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

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In the foregoing paper[1], several kinds of 2-substituted benzimidazole compound were prepared and their antibacterial activities in vitro were examined. As a result 2-mercaptomethylbenzimidazole was found to be most effective against Mycobacterium tuberculosis.

Brown et al.[2] and Kushner et al.[3], who studied the tuberculostatic action of alkylmercapto derivatives, found that structural modification, which increased its ability to release ethylmercaptan, increased the antitubercular activity. Therefore, a series of alkylthioether was prepared for comparative studies as indicated in Table I. A compound which was formed by condensation of *o*-phenylenediamine with alkylthioglycolic acid in the presence of dilute hydrochloric acid was identical with that obtained by condensation of mercaptomethylbenzimidazole with alkyl bromide, thus confirming the fact that *S*-alkylation occurred.

Benzimidazole derivatives having substituents at the phenyl nucleus are shown in Table II. Condensation of 3, 4-diaminophenetole with formic acid in the presence of dilute hydrochloric acid gave 5-ethoxybenzimidazole, which was converted into VI by the acid cleavage of ether group. VII was obtained by amination of the corresponding acid chloride. VIII was

TABLE I

2-ALKYLMERCAPTOMETHYLBENZIMIDAZOLE DERIVATIVES

No.	R	Method of prepn.	Yield (%)	m. p. (°C)	Appearance	Formula	Analysis (%) Calcd. C	Calcd. H	Found C	Found H
I	CH_3	b	90	156—157	Pale yellow needles	$C_9H_{10}N_2S$	60.64	5.60	60.37	5.96
II	C_2H_5	b	60	136—137	White needles	$C_{10}H_{12}N_2S$	62.46	6.29	62.57	6.69
III	n-C_3H_7	b	80	122—124	〃	$C_{11}H_{14}N_2S$	64.04	6.34	63.67	7.01
IV	n-C_4H_9	a	68	143—144	〃	$C_{12}H_{16}N_2S$	65.41	7.31	65.10	7.45
		b	95							

* This constitutes a part of a series entitled "Studies on the Antitubercular Compounds" by S. Kakimoto.

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2) H. D. Brown, M. Solotorvsky and I. H. Quastel, *J. Am. Chem. Soc.*, **76**, 3860 (1954).

3) S. Kushner, H. Dalalian and L. Bach, ibid., **77**, 1152 (1955).

TABLE II
BENZIMIDAZOLE DERIVATIVES

V	5-NO_2[4]
VI	5-OH
VII	5-$CONH_2$
VIII	5-$CONHNH_2$

TABLE III
2,1,3-BENZOTHIADIAZOLE DERIVATIVES

IX	5-NO_2[5]
X	5-OH[6]
XI	4-NO_2[7]
XII	4-$NHCOCH_3$[8]

prepared by the usual method.

2,1,3-Benzothiadiazole derivatives, which were formed by replacing the carbon atom of 2-position in benzimidazole molecule with sulfur atom, are shown in Table III. Reduction of XI with tin or stannous chloride in the presence of hydrochloric acid gave the parent *o*-phenylenediamine and sulfur. Vigorous reduction produced hydrogen sulfide[9]. Khaletskiĭ et al.[10] obtained a 4-amino compound by reduction of the nitro compound with acetic acid and iron powder. However, the present author found that the compound was very readily obtained by reducing the nitro compound with sodium chloride and iron powder in the presence of a minute amount of hexachloroplatinic acid.

Recently, Huebner et al.[11] reported a relation between chemical structure and antibacterial activity in the case of over three hundred compounds of *N,N'*-disubstituted thiourea derivatives and Konopka et al.[12] found that 4-ethoxy-4'-*iso*-butoxythiocarbanilide and 4-*n*-butoxy-4'-dimethylaminothiocarbanilide were the most effective in vivo.

A series of *N*-(Benzothiadiazolyl-4)-*N'*-(*p*-alkoxyphenyl)-thiourea, indicated in Table IV, was prepared. XIII, XIV, XV, XVI and XVII were derived from 4-aminobenzothiadiazole and phenyl-, *p*-methoxyphenyl-, *p*-ethoxyphenyl-, *p*-*n*-propoxyphenyl- and *p*-*n*-butoxyphenyl-isothiocyanate by the usual method.

Upon oxidation of 5-methylbenzothiadiazole with potassium permanganate by the usual procedure, the corresponding 5-benzothiadiazolecarboxylic acid was not obtained; an unknown acidic substance of m.p. 281°C (decomp.) was, on the other hand, formed. The investigation of the structure of this compound is now in progress.

The antitubercular activities of all derivatives described above were examined in vitro, and found less active than 2-mercaptomethyl-benzimidazole[1].

Experimental

IV. (a) A mixture of 2 g. of *o*-phenylenediamine, 3 g. of *n*-butylmercaptoacetic acid, 10 ml. of concentrated hydrochloric acid, and 10 ml. of water was refluxed for 12 hr., and the solution was concentrated under reduced pressure. The residue was dissolved in 10 ml. of water, and the solution was poured slowly into 20 ml. of cold concentrated ammonium hydroxide. The solid thus formed was recrystallized from 70% ethanol to give 3 g. (68%) of white needles m.p. 145°.

V. (b) To a solution of 0.5 g. sodium metal in 30 ml. of *n*-butanol, 3.3g. of 2-mercaptomethylbenzimidazol was added, with stirring. The mixture was cooled and 2.7 g. of *n*-butylbromide in 10 ml. of *n*-butanol was added in small portions during 10 min. The mixture was then stirred for another 15 min., and then refluxed for 5 hr. After removal of the *n*-butanol, 70 ml. of water was added and allowed to stand overnight in an ice box. The solidified product was recrystallized from 70% ethanol to give 4.3 g. (95%) of

TABLE IV
N-(BENZOTHIADIAZOLYL-4)-*N'*-SUBSTITUTED THIOUREA DERIVATIVES

No.	Substituent	Yield (%)	m. p. (°C)	Appearance	Formula	Analysis (%) Calcd. C	Calcd. H	Found C	Found H
XIII	C_6H_5-	73	154—155	Yellow needles	$C_{13}H_{10}N_4S_2$	54.52	3.52	54.40	3.93
XIV	*p*-CH_3O-C_6H_4-	65	161—162	〃	$C_{14}H_{12}ON_4S_2$	53.14	3.82	53.14	4.10
XV	*p*-C_2H_5O-C_6H_4-	70	173—174	〃	$C_{15}H_{14}ON_4S_2$	54.52	4.27	54.56	4.56
XVI	*p*-C_3H_7O-C_6H_4-	54	146—148	〃	$C_{16}H_{16}ON_4S_2$	55.79	4.68	55.83	4.83
XVII	*p*-C_4H_9O-C_6H_4-	57	139—141	〃	$C_{17}H_{18}ON_4S_2$	56.96	5.06	57.32	5.30

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7) L. S. Efros and R. N. Levit, *Zhur. Obshcheĭ Khim.*, **23**, 1552 (1953); *Chem. Abst.*, **48**, 1209 (1956).
8) L. S. Efros and R. N. Levit, ibid **25**, 199 (1955); *Chem. Abst.*, **50**, 1783 (1954).
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10) A. M. Khaletskiĭ and V. G. Pesin, *Zhur. Obshcheĭ Khim.*, **20**, 1914 (1950); *Chem. Abst.*, **46**, 106 (1952).
11) C. F. Huebner, J. L. Marsh, P. H. Mizzoni, R. P. Mull, D. C. Schroeder, H. A. Trovell and C. R. Scholz, *J. Am. Chem. Soc.*, **75**, 2274 (1953).
12) E. A. Konopka, P. C. Eisman, R. L. Mayer, F. Paker and S. L. Pobbins, *Amm. Rev. Tuberc.*, **70**, 130 (1954).

white needles, m.p. 143~144°C, showing no depression on admixture with the above-mentioned sample (a).

Anal. Found: C, 65.10; H, 7.45. Calcd. for $C_{12}H_{16}N_2S$: C, 65.41; H, 7.31%.

VI. A mixture of 7.5 g. of 3, 4-diaminophenetole dihydrochloride, 10 ml. of 80% formic acid, 5 ml. of concentrated hydrochloric acid, and 30 ml. of water was refluxed for 8 hr. The mixture was evaporated under a reduced pressure and the residue was poured into 30 ml. of concentrated ammonium hydroxide. The solid thus formed was recrystallized from ethanol to give 4.6 g. (85%) of 5-ethoxybenzimidazole, m.p. 118~119°C.

Anal. Found: C, 66.64; H, 6.18. Calcd. for $C_9H_{10}ON_2$: C, 66.65; H, 6.15%.

The hydrolysis was carried out by gently refluxing a mixture of 1.2 g. of 5-ethoxybenzimidazole and 4 ml. of hydriodic acid (d=1.7) for 7hr. After removal of the excess of hydriodic acid in vacuo, the residue was dissolved in 5 ml. of water and neutralized with sodium hydrogen carbonate. The product deposited was recrystallized from water to give 0.8 g. (80%) of white needles, m.p. 216~217°.

Anal. Found: C, 62.98; H, 4.84. Calcd. for $C_7H_6ON_2$: C, 62.68; H, 4.51%.

VII. Upon oxidation of 8.5g. of 5-methylbenzimidazole with 35 g. of potassium permanganate by the usual procedure, 5-benzimidazolecarboxylic acid was obtained; the crude product was dissolved in aqueous ammonia solution, and treated with active carbon. Precipitation with acetic acid gave 7 g. (70%) of white needles, m.p. 325°C (decomp.).

Anal. Found: C, 59.05; H, 3.95. Calcd. for $C_8H_6O_2N_2$: C, 59.26; H, 3.73%.

A mixture of 1.2 g. of 5-benzimidazolcarboxylic acid and 12 ml. of thionyl chloride was refluxed for 5 hr. Excessive thionyl chloride was removed and dried off in a vacuum desiccator. The residue was poured slowly, with stirring, into 15 ml. of cold concentrated ammonia water. The solid was recrystallized from water to give 0.6 g. (50%) of white prisms, m. p. 247~248°C (monohydrate).

Anal. Found: C, 53.70; H, 5.43; H_2O 10.13. Calcd. for $C_8H_7ON_3 \cdot H_2O$: C, 53.62; H, 5.62; H_2O 10.05%.

VIII. A mixture of 5 g. of 5-benzimidazolecarboxylic acid, 100 ml. of absolute ethanol, and 3 ml. of concentrated sulfuric acid was refluxed for 10 hr. After removal of the excess of ethanol in vacuo, the residue was treated with 20 ml. of water and neutralized with sodium hydrogen carbonate. A white crystalline precipitate was immediately formed. After standing for several hours at 0°C, the solid was collected and recrystallized from ethanol to give 4.1 g. (70%) of ester, m.p. 101~103°C.

A mixture of 5.3 g. of ester, 2.5 ml. of hydrazinhydrate (80%), and 10 ml. of ethanol was heated on a water bath for 10 hr. After removing the ethanol, the solidified residue was recrystallized from ethanol, affording 4 g. (82%) of acid hydrazide in the form of white needles, m.p. 240°, 248°C (decamp.).

Anal. Found: C, 54.71; H, 4.73. Calcd. for $C_8H_8ON_4$: C, 54.54; H, 4.58%.

Reduction of 4-nitrobenzothiadiazole.—To a suspension of 10 g. of 4-nitrobenzothiadiazole in 100 ml. of 10% sodium chloride solution, 0.3 ml. of 0.5% hexachloroplatinic acid solution was added and stirred in a hot water bath. When 4-nitro derivative was melted, 30 g. of iron powder was added in one portion. The mixture was heated and stirred for an additional 1 hr., cooled, and extracted with 50 ml. of benzene (twice). The benzene layer was dried and distilled. The residue was recrystallized from water to give 4 g. of yellow needles, m.p. 67—68°C[13].

The acetylation was carried out by gently refluxing a mixture of 0.7 g. of 4-amino compound, 4 ml. of acetic acid, and 0.7 ml. of acetic anhydride for 1 hr. Recrystallization from water gave 0.5 g. of white needles, m.p. 152°C[14].

XIII. A mixture of 3 g. of 4-aminobenzothiadiazole, 2.7 g. of phenylisothiocyanate, and 5 ml. of alcohol was refluxed for 1 hr. to give 4.2 g. (73%) of the desired product melting at 150°C. The crude material was recrystallized from ethanol to yield a pure substance melting at 154~155°.

Anal. Found: C, 54.40; H, 3.93. Calcd. for $C_{13}H_{10}N_4S_2$: C, 54.52; H, 3.52%.

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13) m. p. 68°C[8]
14) m. p. 152.5°C[8]