[Chem. Pharm. Bull. 32(8)3053—3060(1984)]

A New Method for the Preparation of 2-(Alkylamino)benzoxazoles and 2-(Alkylimino)benzoxazolines

MASATOSHI YAMATO,* YASUO TAKEUCHI, KYOKO HATTORI, and KUNIKO HASHIGAKI

Faculty of Pharmaceutical Sciences, Okayama University, Tsushima-naka 1–1–1, Okayama 700, Japan

(Received December 9, 1983)

New syntheses of 2-(alkylamino)benzoxazoles (III) and 3-alkyl-2-(alkylimino)benzoxazolines (IV) were developed. Various compounds III were obtained by the reactions of 2-(methylthio)benzoxazole with amines. In the alkylation of 2-(monoalkylamino)benzoxazoles, the use of a base as a catalyst was found to be important for the selective preparation of 2-(*N,N*-dialkylamino)benzoxazoles; in the absence of base, IV was obtained. On the other hand, alkylation of *N,N'*-dialkyl-*N*-(2-hydroxyphenyl)thioureas resulted in the development of another method for the preparation of IV.

Keywords——2-(alkylamino)benzoxazole; 3-alkyl-2-(alkylimino)benzoxazoline; 2-(methylthio)benzoxazole; *N,N'*-dialkyl-*N*-(2-hydroxyphenyl)thiourea; 3-alkylbenzoxazoline-2-thione

As a continuation of our studies[1,2] on the reactivity of benzoxazoles having a hetero atom at position 2, we describe here new and convenient synthetic methods for 2-(alkylamino)benzoxazoles (III) and 3-alkyl-2-(alkylimino)benzoxazolines (IV).

Some analogs of III have hitherto been prepared by the reaction of 2-chlorobenzoxazoles,[3] 2-(alkylthio)benzoxazole *S,S*-dioxides,[4] or 2-mercaptobenzoxazoles[5] with an appropriate amine. However, these methods are somewhat troublesome, because 2-chlorobenzoxazoles and 2-(alkylthio)benzoxazole *S,S*-dioxides have to be prepared by comparatively tedious processes and are unstable compounds, and the reaction of 2-mercaptobenzoxazoles with amine generally requires prolonged heating.

By analogy with the reactivity[6] of 2-(methylthio)benzoxazole (I) with alcoholate to give 2-alkoxybenzoxazoles, the nucleophilic replacement of the methylthio group of I by an amino group might be expected. Indeed, 2-(benzylamino)-5-chlorobenzoxazole (IIIb)[7] was obtained in 85% yield simply by heating of 5-chloro-2-(methylthio)benzoxazole (Ia) with benzylamine. The structure of IIIb was established based on the doublet signal in its nuclear magnetic resonance (NMR) spectrum at 4.57 ppm ($J=6$ Hz), which was assigned to the methylene protons of the benzylamino group at the 2-position. This method using I seemed to be more convenient for the synthesis of III than reported methods in view of the stability, availability, and reactivity of the starting material (I).

As the reaction mechanism, nucleophilic substitution of the methylthio group of Ia with an amine (path A) was firstly considered. However, another mechanism (path B) which involved recyclization of the ring-opening intermediate, *N'*-benzyl-*N*-(5-chloro-2-hydroxyphenyl)-*S*-methylisothiourea (V), could not be ruled out, because Sasaki and co-workers recently reported[8] that the reaction of 2-(acylmethylthio)benzoxazoles with ammonium acetate in acetic acid afforded 2-[(2-hydroxyphenyl)amino]thiazoles.

Several analogs (IIIa—i) were prepared by the reaction of Ia with a corresponding amine (Table I). The reactions of Ia with primary amines in excess gave IIIa—e in high yields, but the yields of 2-(*N,N*-dialkylamino)-5-chlorobenzoxazoles obtained by the reactions of Ia with

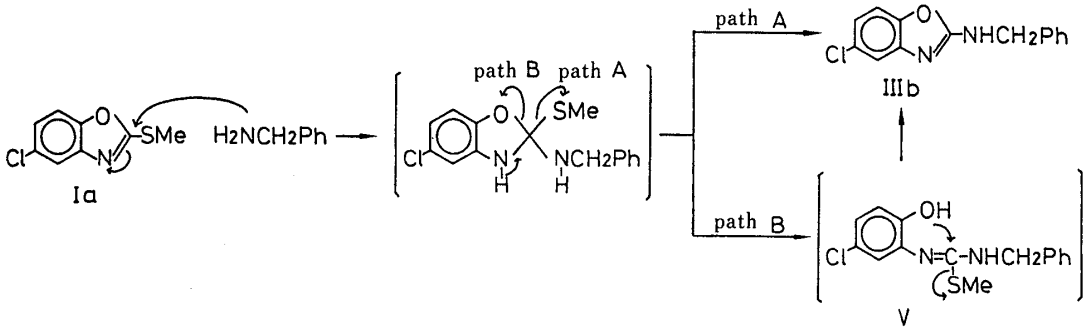
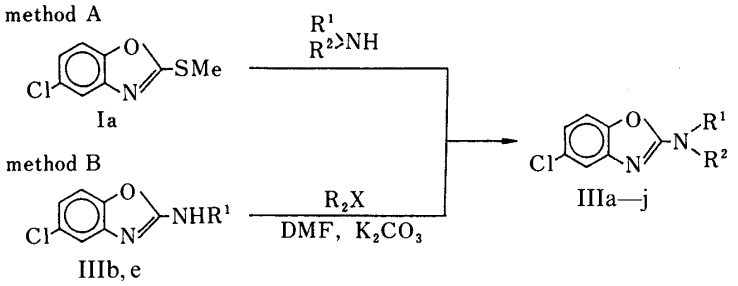


Chart 1

TABLE I. 2-Aminobenzoxazoles



R^1	$R^2(X)$	Method	R.T. (°C)[a]	R.T. (h)[b]	Product	Yield (%)
H	$CH_3CH_2CH_2CH_2$	A	78	2.5	IIIa	89
H	$PhCH_2$	A	100	4.0	IIIb	85
H	$HOCH_2CH_2CH_2$	A	100	0.5	IIIc	81
H	$Et_2NCH_2CH_2CH_2$	A	100	2.0	IIId	85
H	Ph	A	150	2.5	IIIe	82
$-CH_2CH_2OCH_2CH_2-$		A	129	2.5	IIIf	90
$PhCH_2$	Me	A	150	6.0	IIIg	69
$PhCH_2$	Me(I)	B	20	12.0	IIIg	91
$PhCH_2$	$PhCH_2$	A	120	29.0	IIIh	51
$PhCH_2$	$PhCH_2$(Cl)	B	20	15.0	IIIh	96
Ph	$PhCH_2$	A	120	29.0	IIIi	14
Ph	$PhCH_2$(Cl)	B	20	17.0	IIIi	89
Ph	$PhCH_2CH_2$(Br)	B	20	12.0	IIIj	65

a) Reaction temperature. *b*) Reaction time.

secondary amines were not uniform and changed depending on the bulkiness and nucleophilicity of the amines. For example, 5-chloro-2-morpholinobenzoxazole (IIIf) or 2-(*N*-benzyl-*N*-methylamino)-5-chlorobenzoxazole (IIIg) was obtained in high yield by heating of Ia with the corresponding amine, whereas the yield of 5-chloro-2-(*N*,*N*-dibenzylamino)benzoxazole (IIIh) obtained by the reaction of Ia with dibenzylamine or that of 2-(*N*-benzyl-*N*-phenylamino)-5-chlorobenzoxazole (IIIi) obtained by the reaction of Ia with *N*-benzylaniline was poor even if the reaction time was prolonged to 29 h (Table I, method A).

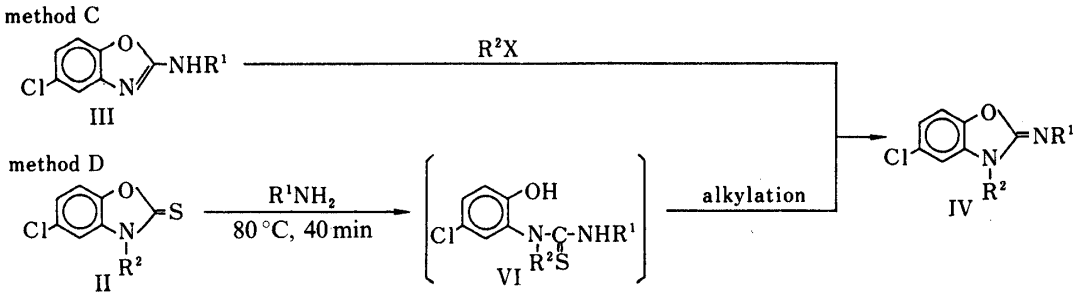
In order to find an improved method for the preparation of 2-(*N*,*N*-dialkylamino)-benzoxazoles (IIIg—i), which could not be obtained in satisfactory yields by method A, alkylation of 2-(alkylamino)benzoxazoles was examined. Namely, the reaction of IIIb with methyl iodide in *N*,*N*-dimethylformamide (DMF) in the presence of potassium carbonate gave IIIg in high yield (91%). Similarly, IIIh, IIIi, and 2-(*N*-benzyl-*N*-phenethylamino)-

5-chlorobenzoxazole (IIIj) were obtained in 96, 89, and 65% yields, respectively (Table I, method B). On the other hand, Sam and co-workers[9] also studied the alkylation of 2-(methylamino)benzoxazole (IIIk) and reported that the reaction of IIIk with methyl iodide in the absence of a base gives 3-methyl-2-(methylimino)benzoxazoline. Thus, the alkylation of III in the presence of a base occurs at the nitrogen atom of the 2-alkylamino group to give 2-(*N,N*-dialkylamino)benzoxazoles, while in the absence of a base it occurs at the nitrogen atom of the benzoxazole ring to give IV.

According to Sam's method, we prepared several analogs of 3-alkyl-2-(alkylimino)-5-chlorobenzoxazolines, IVa—c (Table III, method C). Furthermore, 7-chloro-3,4-dihydro-2*H*-pyrimido[2,1-*b*]benzoxazole (IVd) was prepared in 59% yield by method C through bromination of 5-chloro-2-(3-hydroxypropylamino)benzoxazole (IIIc) followed by cyclization without using a base. The resulting compounds were identified as either 2-(*N,N*-dialkylamino)benzoxazoles (III) or 3-alkyl-2-(alkylamino)benzoxazoles (IV) on the basis of spectral data. Namely, Sam and co-workers previously reported that the ultraviolet (UV) spectra of III and IV both showed a pair of absorption bands, but III gave a more intense absorption band at the shorter wavelength region, whereas IV gave a more intense absorption band at the longer wave length region. These findings were confirmed in the present work with the exception of 2-(*N*-arylamino)benzoxazoles (IIIi—j). Furthermore, we found that an absorption band due to the C=N bond in the benzoxazole ring of III generally appeared at a position of higher than 1710 cm^{-1}, while that of the imino group of IV generally appeared in the region below 1700 cm^{-1}. The structure of IVd was established on the basis of these spectral data (Table IV).

Unfortunately, 5-chloro-2-{[3-(*N,N*-diethylamino)propyl]imino}-3-methylbenzoxazoline (IVh), which was expected to have biological activity, could not be obtained by method C. The methylation of 5-chloro-2-[3-(*N,N*-diethylamino)propylamino]benzoxazole (IIId) with methyl iodide took place at the diethylamino group. Therefore, we looked for another method

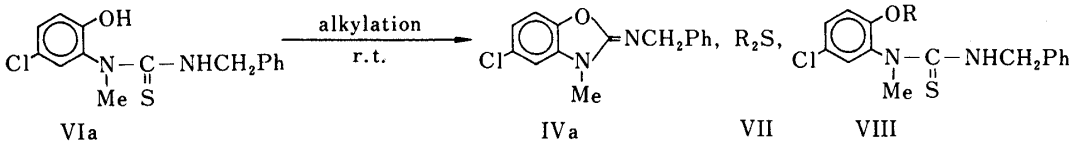
TABLE II. 3-Alkyl-2-(alkylimino)benzoxazolines



R^1	R^2 (X)	Method	R.T. (°C)[a]	R.T. (h)[b]	Alkylating conditions	Product	Yield (%)
$PhCH_2$	Me(I)	C	100	15	—	IVa	82
$PhCH_2$	Me	D	20	2	MeI, K_2CO_3, DMF	IVa	81
$PhCH_2$	$PhCH_2$(Cl)	C	100	15	—	IVb	80
$PhCH_2$	$PhCH_2$	D	20	2	MeI, K_2CO_3, DMF	IVb	58
$PhCH_2$	$PhCH_2CH_2$(Br)	C	100	48	—	IVc	74
$CH_3CH_2CH_2CH_2$	Me	D	20	2	MeI, K_2CO_3, DMF	IVe	90
$PhCH_2CH_2$	Me	D	20	2	MeI, K_2CO_3, DMF	IVf	84
Cyclohexyl	Me	D	20	2	MeI, K_2CO_3, DMF	IVg	59
$Et_2NCH_2CH_2CH_2$	Me	D	20	48	CH_2N_2, Et_2O, THF	IVh	70

a) Reaction temperature. *b*) Reaction time.

Table III. Alkylation of *N'*-Benzyl-*N*-(5-chloro-2-hydroxyphenyl)-*N*-methylthiourea (VIa)



VIa IVa VII VIII

Alkylating reagent	R	R.T. (h)[a]	Other conditions	Product (yield, %)		
				IVa	VII	VIII
MeI	Me	2	K_2CO_3, DMF	91	—	—
CH_2N_2	Me	4 d[b]	Et_2O, THF	63	—	10
DCC,[c] MeOH	Me	3 d	THF	54	—	7
Me_2SO_4	Me	2	$PhCH_2NEt_3 \cdot Cl$, 10% KOH, CH_2Cl_2	38	—	45
$PhCH_2Cl$	$PhCH_2$	10	K_2CO_3, DMF	22	14	65
$PhCH_2Cl$	$PhCH_2$	10	KI, K_2CO_3, DMF	76	83	—
$PhCH_2Br$	$PhCH_2$	10	K_2CO_3, DMF	93	78	—

a) Reaction time. *b*) Days. *c*) *N*, *N'*-Dicyclohexylcarbodiimide.

for the preparation of analogs of IV having an additional reactive site with alkyl halides, such as an amino group in the side chain.

Heating of 5-chloro-3-methylbenzoxazoline-2-thione (IIa)[10] with benzylamine at 80 °C for 40 min gave *N'*-benzyl-*N*-(5-chloro-2-hydroxyphenyl)-*N*-methylthiourea (VIa)[11] as a major product (73%) and IVa in a poor yield (9%). Conversion of VIa into IVa did not occur even on heating or in the presence of catalysis. On the basis of path B in the reaction of Ia with benzylamine giving IIIb (see Chart 1), it was considered that methylation of IVa to form the methylthio group might favor subsequent ring-closure to give IVa. Indeed, a variety of analogs of IV were successfully prepared from II *via* VI according to this method (Table II, method D).

When a soft alkylating agent such as methyl iodide was used in the reaction with VIa, IV was obtained in a high yield. However, it was found that an increase of the hardness of the alkylating agent resulted in an increased yield of the byproduct, *N*-(2-alkoxy-5-chlorophenyl)-*N'*-benzyl-*N*-methylthiourea (VIII), which is the *O*-alkylated derivative of IVa. These results are summarized in Table III. By means of this method, IVh was synthesized in 70% yield by the reaction of IIa with excess 3-(*N*,*N*-diethylamino)propylamine followed by treatment of the reaction mixture with diazomethane.

Experimental

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. NMR spectra were taken on a Hitachi R-24 spectrometer at 60 MHz. Mass spectra (MS) were recorded on a Shimadzu LKB-9000 spectrometer, and infrared (IR) absorption spectra on a Nippon Bunko A-102 spectrometer.

General Procedure for the Preparation of 2-(Alkylamino)- or 2-(*N*,*N*-Dialkylamino)-5-chlorobenzoxazole—— Method A: A mixture of Ia (1 g) and an amine (3—5 ml) was heated under the conditions shown in Table I. Purification of the mixture by recrystallization or column chromatography gave the corresponding IIIa—i.

Method B: A mixture of IIIb or IIIe (1 g) and an alkyl halide (2—4 eq) in dry DMF (10 ml) was stirred at room temperature for the time shown in Table I. The mixture was poured into ice-water and extracted with AcOEt. The AcOEt layer was washed with water, dried, and concentrated. Column chromatography of the residue gave the corresponding IIIg—j.

The Reactions of *N'*-Benzyl-*N*-(5-chloro-2-hydroxyphenyl)-*N*-methylthiourea (VIa) with Alkylating Agents

With Methyl Iodide——A mixture of VIa (0.50 g), methyl iodide (0.5 g), and anhydrous K_2CO_3 (0.5 g) in dry DMF (5 ml) was stirred at room temperature for 2 h. The mixture was poured into ice water, then extracted with Et_2O. The Et_2O layer was washed with water, dried, and concentrated. The resulting residue was recrystallized from petr. ether to give 0.41 g (91%) of IVa.

With Diazomethane——A mixture of VIa (1.00 g), excess CH_2N_2 solution in Et_2O, and dry THF (100 ml) was allowed to stand for 4 d. Acetic acid was added to the solution until the yellow color of the solution disappeared, then the mixture was neutralized with 10% NaOH, and extracted with AcOEt. The AcOEt layer was washed with 10% HCl and brine, dried, and concentrated. Recrystallization of the residue from benzene gave 0.10 g (10%) of *N'*-benzyl-*N*-(5-chloro-2-methoxyphenyl)-*N*-methylthiourea (VIIIa), mp 182—183 °C. IR ν_{max}^{Nujol} cm^{-1}: 3340 (NH). ^{1}H-NMR ($CDCl_3$) δ: 3.63 (3H, s, NCH_3), 3.86 (3H, s, OCH_3), 4.88 (2H, d, J=5 Hz, NCH_2). MS *m/z*: 322 (M^++2), 320 (M^+). *Anal.* Calcd for $C_{16}H_{17}ClN_2OS$: C, 59.89; H, 5.34; N, 8.73. Found: C, 59.67; H, 5.16; N, 8.58. The aqueous layer was neutralized with 10% NaOH and extracted with AcOEt. The AcOEt layer was washed with water, dried, and concentrated. Recrystallization of the residue from petr. ether gave 0.56 g (63%) of IVa.

With Dicyclohexylcarbodiimide (DCC) and Methanol——A mixture of DCC (1.4 g) and MeOH (1 ml) in dry THF (20 ml) in the presence of a catalytic amount of CuCl was stirred at room temperature overnight, then VIa (1.00 g) was added. The mixture was further stirred for 72 h and filtered. The filtrate was diluted with Et_2O and the mixture was shaken with 10% HCl. The organic layer was washed with water, dried, and concentrated. Purification of the residue by column chromatography on silica gel eluting CH_2Cl_2 gave 0.07 g (7%) of VIIIa. The aqueous layer was neutralized with 10% NaOH and extracted with Et_2O. The Et_2O layer was washed with water, dried, and concentrated. The residue was chromatographed on silica gel, and elution with benzene gave 0.48 g (54%) of VIa.

With Dimethyl Sulfate——A mixture of IVa (1.00 g), dimethyl sulfate (1 g), and benzyltriethylammonium chloride (1 g) in 10% KOH (10 ml) and CH_2Cl_2 (20 ml) was stirred at room temperature for 2 h. The organic layer was concentrated. The residue was washed with Et_2O and recrystallized from CH_2Cl_2 to give 0.47 g (45%) of VIIIa. The Et_2O washing was extracted with 10% HCl and the aqueous layer was neutralized with 10% KOH then extracted with Et_2O. The Et_2O layer was washed with water, dried, and concentrated to give 0.34 g (38%) of IVa.

With Benzyl Chloride——Benzyl chloride (2 g) was added to IVa (2.00 g) in dry DMF (20 ml) in the presence of K_2CO_3 (2 g). After being stirred at room temperature for 10 h, the mixture was poured into ice water, then extracted with Et_2O. The Et_2O layer was shaken with 10% HCl. The aqueous layer was washed with Et_2O, then neutralized with 10% NaOH and extracted with AcOEt. The AcOEt layer was dried, washed with water, and concentrated to give 0.40 g (22%) of VIa. The combined Et_2O layer was washed with water, dried, and concentrated. The resulting residue was chromatographed on a column of silica gel with petr. ether to give 0.20 g (14%) of dibenzyl sulfide (VII), which was identical with an authentic sample by comparison of the NMR spectra. Further elution with AcOEt gave 1.68 g (65%) of *N'*-benzyl-*N*-(2-benzyloxy-5-chlorophenyl)-*N*-methylthiourea (VIIIb), mp 124—125 °C (from a mixture of benzene and cyclohexane). IR ν_{max}^{Nujol} cm^{-1}: 3320 (NH). ^{1}H-NMR (in $CDCl_3$) δ: 3.63 (3H, s, NCH_3), 4.88 (2H, d, J= 5 Hz, NCH_2), 5.13 (2H, s, OCH_2). MS *m/z*: 398 (M^++2), 396 (M^+). *Anal.* Calcd for $C_{22}H_{21}ClN_2OS$: C, 66.57; H, 5.33; N, 7.06. Found: C, 66.41; H, 5.48; N, 6.85.

With Benzyl Chloride in the Presence of Potassium Iodide——A mixture of VIa (1.00 g) and benzyl chloride (1 g) in dry DMF (10 ml) in the presence of anhydrous K_2CO_3 (1.5 g) and KI (1 g) was stirred at room temperature for 10 h, then poured into ice water, and extracted with Et_2O. The Et_2O layer was treated as described for the reaction of VIa with benzyl chloride to give 0.68 g (76%) of IVa and 0.58 g (83%) of VII.

With Benzyl Bromide——A mixture of VIa (2.00 g) and benzyl bromide (2.5 g) in dry DMF (20 ml) in the presence of anhydrous K_2CO_3 (2 g) was stirred at room temperature for 10 h, then poured into ice water, and extracted with Et_2O. The Et_2O layer was treated as described for the reaction of VIa with benzyl chloride to give 1.65 g (93%) of IVa and 1.09 g (78%) of VII.

General Procedure for the Preparation of 3-Alkyl-2-(alkylimino)benzoxazoline (IV)——Method C: A mixture of III and an appropriate alkyl halide (2—4 eq) was heated under the conditions shown in Table III, then the mixture was made basic with 10% NaOH and extracted with AcOEt. The AcOEt layer was washed with water, dried, and concentrated. Purification of the product was performed by column chromatography or recrystallization to give the corresponding IVa—c.

Method D: A mixture of II (1 g) and an amine (2—5 ml) was heated at 80 °C for 40 min, then neutralized with 10% HCl, and extracted with Et_2O. The Et_2O layer was washed with water, dried, and concentrated. Methyl iodide (2 eq) was added to the residue in dry DMF (10 ml) in the presence of anhydrous K_2CO_3. The mixture was stirred at room temperature for 2 h, then poured into ice water, and extracted with AcOEt. The AcOEt layer was washed, dried, and concentrated. The resulting residue was chromatographed on a silica gel column to give the corresponding IVa—c, e—g.

7-Chloro-3,4-dihydro-2*H*-primido[2,1-*b*]benzoxazole (IVd)——Bromine was added to a mixture of IIIc (0.50 g) and triphenylphosphine (1.0 g) in dry DMF (30 ml) with cooling until the color of the solution became yellow. The mixture was stirred at room temperature for 1 h, and then at 100 °C for 5 h. The mixture was poured into cold 10% HCl, washed with AcOEt, made basic with 10% NaOH, and extracted with Et_2O. The Et_2O layer was washed with water, dried, and concentrated. The resulting residue was recrystallized from Et_2O to give 0.26 g (59%) of IVd.

TABLE IV. Spectral Data for IIIa—j and IVa—h

Compound	mp (°C) or bp (°C/mmHg)	Formula	Analysis (%) Calcd (Found)			UV $\lambda_{max}^{CHCl_3}$ nm (log ε)	IR ν_{max}^{Nujol} cm^{-1}	^{1}H-NMR ($CDCl_3$) δ	MS (*m/z*)
			C	H	N				
IIIa	112—113	$C_{11}H_{13}ClN_2O$	58.80 (58.77	5.83 5.85	12.47 12.36)	—	1700	0.77—1.98 (7H, m), 3.51 (2H, t, J=7 Hz)	226 (M^++2), 224 (M^+)
IIIb	156—158[a]	$C_{14}H_{11}ClN_2O$	—	—	—	—	1670	4.57 (2H, d, J=6 Hz)[c]	—
IIIc	150—153	$C_{10}H_{11}ClN_2O$	52.99 (52.78	4.89 5.13	12.36 12.31)	—	1650	1.58—2.04 (1H, m), 3.21—3.75 (4H, m)	228 (M^++2), 226 (M^+)
IIId	73—75	$C_{14}H_{20}ClN_3O_2$	59.67 (59.65	7.15 7.30	14.91 14.77)	—	1680	1.04 (6H, t, J=7 Hz), 1.52—2.08 (2H, m), 2.58 (4H, q, J=7 Hz), 2.62 (2H, t, J=7 Hz), 3.59 (2H, t, J=6 Hz)	283 (M^++2), 281 (M^+)
IIIe	212—213[b]	$C_{13}H_9ClN_2O$	—	—	—	—	1640	—	246 (M^++2), 244 (M^+)
IIIf	115—117	$C_{11}H_{11}ClN_2O_2$	55.35 (55.16	4.65 4.78	11.74 11.52)	293 (4.04), 255 (4.14)	1635	3.61—4.03 (8H, m)	240 (M^++2), 238 (M^+)
IIIg	69—70	$C_{15}H_{13}ClN_2O$	66.06 (66.26	4.80 4.66	10.27 10.19)	294 (4.14), 257 (4.25)	1650	3.12 (3H, s), 4.79 (2H, s)	274 (M^++2), 272 (M^+)
IIIh	96—98	$C_{21}H_{17}ClN_2O$	72.30 (72.39	4.91 4.90	8.03 7.82)	294 (4.18), 257 (4.28)	1640	4.68 (4H, s)	350 (M^++2), 348 (M^+)
IIIi	80—84	$C_{20}H_{15}ClN_2O$	71.75 (71.59	4.52 4.76	8.37 8.55)	299 (4.29), 263 (4.13)	1620	5.19 (2H, s)	336 (M^++2), 334 (M^+)

IIIj	65—68	$C_{21}H_{17}ClN_2O$	72.30 (72.21	4.91 4.69	8.03 7.82)	298 (4.32), 261 (4.15)	1640	3.08 (2H, t, J=8 Hz), 4.29 (2H, t, J=8 Hz)	350 (M^++2), 348 (M^+)
IVa	58—60	$C_{15}H_{13}ClN_2O$	66.06 (66.04	4.80 4.81	10.27 10.21)	304 (4.10), 255 (3.91)	1720	3.28 (3H, s), 4.64 (2H, s)	274 (M^++2), 272 (M^+)
IVb	100—101	$C_{21}H_{17}ClN_2O$	72.30 (72.06	4.91 5.16	8.03 8.25)	304 (4.02), 256 (3.83)	1730	4.73 (2H, s), 4.94 (2H, s)	350 (M^++2), 348 (M^+)
IVc	74—76	$C_{22}H_{19}ClN_2O$	72.82 (72.77	5.28 5.03	7.72 7.61)	305 (4.06), 259 (3.87)	1730	3.02 (2H, t, J=6 Hz), 4.01 (2H, t, J=6 Hz), 4.70 (2H, s)	364 (M^++2), 362 (M^+)
IVd	123—126	$C_{10}H_9ClN_2O$	57.56 (57.38	4.35 4.08	13.43 13.15)	301 (3.91), 254 (3.72)	1720	1.80—2.28 (2H, m), 3.33—4.06 (4H, m)	210 (M^++2), 208 (M^+)
IVe	110—120/4	$C_{12}H_{15}ClN_2O$	60.37 (60.11	6.33 6.09	11.74 11.55)	306 (4.15), 259 (3.94)	1720	0.72—1.92 (7H, m), 3.27 (3H, s), 3.44 (2H, t, J=7 Hz)	240 (M^++2), 238 (M^+)
IVf	61—62	$C_{16}H_{15}ClN_2O$	67.01 (66.88	5.27 5.43	9.77 10.02)	305 (4.12), 259 (3.90)	1710	2.90 (2H, t, J=8 Hz), 3.19 (3H, s), 3.71 (2H, t, J=8 Hz)	288 (M^++2), 286 (M^+)
IVg	168—170	$C_{14}H_{17}ClN_2O$	63.51 (63.81	6.47 6.57	10.58 10.53)	307 (4.10), 261 (3.82)	1710	1.19—1.87 (10H, m), 3.26 (3H, s), 3.38—3.81 (1H, m)	266 (M^++2), 264 (M^+)
IVh (Picrate)	172—173	$C_{27}H_{28}ClN_9O_{15}$	43.01 (43.23	3.74 3.92	16.72 16.53)	—	1710	1.21 (6H, t, J=7 Hz),[c] 1.60—2.31 (2H, m), 2.96—3.45 (6H, m), 3.47—3.83 (5H, m)	—

a) Lit.[7] mp 136—139 °C. *b*) Lit.[12] mp 199 °C. *c*) d_6-DMSO.

Physical properties and analytical data for IIIa—j and IVa—h are given in Table IV.

References

1) M. Yamato, Y. Takeuchi, K. Hashigaki, and T. Hirota, *Chem. Pharm. Bull.*, **31**, 733 (1983).
2) M. Yamato, Y. Takeuchi, K. Hashigaki, K. Hattori, E. Muroga, and T. Hirota, *Chem. Pharm. Bull.*, **31**, 1733 (1983).
3) E. Hoggarth, *J. Chem. Soc.*, **1949**, 3311.
4) L. Katz and M. S. Cohen, *J. Org. Chem.*, **19**, 767 (1954).
5) T. P. Sycheva, I. D. Kiseleva, and M. N. Shchukina, *Khim. Geterotsikl Soedine*, **1966** (2), 205.
6) M. Yamato, Y. Takeuchi, K. Hattori, and K. Hashigaki, *Chem. Pharm. Bull.*, **31**, 3946 (1983).
7) J. Sam and J. M. Plampin, *J. Pharm. Sci.*, **5**, 538 (1964).
8) T. Sasaki, E. Itoh, and I. Shimizu, *Heterocycles*, **19**, 2119 (1982).
9) J. Sam, J. N. Plampin, and G. I. Poos, *J. Org. Chem.*, **23**, 1500 (1958).
10) A. Korczynski and Sr. Obarski, *Bull. Soc. Chim.*, **33**, 1823 (1923).
11) L. M. Shindarov, A. S. Galabov, D. S. Antonov, N. A. Neikova, K. A. Davidkov, V. D. Vasileva, V. B. Kalcheva, and D. S. Stoicheva, U. S. Patent 3846491 [*Chem. Abstr.*, **83**, 9577*q* (1975)].
12) J. F. Deck and F. B. Dains, *J. Am. Chem. Soc.*, **55**, 4986.