series was carried out with potassium hydroxide in ethylene glycol. The same compounds were isolated on reduction of the corresponding aminorhodanides with aqueous sodium sulfide. The amino mercaptans (IX, X) are readily oxidized in air and it was not possible to isolate

*Deceased.

Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 9, No. 12, pp. 11-15, December, 1975. Original article submitted February 3, 1975.

TABLE 1. 6-Substituted 2-Amino-6H-imidazo[4,5-g]benzthiazoles

Compound	Yield (%)	Melting point (in degrees) *	Found (%)			Empirical formula	Calculated (%)		
			N	S	Cl		N	S	Cl
V	43,6	236—7	26,98	15,37	—	$C_8H_6N_4S \cdot H_2O$	26,92	15,38	—
V·2HCl	—	300	20,50	11,78	25,25	$C_8H_6N_4S \cdot H_2O \cdot 2HCl$	19,95	11,40	25,23
VI	40	300—1	26,62	15,92	—	$C_9H_8N_4S$	26,45	15,68	—
VII	34	248—9	19,86	11,48	—	$C_{15}H_{12}N_4S$	20,00	11,42	—
VII·2HCl	—	262—4	15,78	9,26	19,34	$C_{15}H_{12}N_4S \cdot 2HCl$	15,85	9,17	20,07
VIII	54	277—8	23,74	14,40	—	$C_{10}H_{10}N_4OS$	23,93	13,68	—
VIII·2HCl	—	258(decomp).	18,55	10,96	22,88	$C_{10}H_{10}N_4OS \cdot 2HCl$	18,24	10,96	23,13
XVI	84	238—40	21,83	12,75	14,15	$C_{10}H_9ClN_4S$	22,17	12,66	14,05
XVII	76	285—7	23,18	10,39	—	$C_{14}H_{17}N_5OS$	23,10	10,58	—
XVII·2,5HCl †	—	240—3 (decomp.)	18,05	8,44	21,73	$C_{14}H_{17}N_5OS \cdot 2,5HCl$	17,80	7,12	22,50
XVIII	57	278—80	43,28	11,21	—	$C_{15}H_{19}N_5S$	23,24	10,68	—
XVIII·3HCl	—	238—41	16,81	7,64	25,66	$C_{15}H_{19}N_5S \cdot 3HCl$	17,05	7,71	25,88
XIX	100	261—3	17,45	10,10	—	$C_{17}H_{14}N_4OS$	17,40	9,95	—
XX	100	255—6	17,93	10,15	—	$C_{14}H_{14}N_4O_3S$	17,62	10,05	—

*Compounds (V, VI, and VIII) crystallized from water and (V) was purified via the dihydrochloride by passing it through a column of IRA-400 (Cl^- form); (VII) from isopropyl alcohol; (VIII) dihydrochloride and compounds (XVI-XX) from alcohol; the dihydrochloride of (V) and (VII), the salt (XVII) and the trihydrochloride of (XVIII) from aqueous alcohol.

†Formed on mixing (XVII) with concentrated hydrochloric acid in alcohol.

them in a pure state. The amino mercaptans obtained were then reacted with chloroacetic and β-chloropropionic acids giving products of substitution at the mercapto group. The resulting amino acids (XI, XII) were readily cyclized in polyphosphoric acid into previously undescribed condensed systems namely 2H,7H-imidazo[4,5-h][1,4]benzthiazin-3-ones(4H) (XIV, XV) and 2,3-dihydro-8H-imidazo[4,5-i][1,5]benzthiazepin-4-one (5H) (XIII). IR spectra confirmed the proposed structures.

Aminoalkyl derivatives (XVI-XVIII) and mono and diacetyl compounds (XIX,XX) were also synthesized for pharmacological study. These compounds were tested in form of water soluble mono-, di-, and trihydrochlorides. Overall action, toxicity, and neurotropic activity were studied. Experiments were carried out on 20-22-g white mice and on rabbits. Doses were used in pharmacological tests corresponding to 1/6 LD_{50} for mice. The investigation of neurotropic activity was carried out according to the following tests: prolongation of the narcotic effect of thiopental sodium (30 mg/kg), potentiation of the narcotic effect of a subthreshold dose of sodium thiopental (12.5 mg/kg), spontaneous motor activity (with the use of the actometer described by K. S. Raevskii and V. A. Timofeev, 1964 [4]), antagonism with amphetamine on the amphetamine (10 mg/kg) hyperactive mouse model, analgesic action by the hot plate method, muscle weakening action by the rotation rod method, and anesthetic action by the method of Rene. The dependence was investigated of the pharmacological action of substances on the size and nature of the heterocycle, substituents at the nitrogen atom of the imidazole ring, at the sulfur atom, and in the side chain of the mercapto derivatives of benzimidazole.

A majority of the synthesized compounds possessed neurotropic activity. The least active, which was relatively more toxic compared with other substances of this series, was the benzthiazole (V) (LD_{50} 310 mg/kg). On substituting a hydrogen atom by a hydroxyethyl group (compound VIII) the toxicity of the compound was reduced and its depressing action was more clearly displayed on motor activity as was the influence in potentiating the effect of thiopental. Introduction of amines into the side chain (morpholine in compound XVII and piperidine in compound XVIII) led to a further reduction in toxicity (LD_{50} 500 and > 800 mg/kg, respectively) and an increase of the neurotropic activity. Thus the benzthiazole (XVIII) caused a nine-fold reduction in motor activity and an 18-fold reduction in amphetamine hyperactivity, the preparation also displayed muscle weakening action. In this way XVIII in all tests showed a depressing influence on the central nervous system. On substituting a piperidine radical for morpholine, compound (XVII) was obtained which was less effective than (XVIII) in its influence on motor activity and amphetamine hyperactivity and in addition showed a clear action on the prolongation of thiopental sleep in mice, reducing it two fold. Introduction of acetyl groups into the hydroxy and amino groups (compound XX) led to a sharp reduction of toxicity: LD_{50} > 1000 mg/kg. At the same time the preparation, more clearly than (VIII), depressed spontaneous motor activity. Substitution of a hydrogen atom by a benzyl residue gave compound (VII) which caused a three-and-one-half-fold prolongation of thiopental sleep and was less toxic than the unsubstituted compound (V). Change of the anionic portion of the molecule i.e. changing from a dihydrochloride to an oxalate, led to an increase of about two fold in the toxicity of the compound and a reduction of the pharmacological activity in all tests; moreover the effect on the prolongation of the narcotic action of hexenal, so marked in (VII), disappeared. The presence of an acetyl group (compound XIX) caused a significant drop in the neurotropic action of a substance. The influence of the size of the ring on the display of pharmacological properties was noted in the pharmacological investigation of the new condensed systems. The compound with a 1,5-thiazepine ring (XIII) did not differ in its spectrum of pharmacological activity from substances with a thiazole ring. On going from a thiazole to a 1,4-thiazine ring the investigated compounds displayed a stimulating influence on the central nervous system. Thus 7-benzyl-2H-7H-imidazo[4,5-h][1,4]benzthiazin-3-one (4H) (XIV) increased motor activity sixfold and amphetamine hyperactivity one-and-one-half-fold, i.e., it showed a stimulating effect on the central nervous system. Substitution of benzyl for the hydroxyethyl radical (compound XV) caused a twofold reduction of toxicity, activity was reduced at the same time although the effect on the prolongation of thiopental sleep was preserved: Sleep in mice was extended threefold. The studied compounds did not show analgesic or anesthetic activity.

Thus the results of the pharmacological investigations, which have been carried out, showed that a majority of the synthesized compounds possessed neurotropic activity of a depressing type, and some displayed a stimulating effect on the central nervous system. The synthesis of similar heterocyclic systems may be of definite interest in a search plan for new substances with neurotropic activity.

EXPERIMENTAL METHOD

IR spectra were taken on a UR-10 instrument.

5-Aminobenzimidazole (I) was obtained by reduction of 5-nitrobenzimidazole [5] with hydrazine hydrate in the presence of Raney nickel and was used in subsequent reactions without further purification. 1-Methyl-5-aminobenzimidazole (II) was synthesized according to [6], 1-benzyl-5-aminobenzimidazole (III) was obtained according to [7] by the reduction of 1-benzyl-5-nitrobenzimidazole [8].

N-(β-Hydroxyethyl)-2-amino-4-nitroaniline [9] was condensed with formic acid and N-(β-hydroxyethyl)-5-nitrobenzimidazole was obtained. Yield was 85%, mp 162-163.5° (from water). Found, %: C 52.26; H 4.67; N 20.27. $C_9H_9N_3O_3$. Calculated, %: C 52.14; H 4.34; N 20.28.

N-(β-Hydroxyethyl)-5-aminobenzimidazole (IV) was obtained by the reduction of N-(β-hydroxyethyl)-5-nitrobenzimidazole with iron in aqueous alcohol in the presence of a small quantity of hydrochloric acid and subsequent treatment of the reaction mixture with hydrogen sulfide. Yield was 63.5%, mp 185-186° (from isopropyl alcohol). Found, %: C 61.12; H 6.29; N 23.85. $C_9H_{11}N_3O$. Calculated, %: C 61.01; H 6.21; N 23.73.

6-Alkyl-2-amino-6H-imidazo[4,5-d]benzthiazoles (V-VIII). To a solution of 0.05 mole 1-alkyl-5 aminobenzimidazole (I-IV) and 0.15 mole ammonium thiocyanate in 200 ml absolute methanol was added a solution of 0.06 mole bromine in 55 ml methanol saturated with ammonium bromide. The addition was conducted dropwise over 2 h with stirring at 0-5°. After the addition of bromine the mixture was stirred for 2 h, the precipitate which had separated was filtered off, washed with a small quantity of water, dried, and 1-alkyl-4-thiocyanato-5-aminobenzimidazole obtained in 40-65% yield. IR spectra (in Nujol or potassium bromide): ν_{NH_2} 3130-3450, ν_{SCN} 2145, ν_{NH_2} 1635 cm^{-1}.

The mother liquor was evaporated down, water was added, and the solution neutralized with aqueous ammonia. 6-Alkyl-2-amino-6H-imidazo[4,5-g]benzthiazoles (V-VIII) were isolated, the properties of which are shown in Table 1.

1-Benzyl-4-mercapto-5-aminobenzimidazole (IX). A solution of 2.78 g benzthiazole (VIII) and 5.6 g potassium hydroxide in 20 ml ethylene glycol was boiled until evolution of ammonia had almost completely ceased (4.5-6 h). The mixture was cooled, diluted with water, and dilute acetic acid added until a neutral reaction was given. The precipitated yellow solid was filtered off, washed with water, and dried in a vacuum desiccator. Compound (IX) was obtained, yield being 1.96 g (77%). On recrystallization from a mixture of toluene and dimethylformamide the disulfide was obtained having mp 219-221°. Found, %: N 15.96; S 12.30. $C_{28}H_{24}N_6S_2$. Calculated, %: N 16.51; S 12.59.

1-Benzyl-4-(β-carboxyethylthio)-5-aminobenzimidazole (XI). To a solution of 1.96 g benzimidazole (IX) and 0.8 g sodium hydroxide in 50 ml absolute alcohol at 50-60° was added dropwise a solution of 1.5 g β-chloropropionic acid in 25 ml absolute alcohol, the mixture was stirred with heating for 2 h, cooled, the solid which had precipitated was dissolved in a small quantity of water, the solution was neutralized with dilute acetic acid, the precipitate separated, dried, and 1.5 g (60%) (XI) was obtained, mp 163-163.5° (from water). Found, %: N 12.74; S 9.96. $C_{17}H_{17}N_3O_2S$. Calculated, %: N 12.84; S 9.78. IR spectrum (Nujol) ν_{NH_2}, ν_{OH} 2850-3450, ν_{CO} 1690, ν_{NH_2} 1624 cm^{-1}.

1-Benzyl-4-carboxymethylthio-5-aminobenzimidazole (XII) was obtained similarly to (XI) from 3.5 g compound (IX), 1.2 g sodium hydroxide, and 1.43 g chloroacetic acid. Yield was 2.8 g (70%), mp 120-125° (from water).

8-Benzyl-2,3-dihydro-8H-imidazo[4,5-i][1,5]benzthiazepin-4-one (5H) (XIII). Compound (XI) (1.54 g) was mixed with 20 g polyphosphoric acid and the mixture was heated for 40 min at 160°. The thick melt was cooled, dissolved in water, and made alkaline with sodium carbonate solution. The white precipitate which separated was filtered off, washed with water, and dried. Compound (XIII) was obtained, yield being 1.27 g (85%), mp 340-345° (from aqueous isopropyl alcohol). Found, %: N 13.27; S 10.70. $C_{17}H_{15}N_3OS$. Calculated, %: N 13.59; S 10.35. IR spectrum (in chloroform) ν_{NH} 3399, ν_{CO} 1687 cm^{-1}.

The hydrochloride of (XIII) had mp 217-219° (from absolute alcohol). Found, %: N 11.95; S 9.27; Cl 10.05. $C_{17}H_{15}N_3OS$,HCl. Calculated, %: N 12.15; S 9.28; Cl 10.28.

7-Benzyl-2H,7H-imidazo[4,5-h][1,4]benzthiazin-3-one (4H) (XIV) was obtained analogously from 5.2 g compound (XII) and 50 g polyphosphoric acid. Yield was 3.62 g (72%) and mp 234-235° (from isopropyl alcohol). Found, %: N 14.30; S 11.15. $C_{16}H_{13}N_3OS$. Calculated, %: N 14.30; S 10.84. IR spectrum (in Nujol): ν_{NH} 3200, ν_{CO} 1670 cm^{-1}.

The hydrochloride of (XIV) had mp 278-284° (with decomposition, from aqueous alcohol). Found, %: N 12.42; S 9.91; Cl 10.67. $C_{16}H_{13}N_2OS$. HCl. Calculated, %: N 12.64; S 9.65; Cl 10.70.

7-(β-Hydroxyethyl)-2H,7H-imidazo[4,5h][1,4]benzthiazin-3-one (4H) (XV). 1-(β-Hydroxyethyl)-4-thiocyanato-5-aminobenzimidazole (4.8 g) was added in small portions to a solution of 11.5 g sodium sulfide in 25 ml water at 60-70° and the mixture was stirred at this temperature for 40 min. The filtrate was stored overnight at 0° and the sodium salt of 1-(β-hydroxyethyl)-4-mercapto-5-aminobenzimidazole (X) filtered off. Yield was 3.4 g (70%). The salt was dissolved in 50 ml 80 % alcohol, 1.2 g sodium hydroxide was added, and a solution of 1.82 g chloroacetic acid in 20 ml alcohol was added dropwise at 60°. The reaction continued for 1 h, then the mixture was filtered, the filtrate was evaporated to half volume, and acidified with hydrochloric acid. The solid which precipitated after cooling was separated and the hydrochloride of 7-(β-hydroxyethyl)-2H,7H-imidazo[4,5-h][1,4]benzthiazin-3-one (4H) (XV) was obtained. Yield was 3 g (81%), mp 250-251° (from aqueous alcohol). Found, %: N 14.25; S 11.17; Cl 12.17. $C_{11}H_{11}N_3O_2S$.HCl. Calculated, %: N 14.71; S 11.20; Cl 12.43. Base mp 301-302° (from water). Found, %: N 16.66; S 13.04. $C_{11}H_{11}N_3O_2S$. Calculated, %: N 16.87; S 12.83. IR spectrum (in Nujol): ν_{NH} 3200, ν_{CO} 1683 cm^{-1}.

6-β-Chloroethyl-2-amino-6H-imidazo[4,5-g]benzthiazole (XVI). Thionyl chloride (10 ml) was added dropwise at room temperature with stirring to a solution of 6.7 g benzthiazole (VIII) in 70 ml dimethylformamide. The thick mass was stirred for 2 h, poured into water, and the solution made alkaline with aqueous ammonia. The solid which had separated was filtered off and (XVI) was obtained (see Table 1).

6-β-Substituted Aminoethyl-2-amino-6H-imidazo[4,5-g]benzthiazoles (XVII, XVIII). A mixture of 1 g chloroethyl compound (XVI), 0.5 g sodium iodide, 2 ml morpholine (or piperidine), and 15-20 ml dioxan was boiled for 20-25 h, diluted with water, the resulting solid was filtered off, washed with water, dried, and (XVII) or (XVIII) was obtained (see Table 1).

6-Benzyl-2-acetamide-6H-imidazo[4,5-g]benzthiazole (XIX). A mixture of 1 g amine (VII) and 25 ml acetic anhydride was boiled for 5-10 min. On cooling a solid was precipitated which was filtered off, washed with water, and dried. Compound (XIX) was obtained (see Table 1).

6- Acetoxyethyl-2-acetamido-6H-imidazo[4,5-g]benzthiazole (XX). A solution of 1g compound (VIII) in 20 ml acetic anhydride was heated for 30 min, poured into water, the solution made alkaline with sodium hydroxide, and the solid which separated was filtered off. Diacetyl derivative (XX) was obtained (see Table 1).

LITERATURE CITED

1. E. A. Kuznetsova, S. V. Zhuravlev, and T. N. Stepanova, Khim. Geterosikl. Soedin., No. 4, 630-633 (1969).
2. E. A. Kuznetsova, S. V. Zhuravlev, T. N. Stepanova, et al., Khim. Geterosikl. Soedin., No. 2, 177-179 (1972).
3. S. G. Fridman and L. I. Kotova, Khim. Geterosikl. Soedin., No. 3, 497-501 (1967).
4. K. S. Raevskii and V. A. Timofeev, Byull. Éksp. Biol., No. 6, 114-116 (1965).
5. J. H. Ridd and B. V. Smith, J. Chem. Soc., 1363-1369 (1960).
6. F. Montanari, Gazz. Chim. Ital., 85, 981-988 (1955).
7. V. M. Mar'yanovskii, A. F. Pozharskii, and A. M. Simonov, Khim. Geterosikl. Soedin., No. 2, 216-218 (1970).
8. L. Joseph and J. Julca, J. Org. Chem., 27, 1101-1102 (1962).
9. G. R. Ramage and G. Trappe, J. Chem. Soc., 4406-4409 (1952).