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A Novel Preparation and Reaction of 2,1-Benzisothiazole Derivatives[1]

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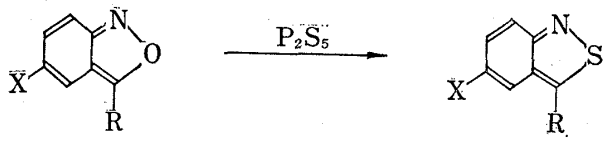
2,1-Benzisoxazole derivatives were converted into 2,1-benzisothiazoles simply by fusing with phosphorus pentasulfide in imidazole. 1-Alkyl-2,1-benzisothiazolium salts, prepared by alkylation of 2,1-benzisothiazoles with trialkyl orthoformates in the presence of Lewis acids, were shown to react with amines to afford 2,1-benzisothiazoline derivatives and with glycine ethyl ester to form a 1,4-benzodiazepin-2-one derivative by the extrusion of the sulfur atom.

In the preceding paper[3] several reactions of 2,1-benzisoxazolium salts with various nucleophiles were discussed. The results together with other interesting chemical properties of the 2,1-benzisoxazolium salts prompted us to investigate the synthesis and chemical properties of the sulfur analogues, 2,1-benzisothiazolium salts and 2,1-benzisothiazoles as well. 2,1-Benzisothiazoles appear to have received little attention for more than 70 years since the parent ring system was first prepared by Gabriel, *et al.*[4] It is only recently that a few methods have been reported for the preparation of 2,1-benzisothiazoles; the methods involve the treatment of *o*-toluidines with thionyl chloride[5] and the pyrolysis of 2-azidoarylthioketones.[6]

In this paper will be described a novel one-step synthesis of 2,1-benzisothiazole derivatives (**2**) from 2,1-benzisoxazoles (**1**) by fusing with phosphorus pentasulfide in imidazole and chemical properties of 1-alkyl-3-aryl-2,1-benzisothiazolium salts (**3**) obtained from these 2,1-benzisothiazoles (**2**) by alkylation with trialkyl orthoformates in the presence of Lewis acids.

Preparation of 2,1-Benzisothiazole Derivatives (2a—c)

We have found that 2,1-benzisoxazole derivatives (**1a—c**)[7] are converted easily into 2,1-benzisothiazoles (**2a—c**) by fusing with phosphorus pentasulfide in imidazole (Chart 1).



1a—c **2a—c**

	X	R
a :	Cl	C_6H_5
b :	Cl	$4\text{-}ClC_6H_4$
c :	H	C_6H_5

Chart 1

One-step conversion of isoxazole derivatives by treatment with phosphorus pentasulfide has never been reported.[8] Effort has been made to optimize the reaction conditions for the

1) A part of this paper was presented at the 92nd Annual Meeting of the Pharmaceutical Society of Japan, Osaka, April, 1972.
2) Location: *Juso-Nishinocho, Higashiyodogawa-ku, Osaka.*
3) Y. Nakagawa, O. Aki, and K. Sirakawa, *Chem. Pharm. Bull.* (Tokyo), **20**, 2209 (1972).
4) S. Gabriel and T. Posner, *Chem. Ber.*, **28**, 1028 (1895); S. Gabriel and R. Stelzner, *ibid.*, **29**, 160 (1896).
5) M. Davis and A.W. White, *Chem. Commun.*, **1968**, 1547; M. Davis and A.W. White, *J. Org. Chem.*, **34**, 2985 (1969).
6) J. Ashby and H. Suschitzky, *Tetrahedron Letters*, **1971**, 1315.
7) K. H. Wunsch and A.J. Boulton, "Advances in Heterocyclic Chemistry," Vol. 8, ed. by A.R. Katritzky and A.J. Boulton, Academic Press, Inc., New York and London, 1967, p. 303.
8) Some isothiazole derivatives were prepared from isoxazoles by the reductive ring opening to the enaminoketones, followed by treatment with P_2S_5 and an oxidizing agent.[9]

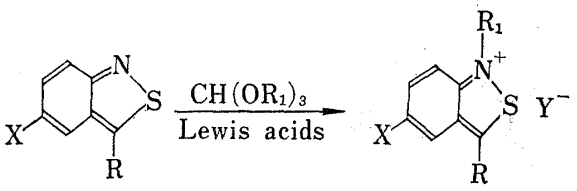
Table I. Preparation of 5-Chloro-3-phenyl-2,1-benzisothiazole (**2a**)

Exp. No.	1a (mole)	P_2S_5 (mole)	Medium (mole)	React. temp. (°C)	React. time (min)	Yield (%)
1	0.01	0.012	Me-Im[a] 0.02	150	15	8
2	0.01	0.02	Me-Im 0.05	150	15	15
3	0.01	0.03	Me-Im 0.05	150	15	31
4	0.01	0.06	Me-Im 0.05	150	15	10
5	0.01	0.03	Im[b] 0.05	120	15	54
6	0.01	0.03	diMe-Py[c] 0.05	150	15	45
7	0.01	0.03	pyridine 0.2	120	30	a trace
8	0.01	0.03	quinoline 0.15	200	5	a trace
9	0.01	0.03	toluene 0.2	120	30	a trace
10	0.01	0.03	xylene 0.2	150	30	a trace
11	0.01	0.03	tetraline 0.2	200	5	—
12	0.01	0.03	HMPT[d]	200	15	—

a) Me-Im: 2-methylimidazole
b) Im: imidazole
c) diMe-Py: 3,5-dimethylpyrazole
d) HMPT: hexamethylphosphoric triamide

preparation of 5-chloro-3-phenyl-2,1-benzisothiazole (**2a**) and to see the effect of other organic bases and solvents on this reaction. The results are summarized in Table I.

From Table I it is clear that the reaction takes place practically only in the presence of azoles and the maximum yield was obtained when a mixture of **1a** (0.01 mole), P_2S_5 (0.03 mole) and imidazole (0.05 mole) was heated at 120° for 15 min. The structure of **2a—c** was established by the elemental analysis, and infrared (IR), ultraviolet (UV) and nuclear magnetic resonance (NMR) spectral data, and subsequent chemical conversions (see below).



2a, b **3a—e**

	X	R	R_1	Y
a	Cl	C_6H_5	CH_3	BF_4
b	Cl	4-ClC_6H_4	CH_3	BF_4
c	Cl	C_6H_5	C_2H_5	BF_4
d	Cl	H	CH_3	BF_4
e	Cl	C_6H_5	CH_3	$SbCl_6$

Chart 2

At present we have no definite explanation for the special effect of imidazole in this reaction, although it should be noted that there are a few reports dealing with the effective use of azoles in some reactions.[10,11]

Preparation and Reactions of 1-Alkyl-2,1-benzisothiazolium Salts

Alkylation of 2,1-benzisothiazoles (**2a, b**) with trialkyl orthoformates in the presence of Lewis acids readily gave the 1-alkyl-2,1-benzisothiazolium salts (**3a—e**) as shown in Chart

9) D.N. McGregor, U. Corbin, J.E. Swigor, and L.C. Cheney, *Tetrahedron*, **25**, 389 (1969).
10) H.C. Beyerman and W.M. van den Brink, *Proc. Chem. Soc.*, **1963**, 266.
11) K. Meguro and Y. Kuwada, *J. Takeda Res. Lab.*, **30**, 9 (1971).

2. The reaction proceeded in most cases at the boiling temperature of toluene in the presence of boron trifluoride etherate or antimony pentachloride. The structure of the products was established by the elemental analysis and NMR spectra.

1-Alkyl-3-aryl-2,1-benzisothiazolium tetrafluoroborates (**3a, c**) were converted smoothly into 1-alkyl-3-aryl-3-dialkylamino-2,1-benzisothiazoline derivatives (**4a—c**) upon treatment with secondary amines in methylene chloride as was described with 1-alkyl-3-aryl-2,1-benzisoxazolium salts in the preceding paper.[3] On the other hand, the reaction of a primary amine ($R_3=CH_3$) with **3c** resulted in the formation of an unexpected compound. From the elemental analysis the product was shown to contain no sulfur atom and the azomethine structure (**6**, $R_3=CH_3$) was given to the product on the basis of IR and NMR spectra. Acid hydrolysis of **6** ($R_3=CH_3$) to 2-ethylamino-5-chlorobenzophenone (**7**)[12] confirmed the proposed structure.

The extrusion of the sulfur atom from this type of compound has not so far been reported and it is reasonable to assume that the sulfur atom was extruded from the compound (**5**, $R_3=CH_3$) which was perhaps formed initially by the nucleophilic attack of the primary amine as depicted in Chart 3.

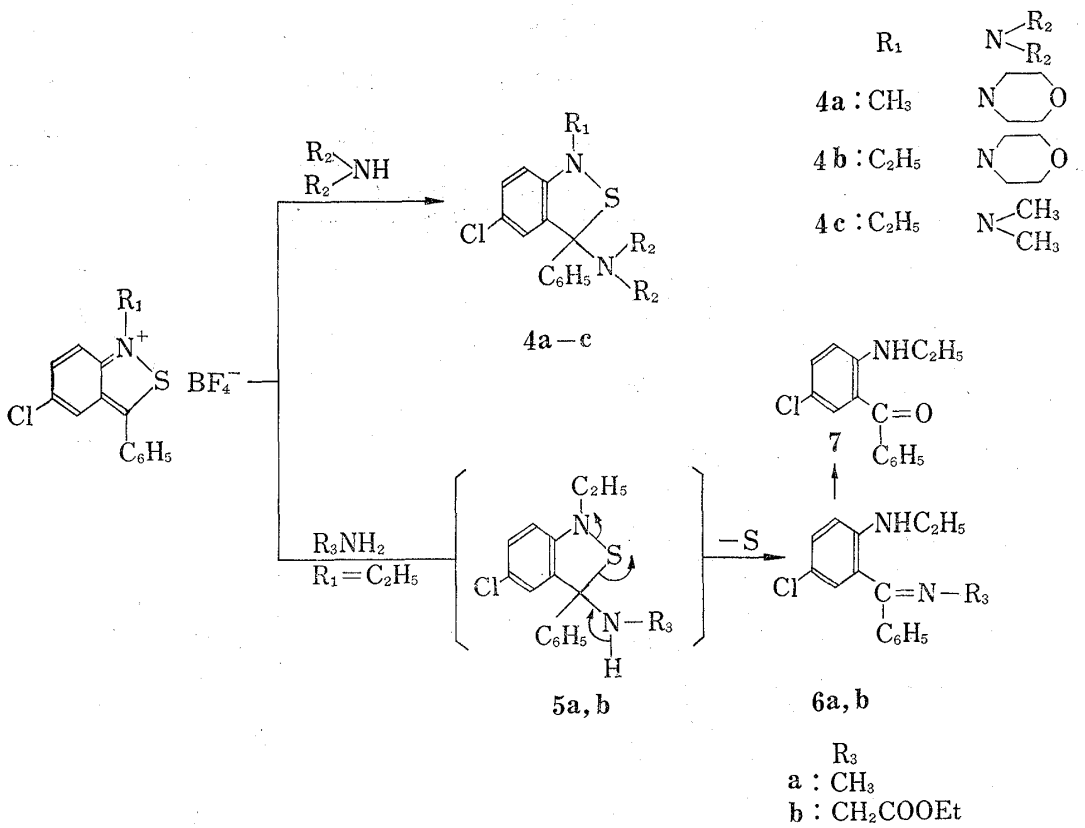


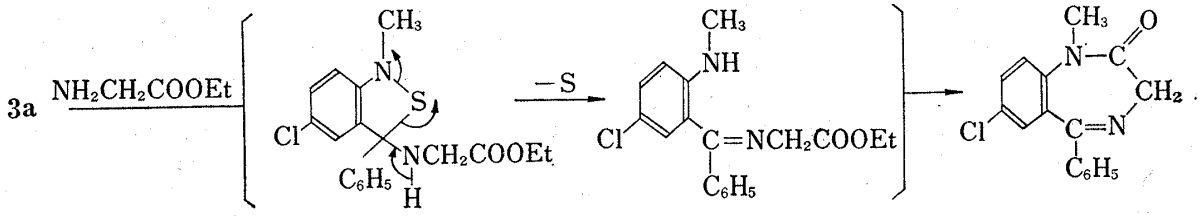
Chart 3

Another primary amine, glycine ethyl ester, gave the corresponding azomethine derivative (**6b**, $R_3=CH_2COOC_2H_5$) upon reaction with 5-chloro-1-ethyl-3-phenyl-2,1-benzisothiazolium tetrafluoroborate (**3c**). Acid hydrolysis of **6b** ($R_3=CH_2COOC_2H_5$) to the known compound **7**[12] confirmed the structure.

Application of this new reaction established an alternative one-step synthesis of 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**10**), a well-known tranquilizer,

12) L.H. Sternbach, R.I. Fryer, W. Metlesics, G. Sach, and A. Stempel, *J. Org. Chem.*, **27**, 3781 (1962).

which is otherwise obtainable by a stepwise synthesis.[13] Thus the reaction of **3a** with glycine ethyl ester in imidazole gave **10** in 47% yield. It may be pertinent to assume from the reactions shown in Chart 3 that the formation of **10** proceeds through the intermediates **8** and **9** (Chart 4).



8 9 10

Chart 4

Experimental[14]

5-Chloro-3-phenyl-2,1-benzisothiazole (**2a**)——A mixture of 5-chloro-3-phenyl-2,1-benzisoxazole (**1a**, 16.3 g), P_2S_5 (49 g) and imidazole (25 g) was heated at 120° for 15 min with vigorous stirring. The dark oily mixture was taken up in AcOEt after treating with 10% aq. NaOH solution, and the AcOEt layer was washed with water and dried over $MgSO_4$. The oily material obtained after evaporaion of the solvent *in vacuo* was dissolved in concentrated hydrochloric acid and the insoluble substances were filtered off. The filtrate was poured into water and allowed to stand overnight in a refrigerator. The precipitated solid was collected and recrystallized from dilute EtOH to give 9.65 g of **2a** (54%), mp 86—88°. *Anal.* Calcd. for $C_{13}H_8NSCl$: C, 63.54; H, 3.28; N, 5.70; S; 13.04. Found: C, 63.53; H, 3.12; N, 5.40; S, 13.26. UV $\lambda_{max}^{n\text{-hexane}}$ mu (ε): 221.5 (26170), 308 (7450) and 346 (9910).

5-Chloro-3-(4-chlorophenyl)-2,1-benzisothiazole (**2b**)——A mixture of 5-chloro-3-(4-chlorophenyl)-2,1-benzisoxazole (**1b**, 15.8 g) P_2S_5 (40.0 g) and imidazole (22.7 g) was heated at 130—140° for 5 min. The dark brown mixture was dissolved in a mixture of AcOEt and 10% aq. NaOH solution. The AcOEt layer was worked up to give crude product. Recrystallization from EtOH gave 1.3 g of **2b**, mp 113—115°. *Anal.* Calcd. for $C_{13}H_7NSCl_2$: C, 55.73; H, 2.51; N, 5.00; S, 11.44; Cl, 25.32. Found: C, 55.81; H, 2.48; N, 4.88; S, 11.54; Cl, 25.34.

3-Phenyl-2,1-benzisothiazole (**2c**)——A mixture of 3-phenyl-2,1-benzisoxazole (**1c**, 1.95 g), P_2S_5 (6.7 g) and imidazole (3.4 g) was heated at 120° for 15 min. The dark brown mixture was dissolved in a mixture of AcOEt and water. The AcOEt layer was washed with water. The oily product obtained after evaporation of the solvent *in vacuo* was dissolved in concentrated hydrochloric acid, and the insoluble substances were filtered off. The filtrate was poured into water and allowed to stand overngiht in a refrigerator. The oily product was chromatographed over 100 g of silica gel (Wakogel Q-23) using *n*-hexane–AcOEt (10:1) as eluent to yield 0.65 g of oily product (31%). *Anal.* Calcd. for $C_{13}H_9NS$: C, 73.90; H, 4.29; N, 6.62; S, 15.19. Found: C, 74.27; H, 4.28; N, 6.85; S, 14.32.

5-Chloro-1-methyl-3-phenyl-2,1-benzisothiazolium Tetrafluoroborate (**3a**)——Boron trifluoride etherate (46 g) was added in one portion to a solution of **2a** (21.4 g) and trimethyl orthoformate (46 g) in toluene (200 ml). The reaction mixture was heated under reflux for 8 hr and then evaporated to dryness *in vacuo*. To the residue was added ether and the mixture was allowed to stand overngiht at room temperature. The precipitated product was recrystallized from EtOH give 17.9 g (59.5%) of **3a**, mp 200—202°. *Anal.* Calcd. for $C_{14}H_{11}NSBClF_4$: C, 48.37; H, 3.18; N, 4.03; S, 9.22; Cl, 10.20. Found: C, 48.23; H, 3.05; N, 4.00; S, 9.44; Cl, 10.42.

5-Chloro-1-methyl-3-(4-chlorophenyl)-2,1-benzisothiazolium Tetrafluoroborate (**3b**)——Treatment of **2b** (6.0 g) with trialkyl orthoformate (10.0 g) and boron trifluoride etherate (8.5 g) in xylene (300 ml) under similar condition used for the preparation of **3a** gave the crude product. Recrystallization from EtOH gave 0.7 g of **3b** (9%), mp 213—215°. *Anal.* Calcd. for $C_{14}H_{10}NSBCl_2F_4$: C, 44.01; H, 2.63; N, 3.63. Found: C, 43.95; H, 2.74; N, 3.56.

5-Chloro-1-ethyl-3-phenyl-2,1-benzisothiazolium Tetrafluoroborate (**3c**)——Treatment of **2a** (23 g) with triethyl orthoformate (66.5 g) and boron trifluoride etherate (66.5 g) in toluene (150 ml) under similar

13) L.H. Sternbach, R.I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *J. Org. Chem.*, 27, 3788 (1962).

14) All melting points are uncorrected. IR spectra were obtained with a Hitachi-215 spectrophotometer and NMR spectra with a Varian A-100 spectrometer using TMS as internal standard. UV spectra were taken with a Perkin-Elmer 450 spectrophotometer.

condition used for the preparation of **3a** gave the crude product. Recrystallization from EtOH gave 12.4 g of **3c** (37%), mp 162—163°. *Anal.* Calcd. for $C_{15}H_{13}NSBClF_4$: C, 49.82; H, 3.62; N, 3.87. Found: C, 50.05; H, 3.45; N, 3.77. NMR (in d_6-DMSO): δ 1.66 (t, CH_3), 4.97 (q, CH_2) and 7.70—8.34 ppm (m, aromatic). UV λ_{max}^{MeOH} mμ (ε): 224.5 (21300), 303 (9900), and 385 (8900).

5-Chloro-1-methyl-2,1-benzisothiazolium Tetrafluoroborate (3d)——To a solution of 5-chloro-2,1-benzisothiazole[15] (9.3 g) and trimethyl orthoformate (10.6 g) in benzene (100 ml) was added boron trifluoride etherate (29.6 g) portionwise and the mixture was stirred at room temperature overnight. After removal of the solvent the residue was treated with a mixture of ether and EtOH. The separated solid was recrystallized from MeOH–ether to give 7.1 g of **3d** (47%), mp 184—186°. *Anal.* Calcd. for $C_8H_7NSBClF_4$: C, 35.39; H, 2.59; N, 5.15. Found: C, 35.41; H, 2.62; N, 5.05.

5-Chloro-1-methyl-3-phenyl-2,1-benzisothiazolium Hexachloroantimonate (3e)——Antimony pentachloride (6.0 g) was added portionwise to a solution of **2a** (2.45 g) and trimethyl orthoformate (2.12 g) in benzene (50 ml). The mixture was stirred at room temperature for 1 hr. The precipitated solid was collected and recrystallized from EtOH to give 3.4 g of **3e** (57%), mp >280°. *Anal.* Calcd. for $C_{14}H_{11}NSCl_7Sb$: C, 28.24; H, 1.86; N, 2.35. Found: C, 28.01; H, 2.09; N, 2.32.

5-Chloro-1-methyl-3-morpholino-3-phenyl-2,1-benzisothiazoline (4a)——A solution of **3a** (1.7 g) and morpholine (3.0 g) in CH_2Cl_2 (30 ml) was heated under reflux for 2 hr. The reaction mixture was washed with saturated aq. NaCl solution and dried over $MgSO_4$. The solvent was evaporated to dryness and the residue was recrystallized from EtOH to give 0.7 g of **4a** (50%), mp 133—134°. *Anal.* Calcd. for $C_{18}H_{19}ON_2SCl$: C, 62.32; H, 5.52; N, 8.07. Found: C, 62.06; H, 5.45; N, 8.11.

5-Chloro-1-ethyl-3-morpholino-3-phenyl-2,1-benzisothiazoline (4b)——A solution of **3c** (1.5 g) and morpholine (2.5 g) in CH_2Cl_2 (30 ml) was heated under reflux for 1.5 hr. The solution was then evaporated to dryness; the residue was crystallized from EtOH, giving 0.8 g of **4b** (60%), mp 101—103°. *Anal.* Calcd. for $C_{19}H_{21}ON_2SCl$: C, 63.23; H, 5.86; N, 7.76. Found: C, 63.70; H, 5.94; N, 7.89. NMR (in CCl_4): δ 1.32 (t, CH_3), 2.00—2.50 and 2.80—3.50 (m, morpholine), 3.35 (q, CH_2) and 6.50—8.10 ppm (m, aromatic).

5-Chloro-1-ethyl-3-dimethylamino-3-phenyl-2,1-benzisothiazoline (4c)——Gaseous dimethylamine was passed through a suspension of **3c** (3.6 g) in CH_2Cl_2 (50 ml) for 15 min at room temperature. Meanwhile the suspension changed to a clear solution which was then evaporated to dryness. The residual solid was recrystallized from dilute EtOH to give 2.85 g of **4c** (90%), mp 63—65°. *Anal.* Calcd. for $C_{17}H_{19}N_2SCl$: C, 64.03; H, 6.00; N, 8.78. Found: C, 64.01; H, 6.01; N, 8.61.

N-(5-Chloro-2-ethylamino-α-phenylbenzylidene)methylamine (6a, R_3=CH_3)——Gaseous methylamine (prepared from methylamine hydrochloride and concentrated NaOH solution) was passed through a suspension of **3c** (3.6 g) in CH_2Cl_2 (50 ml) at room temperature for 5 min. The solution thus obtained was washed with saturated aqueous NaCl solution and dried over $MgSO_4$. The oily product, after removal of the solvent *in vacuo*, was chromatographed over 150 g of silica gel (Wakogel Q-23) using ligroin–acetone (10:1) as eluent. Separation and recrystallization of the product from 80% EtOH gave 6a (R_3=CH_3), 1.47 g (54%), mp 92—94°. *Anal.* Calcd. for $C_{16}H_{17}N_2Cl$: C, 70.44; H, 6.28; N, 10.27. Found: C, 70.58; H, 6.25; N, 10.28. UV λ_{max}^{MeOH} mμ (ε): 252 (23900) and 313 (2450). Hydrolysis of **6a** in dilute hydrochloric acid solution led to the known compound **7**.[12]

Ethyl N-(5-Chloro-2-ethylamino-α-phenylbenzylidene)glycinate (6b, R_3=CH_2COOEt)——To a solution of **3c** (1.80 g) in CH_2Cl_2 (25 ml) was added glycine ethyl ester (1.0 g) and the mixture was heated under reflux for 30 min. The solution was washed with saturated aqueous NaCl solution and dried over $MgSO_4$. The oily product, after removal of the solvent *in vacuo*, was chromatographed over 100 g of silica gel (Wakogel Q-23) using *n*-hexane–acetone (10:1) as eluent. The product obtained was recrystallized from MeOH to give 1.0 g of **6b** (R_3=CH_2COOEt), mp 72—83°. (A mixture of syn- and anti-isomers). *Anal.* Calcd. for $C_{19}H_{21}O_2N_2Cl$: C, 66.17; H, 6.13; N, 8.12. Found: C, 66.12; H, 6.17; N, 8.19.

Heating an aqueous ethanolic solution of **6b** (R_3=CH_2COOEt) containing small amounts of HCl gave **7**, mp 54—55° which was identical with the authentic sample.[12]

7-Chloro-1-methyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (10)——To a solution of **3a** (7.0 g) in CH_2Cl_2 (150 ml) was added glycine ethyl ester (5.0 g). The mixture was stirred at room temperature overnight. After removal of the solvent *in vacuo*, 2-methylimidazole (10 g) was added to the residue and the mixture was heated at 160° for 30 min. To the reaction mixture was added a mixture of AcOEt (100 ml) and H_2O (100 ml), and the AcOEt layer was washed with water. The crude product obtained after evaporation of the solvent was dissolved in dilute hydrochloric acid and the solution was washed with AcOEt to remove insoluble matters. The acidic solution was then made alkaline with dilute aqueous $NaHCO_3$ solution to give crystalline material, which was recrystallized from iso-PrOH to give 2.65 g of **10** (47%), mp 129—130°. The compound was identical with an authentic sample.[15]

Acknowledgement The authors are grateful to Dr. K. Morita for his encouragemet throughout this work.

15) L.H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961).