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

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Imidazo[2,1-*b*]benzoxazoles which have a new ring system were synthesized. Condensation reaction of 2-aminobenzoxazole (I) and bromoacetone afforded 2-imino-3-(2-oxopropyl)-2,3-dihydrobenzoxazole (IIa). When phenacyl bromide was used instead of bromoacetone, 2-imino-3-phenacyl-2,3-dihydrobenzoxazole (IVa) was obtained. Cyclization of these imino-derivatives afforded imidazo[2,1-*b*]benzoxazoles.

On the other hand, imidazo[2,1-*b*]benzoxazole (XIII) was prepared from 1-(*o*-chlorophenyl)-2-hydroxyimidazole (XI) *via* benzyne intermediate.

The derivatives of imidazo[2,1-*b*]benzoxazole are interesting heterocyclic compounds possessing a new ring system which has not yet been reported in the literature. Recently, we reported the synthetic studies about imidazo[2,1-*b*]benzothiazoles[2] and thiazolo[2,3-*a*]-benzimidazoles.[4,5] In this report, we wish to report the preparation of imidazo[2,1-*b*]benzoxazoles and to compare with that of imidazo[2,1-*b*]benzothiazoles.

Treatment of 2-aminobenzoxazole (I) with α-bromoalkyl ketones in alcohol at room temperature for 2—5 days produced 2-imino-3-(2-oxoalkyl)-2,3-dihydrobenzoxazoles (II) as hydrobromide. When phenacyl bromides were used instead of bromoalkyl ketones in the reaction 2-imino-3-phenacyl-2,3-dihydrobenzoxazoles (IV) hydrobromide was obtained in good yield (Chart 1).

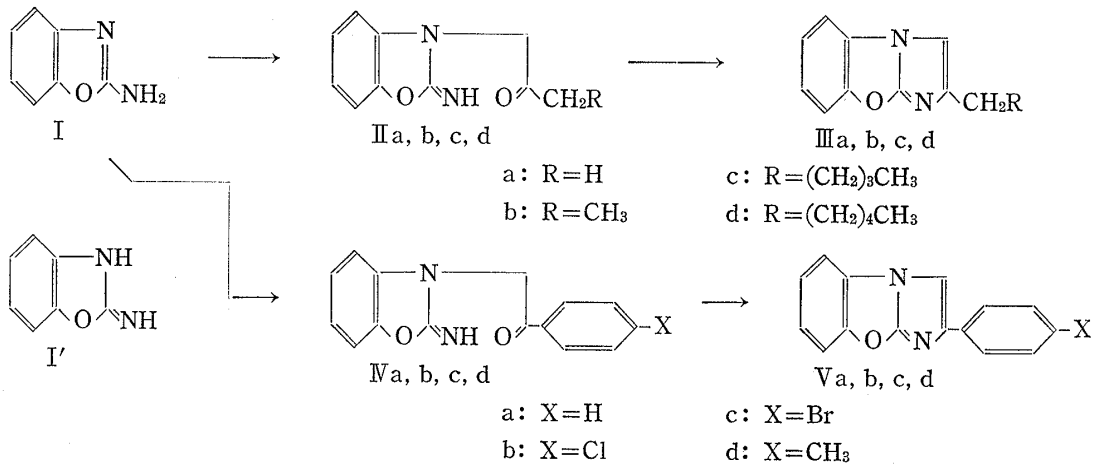
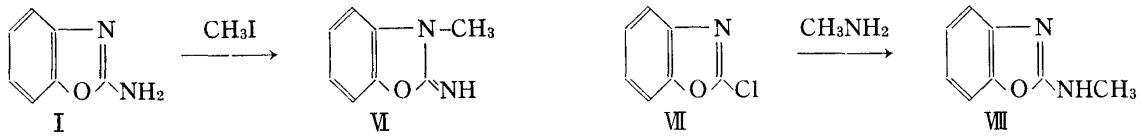


Chart 1

Since 2-aminobenzoxazole may have either amino-form (I) or imino-form (I'), there are two possibilities about the direction of the alkylation. On the similar reaction of 2-aminobenzothiazole, we confirmed that the alkylation occurred at the thiazole ring nitrogen.[2]

1) Presented before the 88th Annual Meeting of the Pharmaceutical Society of Japan, April 1968, p. 100.
2) Part VII: H. Ogura and T. Itoh, *Chem. Pharm. Bull.* (Tokyo), **18**, 1981 (1970).
3) Location: *Shirogane, Minato-ku, Tokyo, 108*, Japan.
4) H. Ogura, T. Itoh, and Y. Shimada, *Chem. Pharm. Bull.* (Tokyo), **16**, 2167 (1968).
5) H. Ogura, T. Itoh, and K. Kikuchi, *J. Heterocyclic Chem.*, **6**, 797 (1969).

Desai, *et al.*[6] reported that I was treated with methyl iodide to yield 2-imino-3-methyl-2,3-dihydrobenzoxazole (VI) (mp 96°) (Chart 2). On the other hand, 2-methylaminobenzoxazole (VIII) (mp 87—88°) was synthesized from 2-chlorobenzoxazole (VII) with methyl amine.[7] Mixing melting point comparison revealed a marked depression between VI and VIII. These experiments support that the alkylation of I occurred at the oxazole ring nitrogen, 2-aminobenzoxazole having the imino-form (I') in the reaction.

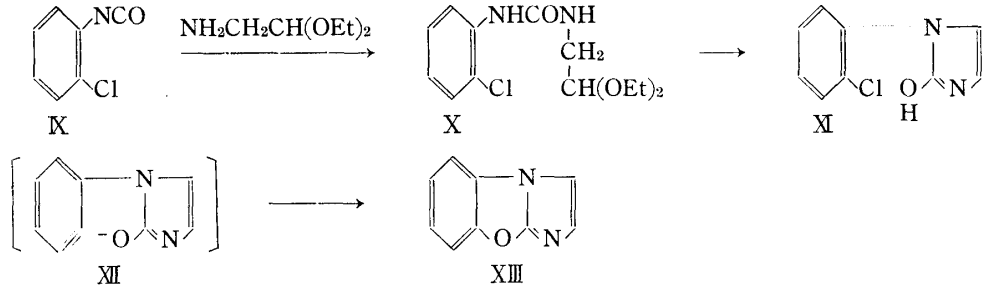


I VI VII VIII

Chart 2

This conclusion is further supported by the infrared (IR) spectrum. Sam, *et al.*[8] have reported that the C=N stretching absorption of the amino-form and the imino-form appeared at around 1690—1700 cm^{-1} in potassium bromide (KBr), and on the other hand, that in chloroform solution the C=N stretching absorption of the amino-form showed a shift to 1660—1665 cm^{-1}. The C=N stretching absorption of 2-imino-3-(2-oxopropyl)-2,3-dihydrobenzoxazole (IVa) in KBr was observed at 1695 cm^{-1}, and this absorption band was not shifted in chloroform solution.

Treatment of II or IV with polyphosphoric acid (PPA) caused cyclization to yield 2-alkyl imidazo[2,1-*b*]benzoxazoles (IIIa,b,c,d), or 2-aryl imidazo[2,1-*b*]benzoxazoles (Va,b,c,d) in 55—70% yield. The IR spectra of these compound show the absorptions due to C=N in the range of 1627—1640 cm^{-1} and those due to C–O–C linkage in the range of 1189—1215 cm^{-1}. Nuclear magnetic resonance (NMR) spectra indicate one proton at 2.65—3.12 τ and mass spectra show molecular ion (M^+) of each compounds (Table II).



IX X XI

XII XIII

Chart 3

When 1-(*o*-chlorophenyl)-2-hydroxyimidazole (XI), prepared from *o*-chlorophenylisocyanate (IX) by the similar method to the preparation of imidazo[2,1-*b*]benzothiazole,[2] was treated with potassium amide in liquid ammonia, imidazo[2,1-*b*]benzoxazole (XIII), mp 100.5°, was obtained in 42% yield. NMR spectrum reveals double doublet of two protons at 2- and 3-positions, and mass spectrum indicated M^+ 158.058 ($C_9H_6ON_2$, calcd. 158.048). This reaction clearly progressed through a benzyne intermediate (XII)[2,9] (Chart 3).

Experimental[10]

General Procedure of 2-Imino-3-(2-oxoalkyl)benzoxazole (IIa,b,c,d) and 2-Imino-3-(2-oxoaryl)benzoxazole (IVa,b,c,d) (Table I)——To a solution of 0.01 mole of 2-aminobenzoxazole (I) in ethanol was added 0.01 mole

6) R.D. Desai, R.F. Hunter, and A.R.K. Khalidi, *J. Chem. Soc.*, **1934**, 1186.
7) H. Ogura, S. Sugimoto, and K. Shimura, *Yakugaku Zasshi*, **90**, 796 (1970).
8) J. Sam, J.N. Plampin, and G.I. Poos, *J. Org. Chem.*, **23**, 1500 (1958).
9) J.F. Bunnett and F. Hrutfiord, *J. Am. Chem. Soc.*, **83**, 1691 (1961).
10) 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-01S mass spectrometer operating with continuous ionization, and samples were introduced with a direct inlet system.

of α-bromoalkyl ketones or *p*-substituted phenacyl bromides with stirring at room temperature for 2—5 days. The separated precipitate (HBr-salt) was collected by filtration and recrystallized from ethanol.

General Procedure of 2-Alkyl Imidazo[2,1-*b*]benzoxazoles (IIIa,b,c,d) and 2-Aryl Imidazo[2,1-b]benzoxazoles (Va,b,c,d) (Table II)——A solution of 0.01 mole of the salt (III or V) in 15 g of phosphorous pentoxide and 15 g of phosphoric acid, was heated at 120° under stirring for 3 hr. After cooling, the reaction mixture was poured into ice-water, and then was made alkaline by 10% sodium hydroxide. The separated crystals were collected by filtration, and recrystallized from hexane.

Table I. 2-Imino-3-substituted Benzoxazoles

Compound	R (X)	mp°C (decomp.)	Yield (%)	IR ν_{max}^{KBr} (cm^{-1})		Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IIa	H	229—231	90	1720	1695	$C_{10}H_{10}O_2N_2 \cdot HBr$	44.30	4.09	10.33	44.36	4.07	10.50
IIb	CH_3	211—212	82	1725	1692	$C_{11}H_{12}O_2N_2 \cdot HBr$	46.33	4.60	9.82	46.15	4.58	9.76
IIc	$(CH_2)_3CH_3$	218—219	75	1730	1692	$C_{14}H_{18}O_2N_2 \cdot HBr$	51.39	5.85	8.56	51.15	5.85	8.76
IId	$(CH_2)_4CH_3$	217—218	70	1730	1692	$C_{15}H_{20}O_2N_2 \cdot HBr$	52.80	6.20	8.21	52.79	6.03	8.23
IIIa	H	230—232	85	1710	1695	$C_{15}H_{12}O_2N_2 \cdot HBr$	54.07	3.93	8.41	54.33	3.62	8.66
IIIb	Cl	239—240	82	1705	1695	$C_{15}H_{11}O_2N_2Cl \cdot HBr$	45.54	3.06	7.08	45.85	3.20	7.21
IIIc	Br	240—241	83	1705	1688	$C_{15}H_{11}O_2N_2Br \cdot HBr$	43.72	2.94	6.80	43.55	2.66	6.51
IIId	CH_3	238—239	74	1705	1690	$C_{16}H_{14}O_2N_2 \cdot HBr$	55.35	4.35	8.07	55.34	4.16	8.04

Table II. 2-Substituted Imidazo[2,1-*b*]benzoxazoles

Compound	R (X)	mp°C (decomp.)	Yield (%)	IR ν_{max}^{KBr} (cm^{-1})		UV λ_{max}^{EtOH} mμ (log ε)
IIIa	H	92— 94	70	1630	1200	281.5 (3.83)
IIIb	CH_3	96— 97	58	1632	1215	282 (3.57)
IIIc	$(CH_2)_3CH_3$	50— 51	60	1640	1205	282.2 (3.65)
IIId	$(CH_2)_4CH_3$	56	65	1637	1210	282.3 (3.60)
Va	H	182—184	65	1630	1206	281.1 (4.40)
Vb	Cl	197—198	58	1630	1210	286.1 (4.33)
Vc	Br	190—191	60	1630	1210	286.7 (4.59)
Vd	CH_3	198—199	56	1627	1205	185.1 (4.46)

Compound	NMR (τ)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IIIa	3.12, s $CDCl_3$	$C_{10}H_8ON_2$	69.75	4.68	16.27	69.68	4.40	16.30
IIIb	2.75, s CF_3COOH	$C_{11}H_{10}ON_2$	70.95	5.41	15.04	71.20	5.22	15.20
IIIc	3.03, s, $CDCl_3$	$C_{14}H_{16}ON_2$	73.66	7.06	12.27	73.55	7.14	12.24
IIId	3.05, s, $CDCl_3$	$C_{15}H_{18}ON_2$	74.35	7.49	11.56	743.1	7.53	11.41
Va	2.87, s, CF_3COOH	$C_{15}H_{10}ON_2$	76.91	7.49	11.96	77.18	4.07	12.05
Vb	2.65, s, CF_3COOH	$C_{15}H_9ONjCl$	67.05	3.38	10.43	67.32	3.02	10.31
Vc	2.75, s, CF_3COOH	$C_{15}H_9ON_2Br$	57.53	2.90	8.95	57.71	2.81	8.67
Vd	2.75, s, CF_3COOH	$C_{16}H_{12}ON_2$	77.40	4.87	11.28	77.44	4.98	11.41

1-(*o*-Chlorophenyl)-2-hydroxyimidazole (XI)——To a solution of 10 g of *o*-chlorophenylisocyanate (IX) in 100 ml of benzene was added dropwise 9 g of aminoacetaldehyde diethylacetal in 100 ml of benzene. The reaction mixture was heated under reflux for 45 min. After cooling, the solvent was removed under reduced pressure to yield 11.2 g (60%) of N-(*o*-chloropyenyl)-N′-(ββ-diethoxyethyl)urea (X) as colorless plates, mp 95°. *Anal.* Calcd. for $C_{13}H_{19}O_3N_2Cl$: C, 54.45; H, 6.68; N, 9.77. Found: C, 54.30; H, 6.77; N, 9.54.

A solution of 5 g of X in 10 ml of 4N hydrochloric acid and 10 ml of ethanol was heated under reflux for 2 hr. After cooling, the solvent was removed under reduced pressure, and the residual solution was made alkaline with 5% sodium hydroxide and then extracted with chloroform. The chloroform solution was washed with water, dried and evaporated. There was obtained 2.7 g (80%) of XI as colorless plates, mp 188—190°. *Anal.* Calcd. for $C_9H_7ON_2Cl$: C, 55.54; H, 3.63; N, 14.40. Found: C, 55.66; H, 3.83; N, 14.41.

Imidazo[2,1-*b*]benzoxazole (XIII)——To a stirred solution of potassium amide in liquid ammonia (prepared from 1.5 g of potassium and 200 ml of liquid ammonia), 5.0 g of XI was added. After stirring for 3 hr at −50°, there was added ammonium chloride and then evaporated. The resulted residue was extracted from chloroform and recrystallized from hexane to yield 1.5 g (42%) of XIII as colorless leaflets, mp 100.5°. NMR τ ($CDCl_3$): 2.85 (d-d, J=7 cps). UV λ_{max}^{EtOH} mμ (log ε): 281.2 (3.61). IR ν_{max}^{KBr} (cm^{-1}): 1630, 1189. *Anal.* Calcd. for $C_9H_6ON_2$: C, 68.35; H, 3.82; N, 17.71. Found: C, 68.11; H, 3.87; N, 17.49.