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Synthesis of Organosulfur Compounds. VIII.[1] Cyclization Products from the Modified Willgerodt-Kindler Reaction[2]

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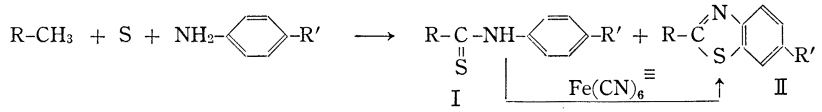
In order to clarify in more detail the cyclization mechanism of thioanilide to benzothiazole under the modified Willgerodt–Kindler reaction conditions, 2-picoline (III) was heated with *meta*-substituted anilines (IV) in the presence of sulfur and the reaction also gave thioanilides and one of the two possible benzothiazoles. The latter was proved to have the structure of 5-substituted 2-(2-pyridyl)benzothiazoles (VI) by independent synthesis.

On the other hand, the expected two isomeric benzothiazoles (VI and VII) were obtained from the oxidative cyclization of thioanilides by the modified Jacobson reaction.

Our previous papers[4] reported that the modified Willgerodt–Kindler reaction,[5] such as the reaction of the compounds having an active methyl group with *para*-substituted anilines in the presence of sulfur easily afforded the corresponding thioanilides (I) and benzothiazoles (II). The latter (II) was also formed by the oxidative cyclization of the former (I) with potassium ferricyanide in an alkaline solution according to the modified Jacobson method.[6,7] The anilines used in those reactions had a substituent in *para*-position so that the resulting cyclization products were the corresponding 6-substituted benzothiazoles.



In order to clarify in more detailed mechanism of cyclization from I to II under the above modified Willgerodt–kindler reaction conditions, the reaction of 2-picoline (III) with *meta*-substituted anilines (IV) was carried out in the presence of sulfur at 170° for 10 hr. It was expected from these reactions that the corresponding V and the two isomers in accordance with the orientation of cyclization from V to benzothiazoles, 5-substituted (VI) and 7-substituted benzothiazoles (VII), would be formed in respective cases different from that in the *para*-substituted anilines (Chart 1).

When a mixture of III and IVa (R=CH_3) with sulfur was heated as described above, benzothiazole was unexpectedly separated as one product from the reaction mixture, as

1) Part VII: T. Hisano, T. Nishi, and M. Ichikawa, *Yakugaku Zasshi*, **92**, 582 (1972).
2) A part of this work was presented at the Kyushu Local Meeting of the Pharmaceutical Society of Japan, Kumamoto, May 1971; Preliminary Communication: T. Hisano and Y. Yabuta, *Organic Preparations and Procedures International*, **4** (3), 105 (1972).
3) Location: *Oe-hon-machi, Kumamoto.*
4) H. Saikachi and T. Hisano, *Chem. Pharm. Bull.* (Tokyo), **7**, 349, 716 (1959); T. Hisano and H. Koga, *Yakuaku Zasshi*, **90**, 552 (1970).
5) *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*) A. Bruno and G. Purrello, *Gazz. Chim. Ital.*, **96**, 986 (1966).
6) Y. Mizuno and K. Watanabe, *Yakugaku Zasshi*, **70**, 540 (1950).
7) Y. Mizuno and K. Adachi, *Ann. Rept. Fac. Pharm. Kanazawa Univ.*, **1**, 8 (1951); see also, B.S. Thyagarajan, *Chem. Rev.*, **58**, 455 (1958).

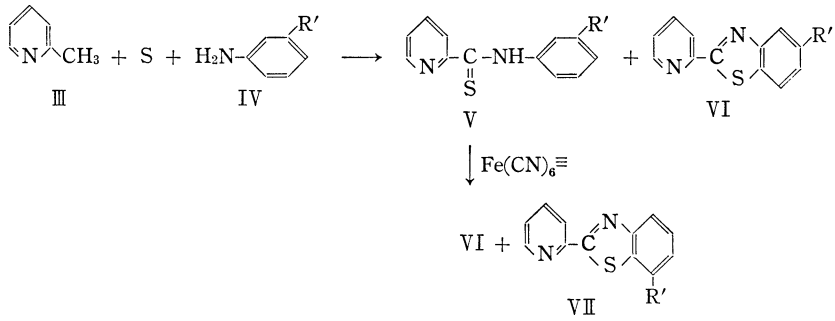


Chart 1

colorless needles melting at 152—153° in a 16.6% yield, along with 2-thiopicolino-*m*-toluidide (Va) as thioanilide.

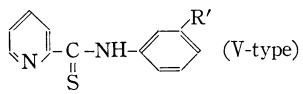
In order to examine this result further, other IVb to IVg were submitted to the similar reaction and their results are summarized in Table I.

As shown in Table I, only two products were obtained in all the compounds studied. The values of elemental analyses of these compounds agreed well with the molecular formula of V and benzothiazoles. All attempts to separate the expected two isomers from the benzothiazole fraction were unsuccesful. This seems to suggest that the benzothiazole fraction would be the pure VI or VII and not the mixture of VI and VII.

To establish the structure of VI or VII, authentic samples of VI were prepared through the routes shown in Chart 2.

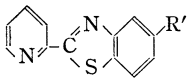
In the course of this procedure, our new preparative method[8] previously reported for the 2-substituted benzazoles was applied to the step from VIII to VI. In this step, it was found that the nitro compound as the *o*-substituted bifunctional compounds behaved just

TABLE I. Chemical Properties of V and VI



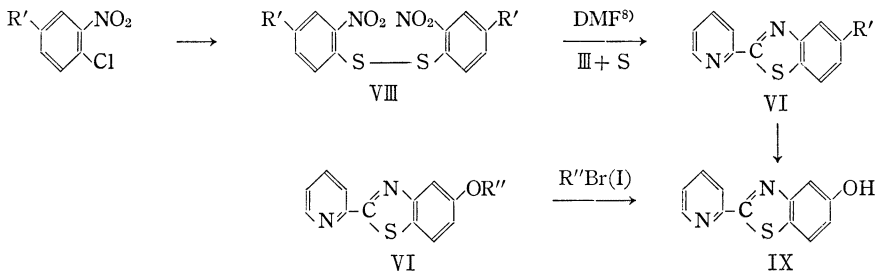
Compd. No.	R′	mp (uncorr.) (°C)	Crystal form (from EtOH)	Yield[a] (%)	Formula	Analysis (%) Calcd. (Found) C	H	N
Va	CH_3	79— 80	orange prisms	20.2	$C_{13}H_{12}N_2S$	68.39 (67.98)	5.30 (5.15)	12.27 (12.22)
Vb	OCH_3	69— 70	orange needles	16.0	$C_{13}H_{12}ON_2S$	63.91 (64.05)	4.95 (4.85)	11.47 (11.18)
Vc	OC_2H_5	55— 56	orange prisms	3.5	$C_{14}H_{14}ON_2S$	65.09 (65.11)	5.46 (5.35)	10.84 (10.62)
Vd	OC_3H_7(iso)	bp 120—123 (2mmHg)	orange oil	2.9	$C_{15}H_{16}ON_2S$	66.15 (66.29)	5.92 (5.87)	10.29 (10.24)
Ve	-O- 	64— 66	orange needles	17.3	$C_{18}H_{14}ON_2S$	70.56 (70.79)	4.61 (4.53)	9.14 (9.08)
Vf	Cl	96— 98	orange prisms	68.5	$C_{12}H_9N_2SCl$	57.95 (57.83)	3.65 (3.56)	11.26 (11.03)
Vg	CF_3	92— 94	orange prisms	45.3	$C_{13}H_9N_2SF_3$	55.31 (55.10)	3.21 (2.98)	9.92 (9.77)

8) T. Hisano and H. Koga, *Yakugaku Zasshi*, **91**, 180 (1971).


(VI-type)[b]

Compd. No.	R′	mp (uncorr.) (°C)	Crystal form (from EtOH)	Yield[a] (%)	Formula	Analysis (%) Calcd. (Found) C	H	N
VIa	CH_3	152—153	colorless prisms	16.6	$C_{13}H_{10}N_2S$	69.00 (69.04)	4.45 (4.33)	12.38 (12.14)
VIb	OCH_3	127	colorless prisms	39.7	$C_{13}H_{10}ON_2S$	64.44 (64.13)	4.16 (4.11)	11.56 (11.47)
VIc	OC_2H_5	120—121	colorless needles	50.0	$C_{14}H_{12}ON_2S$	65.60 (65.32)	4.72 (4.50)	10.93 (10.96)
VId	OC_3H_7(iso)	98—100	colorless prisms	25.2	$C_{15}H_{14}ON_2S$	66.64 (66.59)	5.22 (5.01)	10.36 (10.65)
VIe	-O- 	123—125	colorless needles	13.6	$C_{18}H_{12}ON_2S$	71.03 (71.16)	3.97 (3.82)	9.20 (9.30)
VIf	Cl	171—173	colorless needles	0.2	$C_{12}H_7N_2SCl$	58.42 (58.31)	2.86 (2.80)	11.35 (11.12)
VIg	CF_3	161—163	colorless prisms	0.8	$C_{13}H_9N_2SF_3$	55.71 (55.69)	2.52 (2.89)	10.00 (9.92)

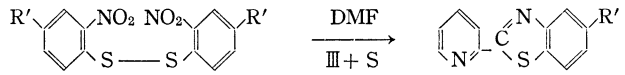
a) Based on amount of anilines started.
b) VI was determined with the authentic sample.



R′ = a: CH_3, b: OCH_3, c: OC_2H_5, f: Cl
R″= d: C_3H_7(iso), e: - 

Chart 2

TABLE II. Reaction of 2-Picoline with Bis(4-substituted 2-nitrophenyl) disulfide in the Presence of Sulfur



VIII(a—c,f) VI(a—c,f)

Starting material Compd. No.	R′	mp (°C) (uncorr.)	Product Compd. No.	mp (°C) (uncorr.)	Yield (%)
VIIIa	CH_3	175—176[b]	VIa	152—153	47.0
VIIIb	OCH_3	166[c]	VIb	126—127	28.0
VIIIc	OC_2H_5	168—170[d]	VIc	120—121	35.0
VIIIf	Cl	210—212[e]	VIf	171—173	73.0

a) Calcd. on the basis of VIII.
b) reported,[9a] 176°
c) reported,[9b] 166—167°
d) *Anal.* Calcd. for $C_{16}H_{16}O_6N_2S_2$:C, 48.47; H, 4.07; N, 7.07. Found: C, 48.64; H, 4.08; N, 7.00;
e) reported,[9c] 212—213°.

9) *a*) *Beilstein*, **6**, II, 401; *b*) *C.A.*, **1947**, 2734; *c*) *Beilstein*, **6**, II, 313.

like the corresponding amino compounds, which was reduced with nascent hydrogen sulfide produced in the first stage of this reaction, and resulted in formation of VI from VIII as the condensation products (Table II).

VIa and VIe were derived by the Ullmann reaction of the corresponding isopropyl bromide and iodobenzene with 5-hydroxy-2-(2-pyridyl)benzothiazole (IX) prepared by the hydrolysis of VIb with hydrobromic acid.

The authentic samples obtained by the above procedures were identical with the product VI obtained under the modified Willgerodt–Kindler reaction condition from mixed melting point test and by comparing their infrared (IR) spectra. Thus the product VI was established as 5-substituted 2-(2-pyridyl)benzothiazoles. This fact suggests that the cyclization from V to VI could occur selectively at the position-*para* to the substituent on the aniline ring to give solely the product VI.

On the other hand, Mizuno and Adachi[7] reported in detail the mechanism for the cyclization of thioanilides in the modified Jacobson method, and its scope and limitations. It could be expected from the proposed mechanism that two isomers would be obtained by different orientation of the cyclization to VI and VII in the oxidative cyclization of V by the above method[6,7] The products obtained from this method were clearly different from VI obtained under the modified Willgerodt–Kindler reaction conditions. A portion of this residue (mixture of benzothiazoles) was purified by recrystallization from ethanol and submitted to elemental analysis, results of which are given in Table III.

Table III. Analysis of the Mixture of Benzothiazole by Jacobson Method

	Analysis (%)					
	Calcd.			Found		
	C	H	N	C	H	N
VIa + VIIa	69.00	4.45	12.38	69.26	4.18	12.36
VIb + VIIb	64.44	4.16	11.56	64.74	4.17	11.49
VIc + VIIc	65.60	4.72	10.93	65.60	4.71	10.53
VId + VIId	66.64	5.22	10.36	66.85	5.20	10.17
VIe + VIIe	71.03	3.97	9.20	70.95	3.90	9.26
VIf + VIIf	58.42	2.86	11.35	58.25	2.75	11.10
VIg + VIIg	55.71	2.52	10.00	55.63	2.37	9.90

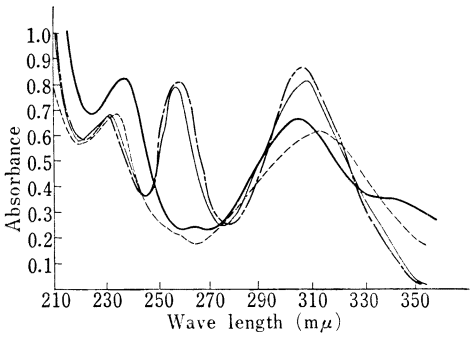


Fig. 1. Absorption Spectra of 5-or 7-Substituted Benzothiazoles

—: VIc, ----: VIb } 3.90×10^{-5}M in EtOH
—: VIIc, ---: VIIb } 3.96×10^{-5}M in EtOH

Table IV. Results of Oxidative Cyclization of V

Compd. No.	5-Substituted (VI) R′	Yield[a] (%)	mp (°C) (uncorr.)	Compd. No.	7-Substituted (VII) Yield[a] (%)	mp (°C) (uncorr.)	Crystal form (from EtOH)
VIa	CH_3	3.4	152—153	VIIa	64.6	102—104	colorless prisms
VIb	OCH_3	18.6	127	VIIb	25.8	145—147	colorless prisms
VIc	OC_2H_5	49.0	120—121	VIIc	29.1	104—106	colorless prisms
VId	OC_3H_7(iso)	28.5	98—100	VIId	44.6	101—103	colorless needles
VIe	O-⟨⟩	13.1	123—125	VIIe	60.5	91— 93	colorless prisms
VIf	Cl	19.2	171—173	VIIf	56.8	126—128	colorless prisms
VIg	CF_3	22.1	161—162	VIIg	42.7	121—122	colorless needles

a) Calcd. on the bais of V

From the elemental analyses, the oxidative products were presumed to be a mixture of two isomers of the corresponding benzothiazoles, and the expected two isomers were isolated from the oxidation products by the silica gel column chromatography (Table IV).

One of the two isomers did not show any depression on admixture with the authentic sample (VI) prepared previously. Therefore, the other isomer would be 7-substituted 2-(2-pyridyl)benzothiazole (VII) from the values of elemental analysis and the similarity of IR and ultraviolet (UV) spectra (Fig 1).

From these facts, ring closure of V with potassium ferricyanide proceeded to both at the *ortho* and *para* position of the substituent on the aniline ring, though the influence of substituent in *meta*-position was considerably observed on the yield of thiazole ring formation from the corresponding thioanilide.

The above results clearly suggested that mechanism different from that of the modified Jacobson method should be considered for the ring closure of V to benzothiazoles in the modified Willgerodt–Kindler reaction.

Discussion

Although there are many reports[10] concerning the mechanism of the Willgerodt–Kindler reaction, our experiment is the only one on its modified reaction.[11] It was found that substitution, formation of amidines, and ring closure occurred simultaneously in thioanilides as a general reaction using *para*-substituted anilines. Consequently, it was presumed that I would first react with excess anilines to give the intermediate such as α-(2-pyridyl)-α,α-N,N′-diphenylaminomethanethiol according to an ionic process, and then the ring closure to II occurred with elimination of aniline. Emmert and Groll[5a] assumed that the thiol compound was first formed from I as an intermediate by the thiolation at *ortho*-position on the amide group, and then the liberation of hydrogen sulfide from thiol compound gave II, but they did not offer further evidence for this postulation.

On the other hand, it was reported[12] that the dehydrogenation-cyclization of thioanilides with sulfur at elevated temperature of 200—250° produced benzothiazoles, but it is considerably different from our experimental conditions.

Mizuno and Adachi[7] reported the ring formation of aryl substituted thioacetanilides by potassium ferricyanide. That was agreed more or less with our experimental result obtained by the Jacobson method, and the yield of benzothiazoles was affected by the property of the substituent on the aromatic ring. This was well exemplified also by the behavior of thiopicolino *meta*-substituted anilides (V), which was possessed an electron-attracting or an electron-releasing group in the position-*meta* to aromatic ring. Further, the importance of steric factors in the oxidative Jacobson reaction of substituted anilides was well emphasized by the extensive work of Sugasawa and his co-workers.[13,14]

No simple explanation for the electronic and the steric effect of substituent of position-*meta* under the modified Willgerodt–Kindler reaction condition could be offered by the present data.

These factors may further complicate the situation. The mechanism for the selective cyclization from V to VI could not be clearly elucidated by the data of this paper. However, certain conclusion can be drawn on the basis of this experiment. It would seem that the product VI probably result from an ionic process, susceptible to steric factors in the

10) 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).
11) T. Hisano, *Yakugaku Zasshi*, **81**, 69 (1961).
12) R. Lantz, *Bull. Soc. Chim. France*, **24**, 1201 (1951).
13) S. Sugasawa and Y. Ban, *Yakugaku Zasshi*, **72**, 1336 (1952).
14) S. Sugasawa and M. Kirisawa, *Chem. Pharm. Bull.* (Tokyo), **3**, 190 (1955).

Willgerodt–Kindler reaction, whereas the products from the oxidative Jacobson reaction are derived from a radical process.[7]

Experimental

Melting and boiling points are uncorrected. IR spectra were recorded on Nippon Bunko DS-301 and Nippon Bunko IR-G spectrophotometer, and UV spectra were measured in EtOH with a Hitachi ESP-3T spectrophotometer.

Condensation of 2-Picoline with *meta*-Substituted Anilides in the Presence of Sulfur——The following general procedure was used for the condensation of compounds listed in Table I.

2-Thiopicolino *meta*-Substituted Anilides (Va—g)——A mixture of 14.0 g (0.15 mole) of 2-picoline, 0.10 mole of *meta*-substituted aniline (IV), and 8.0 g (0.25 mole) of sulfur was refluxed at 170° for 10 hr; H_2S gas was evolved vigorously. The unchanged 2-picoline and IV were completely removed by vacuum distillation in an oil bath. The residue was extracted with hot 3N NaOH solution (100 ml × 10), and the combined extracts were carefully acidified with dil. HCl; the yellowish orange crystalline mass which deposited was collected by suction and recrystallized three times from EtOH.

5-Substituted 2-(2-Pyridyl)benzothiazoles (VIa—g)——The alkali-insoluble residue from the above procedure exhibited only one spot on thin-layer chromatography (TLC) (Kiesel gel G; benzene–MeOH 98: 2). The crystals obtained were recrystallized three times from EtOH, giving VIa—g as colorless crystals.

2-Thiopicolino-*m*-phenoxyanilide (Ve)——A mixture of 14.0 g (0.15 mole) of 2-picoline, 18.5 g (0.10 mole) of *m*-phenoxyaniline (IVe), and 8.0 g (0.25 mole) of sulfur was heated in an oil bath at 170° for 10 hr. After removal of unchanged 2-picoline and *m*-phenoxyaniline *in vacuo*, the brown residue dissolved in small portion of benzene was chromatographed on silica gel column (50 g). From the first effluent fraction 5.3 g (17.3%) of orange prisms (Ve), mp 64—66°, was obtained and was recrystallized from EtOH.

2-(2-Pyridyl)-5-phenoxybenzothiazole (VIe)——In the above procedure, 4.1 g (13.6%) of colorless needles, mp 123—125°, was obtained from the second effluent fraction and was recrystallized from EtOH.

Oxidation of 2-Thiopicolinanilides (V) with Potassium Ferricyanide——To a stirred solution of 88 g of powdered $K_3Fe(CN)_6$ in 220 ml of H_2O, a solution of 20 g of V and 24.2 g of NaOH in 350 ml of H_2O was added dropwise at 60—70° during 2 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 hour. After cooling and extraction with ether, the ether layer was dried over anhyd. Na_2SO_4 and filtered. The Et_2O was removed and the residue was dissolved in benzene, and chromatographed over silica gel (50 g). Each separated fraction was recrystallized from EtOH. One fraction of colorless crystals was found to be identical with the authentic samples of VI by mixed melting points and IR spectra. The other fraction was assumed to be VII.

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

A mixture of 0.1 mole of VIII, 18.6 g (0.2 mole) of III, 16.0 g of sulfur, and 10 ml of dimethylformamide (DMF) was heated under reflux at 160° for 10 hr. The DMF and unchanged III were completely removed by vacuum distillation. The residue was recrystallized from EtOH. The yields of VI are shown in Table II.

2-(2-Pyridyl)-5-hydroxybenzothiazole (IX)——After a solution of 5.1 g (0.02 mole) of VIc in 40 ml of HBr (d=1.48) was refluxed for 3 hr, the reaction mixture was neutralized with Na_2CO_3, and white crystalline mass that deposited was collected by suction and recrystallized from acetone, giving 4.1 g (90.2%) of IX, as colorless needles, mp 275—279°. *Anal.* Calcd. for $C_{12}H_8ON_2S$: C, 63.14; H, 3.53; N, 12.27. Found: C, 62.86; H, 3.48; N, 12.18.

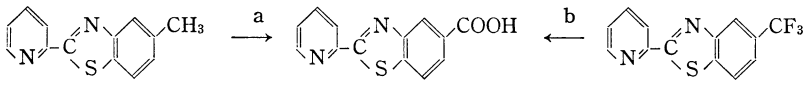
2-(2-Pyridyl)-5-isopropoxybenzothiazole (VId)——A solution of 1.14 g (0.005 mole) of IX in 20 ml of EtOH contained 0.4 g of NaOH was warmed, 1.23 g (0.01 mole) of *iso*-PrBr was added to the solution, and the mixture was refluxed for 3 hr. The solid that deposited was filtered off and the filtrate was concentrated under vacuum. To the residue, 20 ml of H_2O was added and extracted with ether (20 ml × 3), the ether layer was dried over anhyd. Na_2SO_4, and the ether was removed. The residue was recrystallized from EtOH, giving 0.17 g (72%) of VId, as colorless needles, mp 98—100°. *Anal.* Calcd. for $C_{15}H_{14}ON_2S$: C, 66.64; H, 5.22; N, 10.36. Found: C, 66.38; H, 5.31; N, 10.25.

2-(2-Pyridyl)-5-phenoxybenzothiazole (VIe)——A mixture of 1.14 g (0.005 mole) of IX in 20 ml of DMF and equimolar amount of NaH in 20 ml of DMF was stirred for 1 hr, then DMF was removed by vacuum distillation. To the residue, 1.02 g (0.005 mole) of iodobenzene and 0.01 g of Cu powder were added, and the mixture was heated at 220—230° for 10 hr. The unchanged iodobenzene was removed by vacuum distillation in an oil bath. The residue was extracted with ether, and the ether layer was dried over anhyd.

15) M.T. Bogert and A. Stull, *Org. Synth.*, Collect. **I**, 220 (1948).

Na_2SO_4 and filtered. The ether was removed and the residue was recrystallized from EtOH, giving 0.38 g (25.0%) of VIe, as colorless needles, mp 125—126°. *Anal.* Calcd. for $C_{18}H_{12}ON_2S$: C, 71.03; H, 3.97; N, 9.20. Found: C, 71.25: H, 4.20; N, 9.43.

Determinaion of the Position of Trifluoromethyl Group in VIg (Chart 3)——a) A mixture of 6.8 g of $Na_2Cr_2O_7 \cdot 2H_2O$ in 15 ml of H_2O and 3.0 g (0.013 mole) of VIa was stirred, and 17 ml of conc. H_2SO_4 was added during 30 min, and the mixture was warmed at 50—60° for 1 hr, then poured into ice–water. The crystals that deposited was extracted with ether. The ether layer was extracted with 2N Na_2CO_3 solution. The alkaline extract was acidified with 10% HCl, and the precipitate was collected, and recrystallized from EtOH, giving 0.2 g (6.0%) of X, as colorless needles, mp 298—303°. *Anal.* Calcd. for $C_{13}H_8O_2N_2S$: C, 60.93; H. 3.15; N, 10.93. Found: C, 60.99; H, 3.08; N, 11.05.



VIa X VIg

Chart 3

b) A solution of 1.0 g (0.0036 mole) of VIg in 10 ml of conc. H_2SO_4 (98%) was heated at 150° for 5 hr. The mixture was poured into ice–water and the colorless crystals that deposited was recrystallized from EtOH, giving 0.76 g (82.7%) of X, as colorless needles, mp 298—300°. This compound was identified with the product from procedure a) by the mixed mp and IR spectrum.

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