[Chem. Pharm. Bull. 22(9)2051—2057(1974)] UDC 547.789.057 : 547.831.2.04 : 547.551.04

Studies on Organosulfur Compounds. XI.[1] Selective Cyclization to Benzothiazole by the Reaction between Quinaldine and *meta*-Substituted Anilines (or Nitro Compounds) under the Modified Willgerodt-Kindler Reaction[2]

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(Received February 4, 1974)

In order to clarify in more detail the cyclization mechanism of thioanilides to benzothiazoles under the modified Willgerodt-Kindler reaction condition, quinaldine (I) was heated with *meta*-substituted anilines (II) or meta-substituted nitrobenzenes (III) in the presence of sulfur. Further, in order to examine on solvent effects through these processes, dimethylformamide (DMF) was employed. Although the yields of these reactions were different, the reactions also gave similarly thioanilides and one of the two possible benzothiazoles. The latter was proved to have the structure of 5-substituted 2-(2-quinolyl)benzothiazoles (V) by independent synthesis. On the other hand, the expected two isomeric benzothiazoles (V and VI) were obtained from the oxidative cyclization of thioanilides (IV) by the modified Jacobson reaction. Moreover, the thioanilides obtained from I or 2-picoline were found to react with the corresponding II in the presence of sulfur in DMF at 160—170° to give the selective cyclization product, respectively.

Our previous papers[4,5] reported that the modified Willgerodt-Kindler reaction,[6] such as the reaction of 2-picoline or 4-picoline with *meta*-substituted anilines (II) in the presence of sulfur, afforded the corresponding thioanilides (IV) and unexpectedly, one of two isomeric benzothiazoles (V and VI), although an alternate possibility would involve that IV could cyclize to either the 2- or the 6-position of the aniline ring (Chart 1).

In order to study in more detail on such selectively cyclizing process, reactions of quinaldine (I) with *meta*-substituted anilines (or nitrobenzenes) in the presence of sulfur were submitted in this paper.

When a mixture of I and II (or III) was heated with sulfur at 165—170° in an oil bath for 10 hr, V (benzothiazole-type) was separated as one product from the reaction mixture along with IV (thioanilide-type). Subsequently, use of dimethylformamide (DMF) as a solvent in this reaction course resulted in that the yield of IV relatively increased, whereas that of V decreased as shown in Table I. The values of elemental analyses of these compounds agreed with the molecular formula of the thioanilides (IV) and the benzothiazoles (V), respectively.

Additionally, the authentic samples (Vb—c) prepared from the reactions of bis(4-substituted 2-nitrophenyl)disulfides (VIIb—c) with I in the presence of sulfur according to the previous papers[4,5] were identical with the products (V) described in Table I in all respects.

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[1] Part X: T. Hisano and Y. Yabuta, *Chem. Pharm. Bull.* (Tokyo), 22, 316 (1974).

[2] A part of this work was presented at the Kyushu Local Meeting of the Pharmaceutical Society of Japan, Kumamoto, December 1973.

[3] Location: *Oe-hon-machi, Kumamoto.*

[4] T. Hisano and Y. Yabuta, *Chem. Pharm. Bull.* (Tokyo), 21, 511 (1973); see also T. Hisano and Y. Yabuta, *Org. Prep. Proced. Int.*, 4 (3) 105 (1972).

[5] T. Hisano and M. Tamayama, *Yakugaku Zasshi*, 93, 1356 (1973).

[6] *a*) B. Emmert and M. Groll, *Chem. Ber.*, 86, 208 (1953); *b*) B. Emmert and A. Holz, *Chem. Ber.*, 87, 676 (1954); *c*) B. Emmert, *Chem. Ber.*, 91, 1388 (1958); *d*) H. Saikachi and T. Hisano, *Chem. Pharm. Bull.* (Tokyo), 7, 349, 716 (1959).

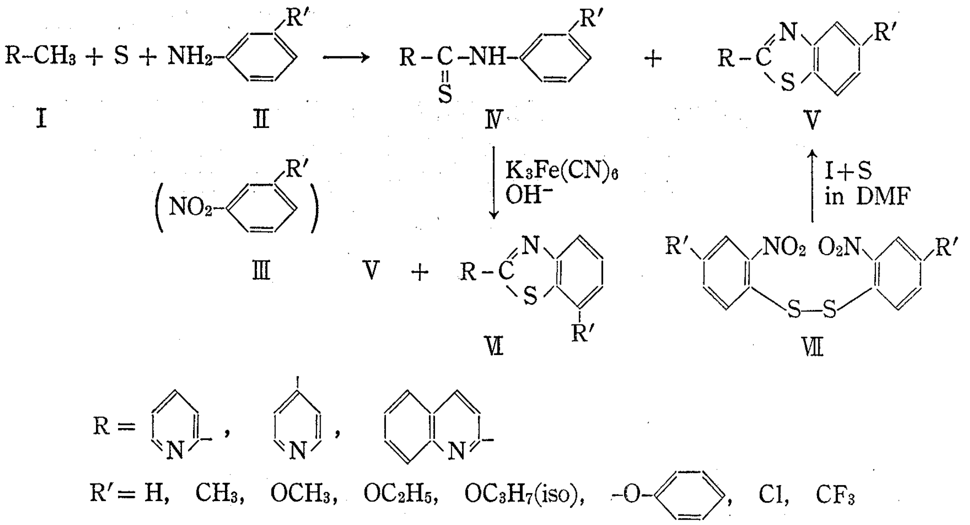
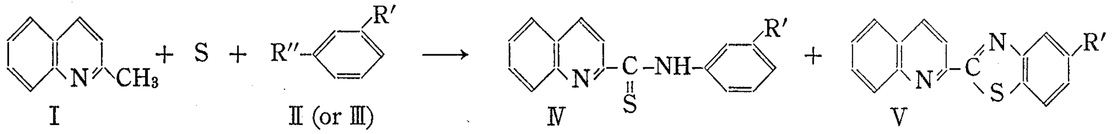


Chart 1

Table I. Yields and Analytical Data of IV and V



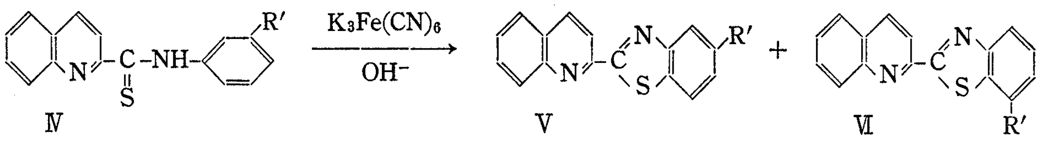
Series	Starting material R''	Starting material R'	Solvent	Yield (%)[a] IV	Yield (%)[a] V
a	NH_2	H	—	38.2	17.1
	NH_2	H	DMF	37.9	5.6
	NO_2	H	—	9.5	—
	NO_2	H	DMF	28.3	—
b	NH_2	CH_3	—	10.8	34.4
	NH_2	CH_3	DMF	31.7	20.7
	NO_2	CH_3	—	trace	5.4
	NO_2	CH_3	DMF	12.2	5.8
c	NH_2	Cl	—	13.1	trace
	NH_2	Cl	DMF	13.8	trace
	NO_2	Cl	—	6.7	9.5
	NO_2	Cl	DMF	37.3	9.5

Compd. No.	mp (°C)	Appearance ( ): recryst. solvent	Formular	Analysis (%) Calcd. (Found) C	H	N
IVa	109—110	orange prisms	$C_{16}H_{12}N_2S$	72.70	4.58	10.60
		(EtOH)		(72.59)	(4.48)	(10.76)
IVb	116—117	orange needles	$C_{17}H_{14}N_2S$	73.35	5.07	10.06
		(EtOH)		(73.35)	(4.90)	(10.13)
IVc	140—141	orange needles	$C_{16}H_{11}N_2SCl$	64.32	3.71	9.38
		(EtOH)		(64.16)	(3.58)	(9.50)
Va	200—201	colorless prisms	$C_{16}H_{10}N_2S$	73.26	3.84	10.68
		(benzene)		(73.34)	(3.66)	(10.89)
Vb	236—237	colorless plates	$C_{17}H_{13}N_2S$	73.88	4.38	10.14
		(benzene)		(73.87)	(4.18)	(10.22)
Vc	271—272	colorless plates	$C_{16}H_9N_2SCl$	64.75	3.06	9.44
		(benzene)		(64.98)	(2.94)	(9.42)

a) calculated on the basis of quinaldine (I)

Thus, the product (V) was established as 5-substituted 2-(2-quinolyl)benzothiazole. This fact suggests that the cyclization from the thioanilide (IV) to the benzothiazole could occur selectively at the position-*para* to the substituent on the aniline ring to give solely the product (V), even by using nitrobenzene series expected as the oxidative cyclization[7] under the modified Willgerodt-Kindler reaction condition and DMF as a solvent.

TABLE II. Results of Oxidative Cyclization of IV



Starting material Compd. No.	R'	V Compd. No.	V Yield[a] (%)	V mp (°C)	VI Compd. No.	VI Yield[a] (%)	VI mp (°C)	Recovery of IV (%)
IVa	H	Va	66.0	200—201				5.7
IVb	CH_3	Vb	16.1	236—237	VIb	30.4	171—172	12.6
IVc	Cl	Vc	15.1	270—271	VIc	30.0	213—215	26.7

Compd. No.	mp (°C)	Appearance ( ): recryst. solvent	Formula	Analysis (%) Calcd. (Found) C	H	N
VIb	171—172	Colorless needles	$C_{17}H_{12}N_2S$	73.88	4.38	10.14
		(benzene)		(73.72)	(4.31)	(10.09)
VIc	213—215	Colorless needles	$C_{16}H_9N_2SCl$	64.75	3.06	9.44
		(EtOH)		(64.75)	(2.93)	(9.51)

a) calculated on the basis of IV

On the other hand, Mizuno and Adachi[8] reported in detail the mechanism for the cyclization of thioanilides in the modified Jacobson method, its scope, and limitations. It could also be expected in a similar manner as above that two isomers would be formed from IV by the alternative orientation cyclizing to either the 2- or the 6-position of the aniline ring in the oxidative cyclization by the Jacobson method. The products obtained from this method were clearly different from the result obtained under the modified Willgerodt-Kindler reaction condition. The oxidative products were presumed to be a mixture of two isomers of the corresponding benzothiazoles and the two isomers were consequently isolated from the oxidative products by the silica gel column chromatography and submitted to elemental analysis, results of which are given in Table II. One of them was identical with V by mixed melting point and infrared (IR) spectral comparison, and the other isomer would be 7-substituted 2-(2-quinolyl)benzothiazoles (VI) from the values of elemental analysis, the similarity of IR, and ultraviolet (UV) spectra. From these facts, the ring closure of IV with potassium ferricyanide occurred at the position-*para* and -*ortho* both to the substituent on the aniline ring, and always cyclizing to the position-*ortho* was superior to that to the position-*para*. The above results clearly suggested that mechanism different from that of the modified Jacobson

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[7] K. Ziegler and H. Zeiser, *Ann.*, **485**, 174 (1931); see also H.T. Clark and A.W. Davis, *Organic Syntheses*, Coll. Vol. I, 2nd ed., 1941, p. 478.

[8] Y. Mizuno and K. Adachi, *Ann. Rept. Fac. Phar. Kanazawa Univ.*, **1**, 8 (1951); see also B.S. Thyagarajan, *Chem. Rev.*, **58**, 455 (1958).

method should be considered for the ring closure of IV to benzothiazoles in the modified Willgerodt-Kindler reaction. Therefore, we focussed our intention on what stage in the modified Willgerodt-Kindler reaction could involve the alternative possibility cyclizing to either V or VI, and the combination of reactants used in our experiment was classified into two categories, processes A and B: in process A, when a mixture of IV (or IX) and sulfur in DMF was heated at 165—170° in an oil bath for 10 hr, the benzothiazoles were not formed

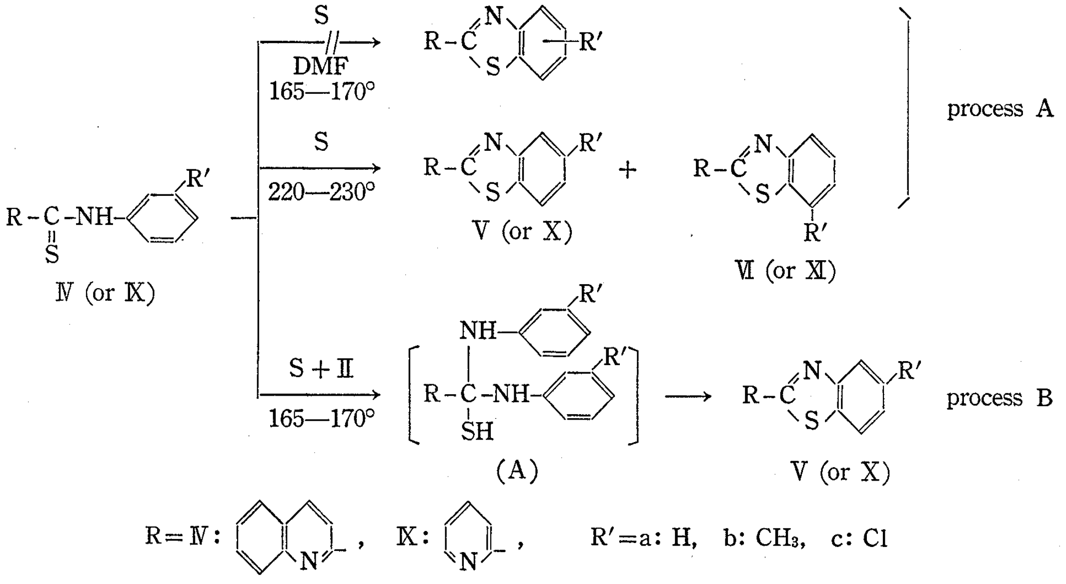
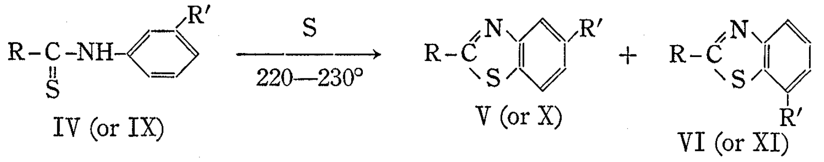
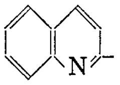
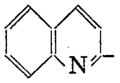
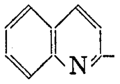


Chart 2

Table III. Results of Dehydrogenation-cyclization of IV and IX with Sulfur

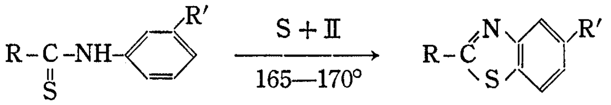


Starting material Compd. No.	R	R′	Product					
			V (or X)			VI(or XI)		
			Compd. No.	Yield[a] (%)	mp (°C)	Compd. No.	Yield[a] (%)	mp (°C)
IVa		H	Va	20	195—200			
IVb		CH_3	Vb	5	225—230	VIb	5	170—172
IVc		Cl	Vc	12	265—270	VIc	10	205—208
IXa		H	Xa	—	—			
IXb		CH_3	Xb	—	—	XIb	—	—
IXc		Cl	Xc	—	—	XIc	—	—

[a] calculated on the basis of IV

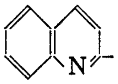
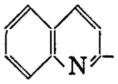
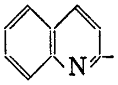
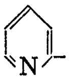
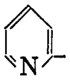
at all, but at elevated temperature of 220—230° in an oil bath the thioquinaldanilides (IV) afforded two isomeric benzothiazoles (V and VI), respectively; neither given temperatures were effective for cyclizing from the thiopicolinoanilides (IX) to the thiazoles (X and XI), although the evolution of hydrogen sulfide gas was slightly accelerated [ascertained by Pb$(CH_3COO)_2$], and in process B, when a mixture of IV (or IX) and sulfur was heated with II having the same substituent as that of IV in each case at 165—170° for 10 hr, the 5-substituted benzothiazole, V (or X), was selectively formed as given in Tables III and IV.

TABLE IV. Results of Cyclization Product from IV (or IX) with II in the Presence of Sulfur



IV (or IX)

V (or X)

Starting material Compd. No.	R	R′	Products (V or X)			Recovery (%) IV(or IX)
			Compd. No.	Yield$^{a)}$ (%)	mp (°C)$^{b)}$	
IVa		H	Va	22.7	197—200	67.4
IVb		CH_3	Vb	37.9	232—235	48.5
IVc		Cl	Vc	9.3	269—271	73.3
IXa		H	Xa	9.5	130—132$^{c)}$	74.4
IXb		CH_3	Xb	18.9	148—150$^{d)}$	54.5
IXc		Cl	Xc	trace	167—170$^{e)}$	86.0

a) calculated on the basis of IV (or IX)
b) recrystallized at two times
c) reported,$^{6a)}$ 130°
d) reported,$^{4)}$ 152—153°
e) reported,$^{4)}$ 171—173°

Discussion

Although there are many works[9] concerning the mechanism of the Willgerodt-Kindler reaction, our experiment is the only one on its modified reaction to our knowledge.[10] It was found that substitution, formation of amidines, and ring closure occurred simultaneously in thioanilides as a general reaction using *para*-substituted anilines. In our earlier work,[11] it was also indicated that the use of *para*-substituted anilines to the reaction of I with sulfur afforded mainly the thioanilide and a trace amount of the benzothiazole. However, by using *meta*-substituted anilines at the present time the benzothiazole is comparatively much as compared with the previous result. This suggests that the thiazole ring formation may appreciably be influenced by the substituent in the *meta*- and *para*-position on the aniline ring. Additionally, it appears that the use of the nitrobenzenes (III) instead of the anilines (II) to this reaction course results in forming IV and V in a poor yield on account of the difficulties

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9) M. Carmack and M.A. Spielman, *Org. React.*, 3, 83 (1946); F. Asinger, W. Schäfer, A. Saus, and H. Triem, *Angew. Chem. Intern. Ed. Engl.*, 3, 19 (1964).
10) H. Saikachi and T. Hisano, *Yakugaku Zasshi*, 81, 64 (1961); T. Hisano, *Yakugaku Zasshi*, **81**, 69 (1961).
11) H. Saikachi and T. Hisano, *Chem. Pharm. Bull.* (Tokyo), **8**, 51 (1960).

in reduction[12] of the nitro group by nascent hydrogen sulfide produced from the active methyl group with sulfur, although nitro compound could be expected to proceed up such thiazole ring formation[7] under the modified Willgerodt-Kindler reaction.

Possibly, the mechanism of the thiazole ring formation in the modified Willgerodt-Kindler reaction may be postulated in several respects: namely, 1) IV would first react with excess anilines to give an intermediate such as N,N′-diphenylaminomethanethiol according to an ionic process, as suggested with our earlier works[10] concerning the reactivity of thioanilide series, and then cyclize to V with elimination of aniline, 2) the thiol compound would be first formed from IV as an intermediate by the thiolation at *ortho*-position on amide group, and then cyclize to V with the liberation of hydrogen sulfide from thiol compound, according to Emmert and Groll,[6a] and 3) the enol-form of the thioanilide would cyclize to V through dehydrogenation by sulfur at elevated temperature of 200—250°.[13] This agreed more or less with our results in process A, and interestingly the ring closure occurred both to the position-*para* and -*ortho* to the substituent on the aniline ring at elevated temperature of 220—230°. In process B, as can be given in Table IV, it seems reasonable to assume that an intermediate (A) such as α-(2-quinolyl)-α,α-N,N′-diphenylaminomethanethiol would be first formed, and then the ring closure to the benzothiazole, V (or X), occurs with dehydrogenation by sulfur and simultaneously elimination of aniline.

Mizuno and Adachi[8,14] have reported that the ring formation of aryl substituted thioacetanilides in two ways forming isomeric such benzothiazoles by potassium ferricyanide (the Jacobson method) would be influenced considerably by steric hindrance of the substituent in the *meta*-position on the aniline ring. However, from our results given in Table II in addition to our earlier works,[4,5] not only seems it that steric factors of the substituent in the *meta*-position on the aniline ring are independent of the oxidative cyclization of IV (or (IX) by the Jacobson method toward VI (or XI), but even more interesting is the formation in larger amount of VI (or XI) than that of V (or X). In any event, forming the relatively small amount of the benzothiazoles (V and VI) may be attributed to the difficulties of the thioanilides for transforming into the enol-form, for example, because IV is slightly soluble in 3N sodium hydroxide aqueous solution used to the Jacobson method and is recovered to some extent during the reaction. Certain conclusion can be drawn on the basis of this experiment. It seems that the intermediate (A) according to an ionic process may contribute to the ring closure, although the mechanism for the selective cyclization from IV to V under the modified Willgerodt-Kindler reaction condition could not clearly be elucidated by the data of this paper.

Experimental

All melting points are uncorrected. IR spectra were recorded by Nippon Bunko IR-G spectrophotometer and UV spectra were measured with a Hitachi ESP-3T spectrophotometer.

Condensation of Quinaldine (I) with *meta*-Substituted Anilines (II) in the Presence of Sulfur——The following general procedure was used for the condensation of compounds listed in Table I.

5-Substituted 2-(2-Quinolyl)benzothiazoles (Va—c)——A mixture of 14.3 g (0.10 mole) of I, 0.12 mole of II (or III), and 8.0 g (0.25 mole) of sulfur was refluxed at 165—170° for 10 hr (or in 10 ml of DMF). After the reaction was over, the reaction mixture was allowed to stand at room temperature. The precipitated crystals were collected by suction and washed with EtOH. The crystals obtained were recrystallized three times from benzene, giving only Va—c as colorless crystals.

3′-Substituted Thioquinaldanilides (IVa—c)——In the above procedure, the washing and filtrate were combined and the unchanged I and II (or III) were completely removed from the combined solution by vacuum distillation in an oil bath. The residue was purified by three recrystallizations from EtOH.

Oxidation of 3′-Substituted Thioquinaldanilides (IVa—c) with Potassium Ferricyanide——To a solution of 88 g of powdered $K_3Fe(CN)_6$ in 220 ml of H_2O, a solution of 0.01 mole of IV and 24 g of NaOH in 350 ml

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[12] J.B. Cohen and D. McCandlish, *J. Chem. Soc.*, **1905**, 1257.
[13] R. Lantz, *Bull. Soc. Chim. France*, **24**, 1201 (1951).
[14] Y. Mizuno and K. Watanabe, *Yakugaku Zasshi*, **70**, 540 (1950).

of H_2O was added dropwise at 60—70° during 1 hr. After completion of the addition, the mixture was stirred for additional 2 hr, and 60 g of K_2CO_3 was added to the reaction mixture, and the mixture was kept at 50—60° for another 1 hr. After cooling, the colorless crystalline mass deposited was collected by suction and washed with water, and the residue was dissolved in 100 ml of benzene, and chromatographed over silica gel (50 g). Each separated fraction was recrystallized from benzene. One fraction of colorless crystals was found to be identical with the authentic samples of V by mixed melting point and IR spectra. The other fraction was assumed to be VI.

Synthesis of Authentic Samples of 5-Substituted 2-(2-Quinolyl)benzothiazoles (V)——Bis(4-substituted 2-nitrophenyl)disulfides (VII) were prepared from 5-substituted 2-chloronitrobenzenes by the reported procedure.[15]

A mixture of 0.02 mole of VII, 7.2 g (0.05 mole) of I, 3.2 g (0.10 mole) of sulfur, and 6 ml of DMF was heated under reflux at 160° for 10 hr. The DMF and unchanged I were completely removed by vacuum distillation. The residue was recrystallized from benzene, giving products, Vb (mp 236—238°) as colorless plates and Vc (mp 271—272°) as colorless plates, in about 70% yield, respectively.

Cyclization Product from IV (or IX) with II in the Presence of Sulfur——A mixture of 0.01 mole of IV (or IX), 0.015 mole of II, and 0.5 g (0.015 mole) of sulfur was heated at 165—170° for 10 hr. The reaction mixture was dissolved in 50 ml of benzene, and chromatographed over silica gel (50 g).

From the first effluent fraction, the unchanged sulfur was obtained. From the second effluent fraction, the starting material IV (or IX) was recovered. Colorless crystals from the third fraction was found to be identical with the authentic samples of V (or X) by mixed melting points and IR spectra.

Acknowledgement The authors wish to thank the staffs of the Analysis Room of Hisamitsu Pharmaceutical Co., Inc., for the micro-analysis and spectral measurements. They also are grateful to Mr. M. Nakatomi, President of Hisamitsu Pharmaceutical Co., Inc., for the supply of several chemicals.

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[15] M.T. Bogert and A. Stull, *Organic Syntheses*, Coll. Vol. I, 1948, p. 220.