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Derivatives of Imidazo[2,1-*b*]benzothiazole[1] (Studies on Heterocyclic Compounds. VII[2])

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Condensation reaction of 2-aminobenzothiazole and bromoacetone under the condition of boiling alcohol afforded a molecular compound of equimolecular of 2-aminobenzothiazole and 2-methylimidazo[2,1-*b*]benzothiazole. When the reaction condition under standing at room temperature was adopted, 2-imino-3-acetonyl-2,3-dihydrobenzothiazole was obtained. 3-Phenylimidazo[2,1-*b*]benzothiazole was prepared from 1-(*m*-chlorophenyl)-2-mercapto-4-phenylimidazole and potassium amide in liquid ammonia. Imidazo[2,1-*b*]benzothiazole was also prepared from 1-(*m*-chlorophenyl)-2-mercaptoimidazole.

During the course of the studies of the imidazo[2,1-*b*]benzothiazole derivatives, 2-phenyl derivatives have been synthesized by Ochiai and Nishizawa[4] in 1940, and recently Iwai and Hiraoka[5] obtained 2-methylimidazo[2,1-*b*]benzothiazole (III) by the reaction of propargylbromide with 2-aminobenzothiazole (I). The resulting product (III) was identified by comparing it with a product from an another synthetic way, condensation of 2-acetamidobenzothiazole (IV) and monobromoacetone *via* 2-acetylimino-3-acetonyl-2,3-dihydrobenzothiazole hydrobromide, for the determination of the position of methyl group. An unconfirmed product with melting at 125—127° obtained from I and bromoacetone in a boiling alcohol has also been reported by Iwai, *et al.*[5] The present study deals with the synthesis of various derivatives of imidazo[2,1-*b*]benzothiazole and the examination of their chemical properties, and the confirmation of the above mentioned compound mp 125—127°.

This compound (VI) was further recrystallized from ethanol, and the melting point raised to 137°. The mixed examination performed with I or III, respectively, showed a depression of the melting points. Thin-layer chromatography (TLC) of VI gave two spots corresponding

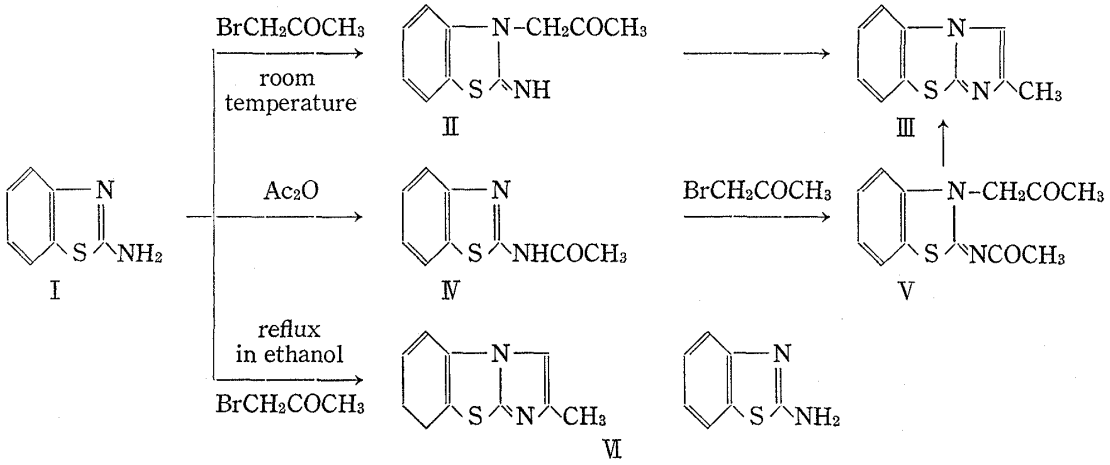
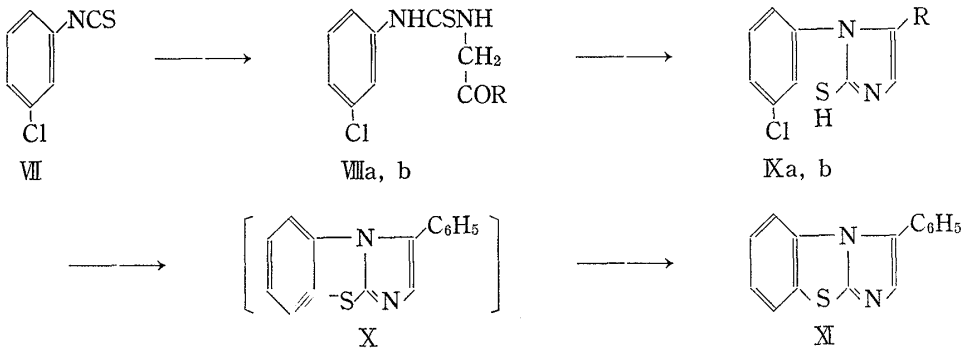


Chart 1

1) Presented before the 88th Annual Meeting of the Pharmaceutical Society of Japan, April, 1968, p. 100.
2) Part VI: H. Ogura, S. Sugimoto, and K. Shimura, *Yakugaku Zasshi*, **90**, 796 (1970).
3) Location: *Shirogane, Minato-ku, Tokyo, 108, Japan.*
4) E. Ochiai and T. Nishizawa, *Yakugaku Zasshi*, **60**, 132 (1940).
5) I. Iwai and T. Hiraoka, *Chem. Pharm. Bull.* (Tokyo), **12**, 813 (1964).

I and III, and the values of elemental analysis were equal to that of a mixture of I and III in an equimolecular portion. In the mass spectra, VI showed two strong peaks of *m/e* 188 and *m/e* 150, respectively and which represent 100% in the relative abundance. Boiling of a mixture of I and III in an equimolecular portion in ethanol yielded a product with mp 137°, which has properties identical to those of VI. Thus, VI was concluded to be a molecular compound composed of I and III.

On the other hand, when I and bromoacetone are allowed to stand at room temperature in ethanol, 2-imino-3-acetonyl-2,3-dihydrobenzothiazole (II) with mp 267° was obtained. Heating of the resulting compound in polyphosphoric acid (PPA) or ethyl polyphosphorate (PPE), yielded III with mp 90°. The data of infrared (IR) and ultraviolet (UV) absorption spectra and mixed melting points comparisons showed identical with III, synthesized in accordance with the method reported by Iwai (IV→V→III).[5] As a result, 2-substituted compound (III) was synthesized directly from I and bromoacetone.



Ⅶ Ⅷa, b Ⅸa, b X Ⅺ

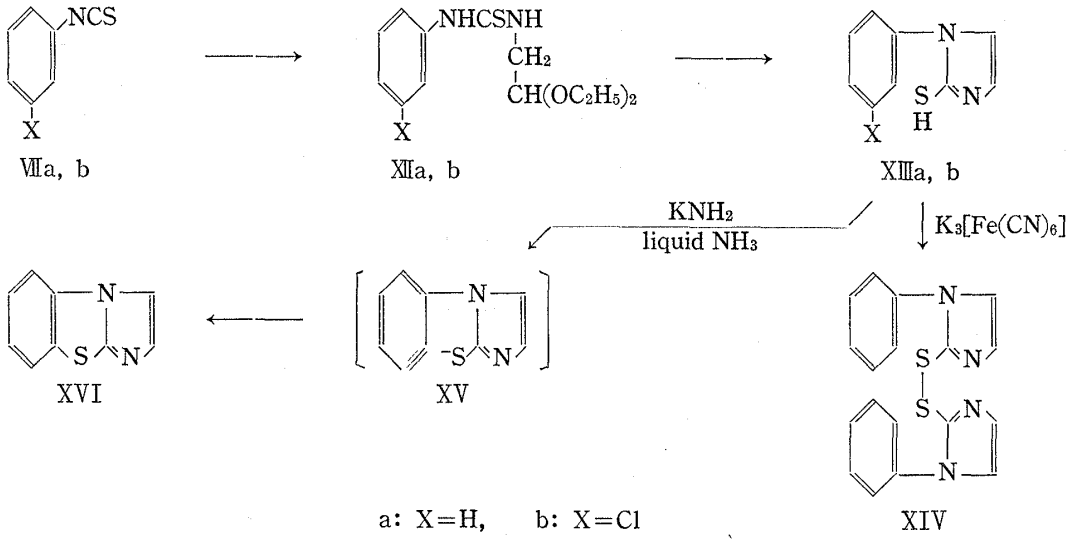
a: R=CH_3, b: R=C_6H_5

Chart 2

On the other hand, the synthesis of 3-substituted imidazo[2,1-*b*]benzothiazole was attempted by an another method as described in Chart 2. When amino acetone was allowed to react with *m*-chlorophenylisothiocyanate (VII), 1-(*m*-chlorophenyl)-2-mercapto-4-methylimidazole (IXa) with mp 197—200° was obtained through an intermediate (VIIIa).[6] Since, IXa was characterized from the data of nuclear magnetic resonance (NMR) spectrum, which indicates a methyl group at 8.0 τ and one proton at C_3 position at 3.4 τ; IR revealed no absorption of carbonyl; and mass spectrum indicated M^+ 224. Because of a poor yield of IXa further experiment was not performed. The reaction with amino acetophenone and VII produced an intermediate, N-(*m*-chlorophenyl)-N-phenacylthiourea (VIIIb) with mp 109—112°. Heating of VIIIb with 4N hydrochloric acid produced a compound with mp 260°, which was characterized as 1-(*m*-chlorophenyl)-2-mercapto-4-phenylimidazole (IXb) based on a disappearance of the carbonyl absorption in IR and the results of mass spectra. The cyclization reaction of IXb occurred with potassium amide in liquid ammonia to yield 3-phenylimidazo[2,1-*b*]benzothiazole (XI) melting at 165° in 68% yield. The reaction clearly progressed through a benzyne intermediate (X).[7] This was found to be not identical with 2-phenyliimidazo[2,1-*b*]benzothiazole (XIXa), which was obtained from 2-aminobenzothiazole and bromoacetophenone, on the basis of UV, IR and mass spectra. As a result, it was confirmed that the position of phenyl group of XI was 3-position. Accordingly the direction of the alkylation of 2-aminobenzothiazole with α-halogenocarbonyl compounds was concluded at the nitrogen of 3-position of the thiazole ring rather than 2-amino group. The reaction of bromoacetaldehyde diethylacetal with I and that of aminoacetaldehyde

6) R. Burtles, F.L. Pyman, and J. Roylance, *J. Chem. Soc.*, **127**, 581 (1925).
7) J.F. Bunnett and F. Hrutfiord, *J. Am. Chem. Soc.*, **83**, 1691 (1961).

diethylacetal with 2-chlorobenzothiazole did not gave the expected material, imidazo-[2,1-*b*]benzothiazole (XVI).



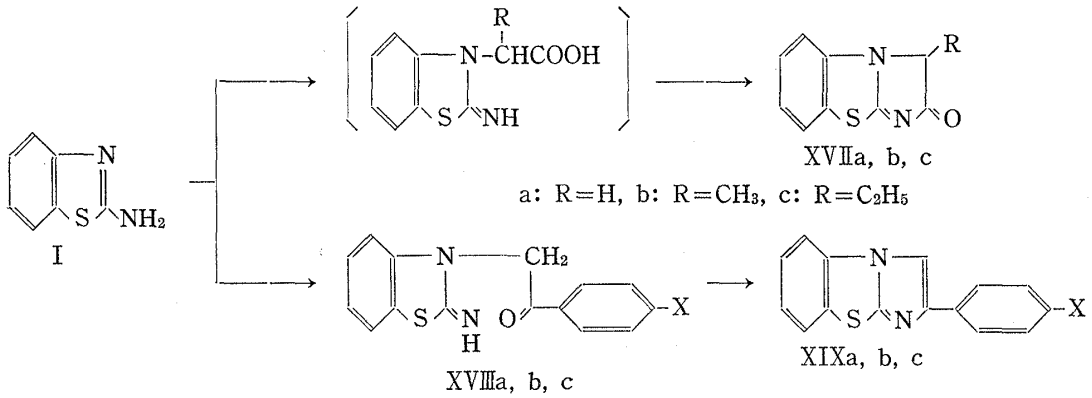
VIIa, b XIIa, b XIIIa, b

XVI XV XIV

a: X=H, b: X=Cl

Chart 3

As described in Chart 3, condensation of aminoacetaldehyde diethylacetal with phenyl-isothiocyanate (VIIa) according to the method reported by Shirley, *et al.*[8] produced 1-phenyl-2-mercaptoimidazole (XIIIa), mp 159—160° (Reported mp 179—180°).[9] When this compound was oxidized by potassium ferricyanide[10,11,12] in order to obtain XVI, a bis-form, 2,2'-dithio-bis (1-phenylimidazole) (XIV) with mp 146—148°, M^+ 350, was obtained. Reaction of aminoacetaldehyde diethylacetal with *m*-chlorophenyl isothiocyanate (VIIb) in benzene yielded N-(*m*-chlorophenyl)-N-(*β*,*β*-diethoxyethyl)-thiourea (XIIb) having mp 53°. Boiling XIIb in 2N hydrochloric acid for 45 minutes produced a compound with mp 160°, which was characterized to be 1-(*m*-chlorophenyl)-2-mercaptoimidazole (XIIIb) by IR, UV and mass spectra. Treatment of this compound with potassium amide in liquid ammonia as described above yielded needles with mp 48°. It was tonfirmed to be imidazo[2,1-*b*]benzothiazole (XVI)



I

XVIIa, b, c

a: R=H, b: R=CH3, c: R=C2H5

XVIIIa, b, c XIXa, b, c

a: X=H, b: X=Cl, c: X=Br

Chart 4

8) D.A. Shirley and P.W. Alley, *J. Am. Chem. Soc.*, **79**, 4922 (1957).
9) R.G. Jones, E.C. Kornfeld, K.C. Mclaughlin, and R.C. Anderson, *J. Am. Chem. Soc.* **71**, 4000 (1949).
10) R.H. Sahasrabudhey, *J. Indian. Chem. Soc.*, **27**, 524 (1950).
11) F.L. Scott, *Experientia*, **13**, 275 (1957).
12) Y. Mizuno, K. Adachi, T. Hashimoto, and Y. Saito, *Yakugaku Zasshi*, **76**, 329 (1956).

based on the mass spectra, elemental analysis, approximate coincidence with 2-methylimidazo-[2,1-*b*]benzothiazole (III) in UV, and the observation of two protons in the range of 2.4—2.9 τ by NMR. The reaction also progressed through a benzyne intermediate (XV).

Condensation of 2-bromo fatty acids with 2-aminobenzothiazole (I) in the presence of alkali, followed by the reaction of acetic acid anhydride and pyridine, produced 2-oxo-3-substituted-2,3-dihydroimidazo[2,1-*b*]benzothiazole (XVIIa,b,c). Also, when I was heated in alcohol with phenacylbromides,[13] 2-imino-3-(*p*-substituted)-phenacyl-2,3-dihydrobenzothiazole (XVIIIa,b,c) were obtained (Chart 4).

Experimental[14]

2-Imino-3-acetonyl-2,3-dihydrobenzothiazole Hydrobromide (II-HBr)——A mixture of 7.5 g of I and 6.85 g of bromoacetone in 75 ml of ethanol was stood at room temperature for over night. The separated white crystals were filtered and recrystallized from ethanol to yield 3.8 g (27%) of II-HBr, mp 267°. Reported, mp 219—220°.[5] NMR τ (CF_3COOH): 7.30 (singlet, $C\underline{H}_3$), 4.40 (singlet, $-C\underline{H}_2-$), 2.00—2.30 (multiplet, aromatic protons), 1.65 (=N$\underline{H}$). UV λ_{max}^{EtOH} mμ (log ε): 258 (4.80), 280 (4.61), 288 (4.65). IR ν_{max}^{KBr} (cm^{-1}): 3200 (–NH), 1720 (C=O), 1610 (C=N), 1590 (C=C).

2-Methylimidazo[2,1-*b*]benzothiazole (III)——(a) By PPA: A mixture of 1.5 g of II in 15 g of PPA was heated at 140—150° for 4 hr. After cooling the reaction mixture was poured into 200 ml of ice water and then made alkaline with 5% sodium hydroxide solution, and the separated product was collected by filtration. Recrystallization from hexane afforded 0.72 g (73%) of III, mp 90°.

(b) By PPE: A mixture of 1.7 g of II in PPE which prepared from 10 g of phosphorus pentoxide and 9.5 g of ethanol, was heated at 50—60° for 2 hr. After cooling the reaction mixture was worked up in the same way as described above (a). There was obtained 0.95 g (85%) of III, mp 90° (from hexane). Reported mp 89—90°.[5] NMR τ: 7.84 (singlet, $-C\underline{H}_3$), 2.50—2.90 (multiplet, aromatic protons). UV λ_{max}^{EtOH} mμ (log ε): 242 (4.15), 286 (3.34), 294.5 (3.17). IR ν_{max}^{KBr} (cm^{-1}): 2960 (–NH), 1635—1660 (broad C=N), 1600, 1500 (C=C).

Molecular Compound of 2-Methylimidazo[2,1-*b*]benzothiazole and 2-Aminobenzothiazole (VI)——A mixture of 7.0 g of 2-aminobenzothiazole (I) and 6.4 g of bromoacetone in 60 ml of ethanol was heated under reflux for 2 hr, and ethanol was removed by evaporation under reduced pressure. The resulitng residue was made alkaline with 5% sodium hydroxide solution, the product was taken up in benzene, and the extract was dried over anhydrous sodium sulfate. After evaporation of benzene, the remaining solid was recrystallized from ethanol. There was obtained 8.5 g (54%) of VI, mp 137°. Reported mp 125—127°.[5] NMR τ: 7.84 (singlet, $-C\underline{H}_3$), 4.00—4.30 (broad, $N\underline{H}_2$), 2.50—2.90 (multiplet, aromatic protons). UV λ_{max}^{EtOH} mμ (log ε): 221 (4.62), 252 (4.31), 286 (3.74), 295 (3.59). IR ν_{max}^{KBr} (cm^{-1}): 3200—2900 (NH), 1655 (C=N), 1600, 1500 (C=C). *Anal.* Calcd. for $C_{17}H_{14}N_4S_2$: C, 60.33; H, 4.17; N, 16.55. Found. C, 60.32; H, 4.30; N, 16.47.

N-(*m*-Chlorophenyl)-N-phenacyl-thiourea (VIIIb)——To a stirred solution of 7.9 g of *m*-chlorophenylisothiocyanate (VII) in 30 ml of benzene was added dropwise 8.0 g of ω-aminoacetophenone in 15 ml of benzene. There was obtained 13 g (90%) of VIIIb, mp 109—112°, after recrystallization from methanol. IR ν_{max}^{KBr} (cm^{-1}): 1680 (C=O), 1690 (benzene), 1540, 1460 (SCN). *Anal.* Calcd. for $C_{15}H_{13}ON_2SCl$: C, 59.11; H, 4.30; N, 9.19. Found. C, 58.94; H, 4.24; N, 9.10.

1-(*m*-Chlorophenyl)-2-mercapto-5-methylimidazole (IXa)——To a stirred solution of 3.4 g of *m*-chlorophenylisothiocyanate (VII) and 1 g of aminoacetone hydrochloride in 30 ml of benzene was added 2 g of triethylamine and the mixture was stirred for 1 hr on a water bath, and the reaction mixture was allowed to stand over night. After the separated triethylamine hydrochloride was filtered off, the filtrate was evaporated. There was separated 0.8 g (18%) of IXa, mp 197—200° (from methanol). NMR τ: 8.0 ($-C\underline{H}_3$), 3.4 (1H). IR ν_{max}^{KBr} (cm^{-1}): 3000, 2900, 1615 (C=N). Mass spectrum: M^+ 224. *Anal.* Calcd. for $C_{10}H_9N_2SCl$: C, 53.45; H, 4.04; N, 12.47. Found: C, 53.75; H, 4.35; N, 12.45.

1-(*m*-Chlorophenyl)-2-mercapto-5-phenylimidazole (IXb)——A solution of 13.0 g of VIIIb in 80 ml of 4N hydrochloric acid was heated under reflux. After cooling the separated crystals were resolved in methanol and neutralized with 10% sodium hydroxide. There was obtained 8.5 g (70%) of IXb as colorless needles, mp 260° (from methanol). IR ν_{max}^{KBr} (cm^{-1}): 3150 (NH), 1600 (phenyl). *Anal.* Calcd. for $C_{15}H_{11}N_2SCl$: C, 62.80; H, 3.87; N, 9.77. Found. C, 62.78; H, 4.00; N, 10.01.

13) N.P. Buu-Hoi, Nguyen-Dat-Xuong, and Ta-Thu-Cuc, *Bull. Soc. Chim. France*, **1966**, 1277 [*C.A.*, **65**, 7164a (1966)].

14) All temperatures are uncorrected. NMR spectra were recorded at 60 Mc with a Hitachi-Perkin H-60 spectrometer. Mass spectra were taken with a Japan Electron Optics JMS-OlS mass spectrometer operating with continuous ionization, and samples were introduced with a direct inlet system.

N-(*m*-Chlorophenyl)-N-(*β*,*β*-diethoxyethyl)-thiourea (XIIb)——To a stirred solution of 10.8 g of *m*-chlorophenyl isothiocyanate in 40 ml of benzene, 8.5 g of 2-aminoacetaldehyde diethylacetal in 20 ml of benzene was added under ice cooling. After heating under reflux for 45 min, there was obtained 16 g (88%) of XIIb, mp 51—53° (from benzene-hexane) as white needles. *Anal.* Calcd. for $C_{15}H_{19}O_2N_2SCl$: C, 51.56; H, 6.32; N, 9.25. Found: C, 51.31; H, 6.35; N, 9.43.

3-Phenylimidazo[2,1-*b*]benzothiazole (XI)——To a stirred solution of potassium amide in liquid ammonia (prepared from 1.68 g of potassium and 200 ml of liquid ammonia) 8.0 g of IXb was added. After stirring for 3 hr at −50°, there was added ammonium chloride and was evaporated the ammonia. The resulted residue was extracted with chloroform and recrystallized from benzene to yield 3.6 g (68%) of XI as white needles, mp 165°. IR ν_{max}^{KBr} (cm^{-1}): 1620 (C=N), 1600, 1580 (phenyl). Mass spectrum: M^+ 250. *Anal.* Calcd. for $C_{15}H_{10}N_2S$: C, 71.97; H, 4.03; N, 11.20. Found: C, 71.67; H, 4.02; N, 11.15.

1-(*m*-Chlorophenyl)-2-mercaptoimidazole (XIIIb)——A solution of 13.0 g of XIIb in 75 ml of 4N hydrochloric acid and 75 ml of ethanol was heated on a water bath for 2 hr. After removal of the solvent, the residue was neutralized with 5% sodium hydroxide and extracted with methylene chloride. The evaporation of the dried solution gave 6.5 g (73%) of XIIIb as white needles, mp 159—160° (from ethanol). *Anal.* Calcd. for $C_9H_7N_2SCl$: C, 51.31; H, 3.35; N, 13.30. Found: C, 51.28; H, 3.45; N, 13.68.

Imidazo[2,1-*b*]benzothiazole (XVI)——To a stirred solution of potassium amide in liquid ammonia (prepared from 1 g of potassium and 200 ml of liquid ammonia) 5 g of XIIIb was added. After treatment in the same way as described in the preparation of XI, a crude substance was chromatographed on silica gel and eluted with chloroform-acetone (4:1). There was obtained 1.65 g (40%) of XVI as white needles, mp 43—45°. *Anal.* Calcd. for $C_9H_6N_2S$: C, 62.05; H, 3.47; N, 16.08. Found: C, 61.93; H, 3.44; N, 15.87.

Oxidation of 1-Phenyl-2-mercaptoimidazole (XIIIa) with Potassium Ferricyanide——To a solution of 30 g of potassium ferricyanide in 60 ml of water, a solution of 8 g of XIIIa in 30 ml of 5% sodium hydroxide was added dropwise with stirring. Separated crystals were collected by the filtration and recrystallized from chloroform to obtain 4.4 g (55%) of XIV mp 146—148° as white needles. Mass spectrum: M^+ 350. *Anal.* Calcd. for $C_{18}H_{14}N_4S_2$: C, 61.69; H, 4.03; N, 15.99. Found: C, 61.83; H, 3.92; N, 16.05.

2-Oxo-3-alkyl-2,3-dihydro-imidazo[2,1-*b*]benzothiazole (XVIIa,b,c)——A mixture of 0.05 mole of 2-aminobenzothiazole, 0.05 mole of potassium hydroxide, and 0.05 mole of 2-bromoaliphatic acid in 40—50 ml of ethanol was heated under reflux for 3 hr. After evaporation of the solvent, separated sirup was heated with acetic anhydride in pyridine for 0.5—1 hr. After cooling the reaction mixture was poured into ice-water and precipitated material was collected and recrystallized from ethanol. Data of XVIIa,b,c are summarized in the Table I.

Table I. 2-Oxo-3-alkyl-2,3-dihydro-imidazo [2,1-*b*]benzothiazole (XVIIa,b,c)

Compound	R	mp (°C)	Yield (%)	IR ν_{max}^{KBr} (cm^{-1}) CO		C=N
XVIIa	H	210—212	45	1700	1600	1480
XVIIb	CH_3	183—185	43	1700	1600	1550
XVIIc	C_2H_5	179—181	42	1680	1600	1550

Compound	UV λ_{max}^{EtOH} mμ (log ε)			Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
XVIIa	217 (4.46	283 3.82	309 4.24)	$C_9H_6ON_2S$	56.83	3.18	14.73	56.64	3.19	14.40
XVIIb	221 (4.33	274 4.16	298 3.97)	$C_{10}H_8ON_2S$	58.80	3.95	13.72	58.76	3.82	13.68
XVIIc	220 (4.40	275 4.22	298 4.04)	$C_{11}H_{10}ON_2S$	60.53	4.62	12.83	60.74	4.60	12.79

2-Imino-3-substituted-2,3-dihydrobenzothiazole (XVIIIa,b,c) (Table II) and 2-Substituted-imidazo[2,1-*b*]-benzothiazole (XIXa,b,c) (Table III)——A mixture of 0.05 mole of 2-aminobenzothiazole and 0.05 mole of phenacyl bromide in ethanol was heated under reflux for 0.5—1 hr. After evaporation of the solvent, re-

sidual material was neutralized with 10% sodium hydroxide. Separated crystals (XVIIIa,b,c) were recrystallized from hexane–chloroform.

Heating of XVIIIa,b,c under reflux in ethanol for 1 hr, XIXa,b,c were separated quantitatively.

Table II. 2-Imino-3-substituted-2,3-dihydrobenzothiazole (XVIIIa,b,c)

Compound	X	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
XVIIIa	H	145—146.5	60	$C_{15}H_{12}ON_2S$	67.14	4.51	10.44	67.23	4.37	10.21
XVIIIb	Cl	182—184	55	$C_{15}H_{11}ON_2SCl$	59.50	3.66	9.25	59.64	3.58	9.04
XVIIIc	Br	182—183	56	$C_{15}H_{11}ON_2SBr$	51.89	3.19	8.07	51.77	3.14	7.97

Table III. 2-Phenylimidazo[2,1-*b*]benzothiazoles (XIXa,b,c)

Compound	X	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
XIXa	H	110[a]	95	$C_{15}H_{10}N_2S$	71.97	4.03	11.19	71.71	3.92	11.06
XIXb	Cl	164—165[b]	93	$C_{15}H_9N_2SCl$	63.27	3.19	9.84	63.40	2.96	10.03
XIXc	Br	166—167[c]	93	$C_{15}H_9N_2SBr$	54.72	2.76	8.51	54.82	2.77	8.51

a) Reported mp100°.[4] *b*) Reported mp 159°.[13] *c*) Reported mp 161°.[13]