Studies on the Antitubercular Compounds. XVI. Preparation of Some Derivatives of 2, 1, 3-Benzothiadiazole***

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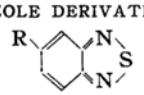
In a previous paper[1] the author has reported the syntheses of several kinds of 4- and 5-substituted 2, 1, 3-benzothiadiazole compound. These compounds have been shown to have no antitubercular activity in vitro. In the present paper, the new compounds listed in Table I and Table II were prepared in order to increase the antibacterial effect of the compounds of this series against *Mycobacterium tuberculosis*. 5-Bromomethyl-2, 1, 3-benzothiadiazole (I) was prepared by bromination of 5-methyl-2, 1, 3-benzothiadiazole with *N*-bromosuccinimide by the usual method, and readily converted into aminomethyl hydrochloride (II) by the Delepine reaction[2].

2, 1, 3-Benzothiadiazole-5-aldehyde (VI) was prepared from I in excellent yields through the hexaminium salt by Sommelet reaction[3]. Reaction of 2, 1, 3-benzothiadiazole with *N*-methylformanilide and phosphorous oxychloride in *o*-dichlorobenzene gave no formyl compound.

VI was readily oxidized into 5-benzothiadiazolecarboxylic acid (III) by the Delepine's method[4] in an alcoholic solution.

TABLE I. 5-SUBSTITUTED 2, 1, 3-BENZOTHIADIAZOLE DERIVATIVES



I	$-CH_2Br$
II	$-CH_2NH_2 \cdot HCl \cdot H_2O$
III	$-COOH$
IV	$-CONHNH_2$
V	$-CONH_2$
VI	$-CHO$

By the oxidation of 5-methyl-2, 1, 3-benzothiadiazole with potassium permanganate, not only methyl group but also benzene nucleus was attacked, so that III could not be obtained. Chlorination of III with thionyl chloride afforded an acid chloride, which was smoothly converted into acid amide V. Acidhydrazide IV was prepared from III by the usual method. Semicarbazone (VII), thiosemicarbazone (VIII), picolinoylhydrazone (IX), nicotinoylhydrazone (X) and isonicotinoylhydrazone (XI) were derived from VI by condensation with semicarbazide, thiosemicarbazide, α-, β- and γ-pyridinecarbohydrazide, respectively.

A detailed report on the antitubercular activity of these compounds will appear elsewhere.

Experimental

I.—A mixture of 4.5 g. of 5-methyl-2, 1, 3-benzothiadiazole, 5.4 g. of *N*-bromosuccinimide and 150 ml. of tetrachloromethane was refluxed for 18 hr. After cooling in ice bath, succinimide was removed by filtration and washed with 50 ml. of tetrachloromethane. After removing tetrachloromethane, the solidified residue was recrystallized from methanol to give 4.9 g. (70%) of lachrymatory white needles, m. p. 89~90°C.

Anal. Found: C, 36.41; H, 2.36. Calcd. for $C_7H_5N_2SBr$: C, 36.70; H, 2.20%.

II.—To a solution of 2.3 g. of I in 22 ml. of chloroform, 1.4 g. of hexamethylenetetramine was added. The mixture was allowed to stand overnight at room temperature, and the hexaminium salt was filtered and washed with 20 ml. of ether; yield 3.5 g., m.p. 182°C (decomp.)

A mixture of 1.2 g. of the hexaminium salt, 3 ml. of concentrated hydrochloric acid and 7 ml. of water was refluxed for 30 min., and the reaction mixture was concentrated to dryness under reduced pressure. The residue was recrystallized from water to give 0.4 g. of white needles, which softened at 235°C, became brown and decomposed at 245~246°C.

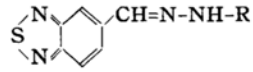
Anal. Found: C, 38.24; H, 4.87; H_2O, 8.10. Calcd. for $C_7H_5N_3S \cdot HCl \cdot H_2O$: C, 38.27; H, 4.59; H_2O, 8.20%.

VI.—A mixture of 3 g. of the hexamethylenetetramine salt, 0.1 g. of hexamethylenetetramine and 6 ml. of 50% acetic acid was refluxed

* This paper constitutes a part of a series entitled "Studies on the Antitubercular Compounds", by S. Kakimoto. Paper XV, S. Kakimoto and J. Nishie, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **79**, 1403 (1958).

** A part of this study was presented at the Annual Meeting of the Chemical Society of Japan in Tokyo on April 3, 1958.

1) I. Sekikawa, This Bulletin, **31**, 252 (1958).
2) M. Delepine, *Compt. rend.*, **120**, 501 (1895).
3) M. Sommelet, ibid., **157**, 852 (1913).
4) M. Delepine and P. Bonnet, *Bull. soc. chim. France*, (4) **5**, 879 (1909).

TABLE II. 

No.	R	m.p. (°C)	Appearance	Formula	Analysis (%) Calcd. C.	H.	H_2O	Found C.	H.	H_2O
VII	$-CO-NH_2$	251~252 d.*	White needles	$C_8H_7ON_5S$	43.43	3.19		43.09	3.37	
VIII	$-CS-NH_2$	228 d.	Yellow needles	$C_8H_7N_5S_2$	40.49	2.97		40.41	3.13	
IX	$-CO-C_5H_4N$ (α)	233~235	Pale yellow needles	$C_{13}H_9ON_5S$	55.11	3.20		55.13	3.51	
X	$-CO-C_5H_4N\cdot 2H_2O$ (β)	216~217	Pale yellow needles	$C_{13}H_{13}O_3N_5S$	48.89	4.10	11.28	48.86	4.43	11.16
XI	$-CO-C_5H_4N\cdot H_2O$ (γ)	218~219	White needles	$C_{13}H_{11}O_2N_5S$	51.82	3.68	5.98	51.63	3.91	6.09

* Decomp.

for 20 min. On cooling, a solid resulted. Recrystallization from methanol afforded 0.6 g. (47%) of white needles, m. p. 94°C.

Anal. Found: C, 51.25; H, 2.56. Calcd. for $C_7H_4ON_2S$: C, 51.21; H, 2.46%.

III.—To a solution of 0.9 g. of VI in 30 ml. of ethanol 2.3 g. of silver nitrate dissolved in 3 ml. of water was added. To the mixture was added 1.5 g. of sodium hydroxide in 10 ml. of water in small portions under stirring.

After being kept overnight, the deposited silver was removed and washed with 10 ml. of water. The solution was acidified with acetic acid to give an orange precipitate which was recrystallized from water to give 0.3 g. of white sandy crystals. It softened at 214°C and melted at 224~225°C.

Anal. Found: C, 46.63; H, 2.57. Calcd. for $C_7H_4O_2N_2S$: C, 46.66; H, 2.24%.

V.—A mixture of 0.4 g. of III and 5 ml. of thionyl chloride was refluxed for 1 hr. The excess of thionyl chloride was removed in a vacuum desiccator. The residue was dissolved in ether, saturated with ammonia and kept at room temperature for 1 hr. After removing ether, the solidified residue was recrystallized from water to give 0.3 g. of white needles, m.p. 202~203°C.

Anal. Found: C, 46.96; H, 3.01. Calcd. for $C_7H_5ON_3S$: C, 46.92; H, 2.81%.

IV.—A mixture of 0.15 g. of III, 3 ml. of absolute ethanol and 0.3 ml. of concentrated sulfuric acid was refluxed for 8 hr. After removing ethanol, the residue was treated with water and neutralized with sodium hydrogen carbonate. The resulting gray solid was heated with 0.1 ml. of hydrazine hydrate (80%) in 5 ml. of ethanol for 8 hr. The mixture was evaporated to dryness and the residue was recrystallized from water to give 0.1 g. of white needles, m.p. 180~181°C (decomp.).

Anal. Found: C, 42.99; H, 3.21. Calcd. for $C_7H_6ON_4S$: C, 43.29; H, 3.11%.

IX.—A mixture of 0.2 g. of VI, 0.16 g. of picolinic acidhydrazide and 5 ml. of ethanol was refluxed for 1 hr. The product was collected and recrystallized from ethanol to give 0.3 g. of yellow needles, m. p. 233~235°C.

Anal. Found: C, 55.13; H, 3.51. Calcd. for $C_{13}H_9ON_5S$: C, 55.11; H, 3.20%.

VII, VIII, X and **XI** were prepared by analogous methods.

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