SYNTHESIS AND TUBERCULOSTATIC ACTIVITY OF SOME NEW 2-BENZIMIDAZOLYL DERIVATIVES

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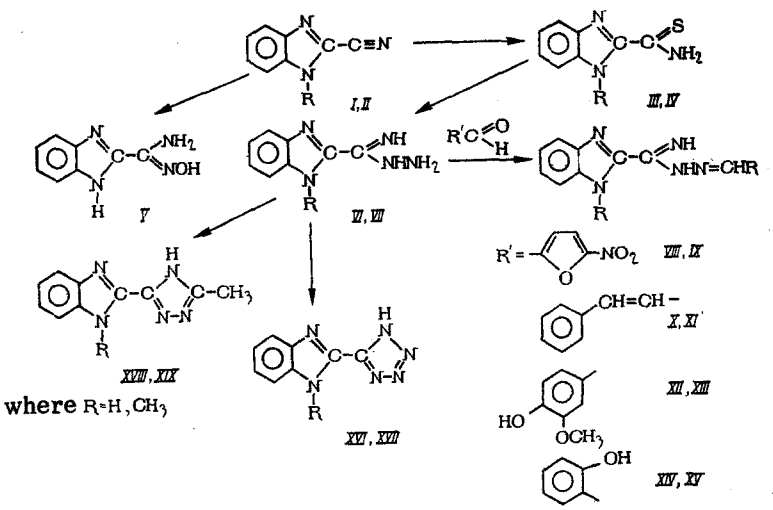
UDC 615.281.221.1:547.785

Continuing work on the search for potential antituberculosis compounds, we have synthesized a series of new benzimidazole derivatives. As starting materials we took 2-cyanobenzimidazole (I) and 1-methyl-2-cyanobenzimidazole (II). From I and II we synthesized compounds III-XIX, indicated in the scheme.

The thioamides of 2-benzimidazolecarboxylic acids (III, IV) presented special interest for testing for tuberculostatic activity, since some thioamides are active antituberculosis preparations (ethionamide, protionamide) [1]. Compounds III and IV were obtained from the action of hydrogen sulfide on I and II pyridine solution in the presence of triethylamine. Upon reaction with hydroxylamine hydrochloride, 2-benzimidazolecarboxamidoxime (V) was isolated from I; it is capable of complex formation with a number of metals.

From III and IV the corresponding amidrazones of benzimidazole-carboxylic acids were synthesized upon additon of hydrazine hydrate; these served as starting materials for the preparation of hydrazones with 5-nitrofurfural, cinnamaldehyde, salicylaldehyde, and vanillin (VIII, XV).



It is known from the literature that 2-(2-thiazolyl)benzimidazole possesses high antihelminthic activity [2]. In this connection, it would be interesting to make a thorough study of the physiological properties of the tetrazolylbenzimidazoles (XVI-XVII) and the 1,2,4-triazolylbenzimidazoles (XVIII-XIX) obtained from VI and VII. Compounds XVI-XVII were obtained on reaction of VI and VII with sodium nitrite in acid; and XVIII-XIX, on boiling VI or VII with acetic anhydride.

The tuberculostatic activity of the synthesized compounds, III-XI, was investigated in vitro in synthetic Soton medium without serum and with addition of 10% normal native serum. Laboratory strains H_{37} Rv and

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TABLE 1. 2-Benzimidazolyl Derivatives

Compound	Yield, %	Mp, °C	Found, % C	Found, % H	Empirical formula	Calcd, % C	Calcd, % H	Bacteriostatic titer in Soton medium (μg/ml) strain K_1 a	strain K_1 b	strain H_{37} Rv a	strain H_{37} Rv b
III	77	213—5	54,34	3,94	$C_8H_7N_3S$	54,21	3,98	2	250	—	—
IV	88	170—2	56,80	5,11	$C_9H_9N_3S$	56,52	4,74	62,5	125	—	—
V	94	212—3	54,24	4,61	$C_8H_8N_4O$	54,53	4,57	62,5	125	—	—
VI	96	194—5	52,03	5,46	$C_8H_9N_5$	54,61	5,17*	16	16	—	—
VII	88	187—9	57,31	5,94	$C_9H_{11}N_5$	57,12	5,85	—	—	2	31
VIII	80	219—21	52,69	3,39	$C_{13}H_{10}N_6O_3$	52,35	3,30	2	8	1	4
IX	87	241—2	53,94	3,91	$C_{14}H_{12}N_6O_3$	53,84	3,87	—	—	62,5	2500
X	60	241—2	70,56	5,49	$C_{17}H_{15}N_5$	70,56	5,92	1000	1000	—	—
XI	75	208—9	70,82	5,64	$C_{18}H_{17}N_5$	71,26	5,64	—	—	500	1000
XII	84	217—8	62,05	5,01	$C_{16}H_{15}N_5O_2$	62,20	4,85	500	1000	—	—
XIII	91	178—80	63,01	5,30	$C_{17}H_{17}N_5O_2$	63,14	5,29	—	—	8	500
XIV	95	234—5	64,22	4,74	$C_{15}H_{13}N_5O$	64,55	4,69	1000	—	—	—
XV	90	202—3	65,74	5,41	$C_{16}H_{15}N_5O$	65,51	5,15	—	—	250	1000
XVI	77	>300	51,00	3,44	$C_8H_6N_6$	51,60	3,24	—	—	—	—
XVII	93	273—4	53,87	4,07	$C_9H_8N_6$	53,99	4,02	—	—	—	—
XVIII	94	>300	60,32	4,75	$C_{10}H_9N_5$	60,29	4,50	—	—	—	—
XIX	93	258—9	61,60	5,09	$C_{11}H_{11}N_5$	61,95	5,19	—	—	—	—

*Picrate: Found, %: C, 41.35; H, 3.10. Calculated, % C, 41.58; H, 2.97.

Note. Compounds III, IV, VIII, X, XII, XIV, XV, XVIII, and XIX were crystallized from dilute alcohol; V, VI, and VII, from water; IX and XI, from alcohol; XIII and XVII, from aqueous dimethylformamide; XVI, from dimethylformamide. a) Without serum; b) with serum.

K_1 of the tuberculosis mycobacterium were used. As a result of the tests, it was observed that some compounds have a medium tuberculostatic activity in the absence of serum. In the presence of serum, the activity is reduced. The most active compound proved to be the nitrofurfurylidene compound, VIII. It is interesting to note that when the NH group in the ring in VIII is replaced by an NCH_3 group (compound IX), activity is sharply reduced. For VIII, which showed the greatest activity, we determined toxicity. Studies on white mice made it possible to conclude that 100 mg of the preparation is tolerable in an acute experiment. The chemotherapeutic activity of VIII was studied on guinea pigs inoculated subcutaneously with laboratory strain H_{37} Rv in a dose of 0.001 mg. Medication was started on the second day after inoculation and was continued for one month. When the animals were dissected, it was ascertained that VIII does not display medical action.

EXPERIMENTAL

Analyses, mp, crystallization solvents, and results of investigation of antitubercular properties are given in Table 1.

2-Cyanobenzimidazole (I) and 1-methyl-2-cyanobenzimidazole (II) were prepared in accordance with the procedure of [3].

Thioamides of 2-Benzimidazolecarboxylic and 1-Methyl-2-benzimidazolecarboxylic Acids (III and IV). Compound I or II (0.0185 mole) was dissolved in 27 ml of pyridine, 5.5 ml of triethylamine was added, and hydrogen sulfide was passed through for 2 h. The solution was poured into a small amount of water (50 ml). The yellow-colored precipitate which fell was filtered off and washed with water.

2-Benzimidazolecarboxamidoxime (V). To a hot solution of 0.01/mole of I in 50 ml of alcohol was added 0.01 mole of hydroxylamine hydrochloride and 0.005 mole of sodium carbonate dissolved in 16 ml of water. The mixture was boiled for 1 h. The precipitate which settled was filtered off and recrystallized.

Amidrazones of 2-benzimidazolecarboxylic and 1-Methyl-2-benximidazolecarboxylic Acids (VI and VII). Hydrazine hydrate (11.5 ml) was added to 0.013 mole of III or IV. Hydrogen sulfide was evolved thereupon. After one day, the precipitate was filtered off, washed with a small amount of water, and recrystallized.

Hydrazones from the Amidrazones of 2-Benzimidazolecarboxylic Acid and 1-Methyl-2-benzimidazolecarboxylic Acid (VIII-XV). Compound VI or VII (0.0011 mole) was dissolved in 12 ml of alcohol, a solution of 0.0011 mole of the appropriate aldehyde in 2 ml of alcohol was added, and the mixture was

boiled for a few minutes. The precipitate which fell after cooling was filtered off and recrystallized.

2-(5-Tetrazolyl)benzimidazole and 1-Methyl-2-(5-tetrazolyl)benzimidazone (XVI and XVII). Compound VI or VII (0.0017 mole) was dissolved in 10 ml of 2N hydrochloric acid, the solution was cooled, and 0.0037 mole of sodium nitrite dissolved in 2 ml of water was added dropwise with stirring. The reaction mixture was allowed to stand for 1 h at room temperature. The precipitate was filtered off and recrystallized.

2-(3-Methyl-1,2,4-triazolyl-5)benzimidazole and 1-Methyl-2-(3-methyl-1,2,4-triazolyl-5)benzimidazole (XVIII and XIX). To 0.0017 mole of VI or VII was added 10 ml of acetic anhydride and the mixture was boiled for 2 h. The reaction solution was evaporated to one-half its volume at room temperature, and the residue was diluted with water. The precipitate which fell was filtered off and recrystallized.

LITERATURE CITED

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