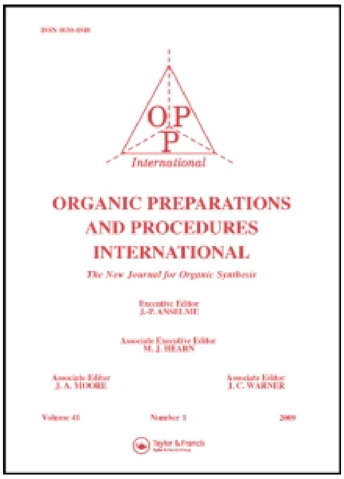

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SELECTIVE CYCLIZATION IN THE MODIFIED WILLGERODT-KINDLER REACTION

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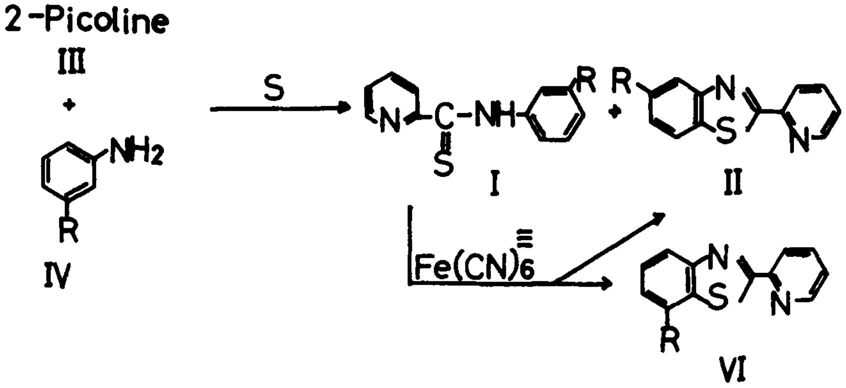
We had previously[1] shown that heating compounds with active methyl groups with p-substituted anilines in the presence of sulfur formed the thioanilides and benzothiazoles corresponding to I and II; the former were converted to the latter by alkaline potassium ferricyanide.[2,3] We now report that heating 2-picoline (III) with m-substituted anilines (IV) in the presence of sulfur also gives the thioanilides and one of the two possible benzothiazoles. The latter were proven to have the structure shown in equation 2 by independent synthesis.



The structure of II was established by mixture mps. and by comparison of their infrared spectra with those of authentic samples which were prepared by the following route.

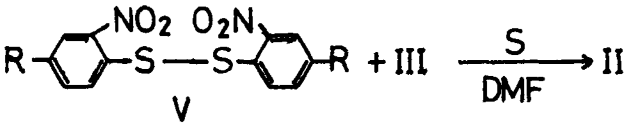


Table I. Yields and Mps. of Thioanilides and Benzothiazoles.

	Thioanilides (I)[a]		Benzothiazoles (II)[b]	
	Yield (%),[c]	mp.(^{o}C)[d]	Yield (%),[c]	mp.(^{o}C)[d]
A, $R=CH_3$	20.2	79-80	16.6	152-153
B, $R=OCH_3$	16.0	69-70	39.7	127
C, $R=OC_2H_5$	3.5 (4.1)[c]	55-56	52.0 (60.5)[c]	120-121

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a) Orange prisms. b) Colorless prisms except IIC which crystallized as needles. c) Based on amount of anilines started. However, the conversions are higher as shown by the fact that (0.014 mole) of m-phenetidine was recovered as the urea (See ref. 6). d) Uncorrected.

The conversion of V to II made use of our novel preparative method for 2-substituted benzazoles.[4]

The fact that only isomer II was formed suggests that the cyclization of I to II occurred selectively at the para position of the aniline ring. On the other hand, as anticipated from the proposed mechanism[3] for the modified Jacobson reaction, the two isomeric benzothiazoles (II and VI) should have been produced in the oxidative cyclization of I by the above modified method.[2] In fact, we indeed obtained the expected two isomers[5] (isolated by silica gel column chromatography) from the oxidative cyclization of I (R = CH_3, OCH_3, OC_2H_5). The melting points of these compounds are listed in Table II.

Table II. Results[a] of Oxidative Cyclization of I.

	5-substituted (II)		7-substituted (VI)	
	Yield (%)[b]	mp.(°C)	Yield (%)[b]	mp.(°C)
A, R=CH_3	3.4	151-153	64.6	102-104
B, R=OCH_3	18.6	125-126	25.8	145-146
C, R=OC_2H_5	49.0	118-120	29.1	104-106

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a) All colorless prisms except for IIC which crystallized as needles. b) Based on amount of I started with.

The present results clearly suggest that a mechanism different from that suggested for the modified Jacobson method should be considered for the cyclization of I to II in the modified Willgerodt-Kindler reaction. However, the mechanism for the selective cyclization of I to II cannot be clearly elucidated from the data obtained here. Further investigations will be necessary to clarify the mechanism of the modified Willgerodt-Kindler reaction. Details on these will be reported in the near future.

EXPERIMENTAL

<u>Condensation of 2-Picoline with Anilines and Sulfur</u>. <u>General Procedure</u>.

2-Thiopicolinoyl-m-substituted Anilines (IA-C).— A mixture of 14.0 g (0.15 mole) of 2-picoline, 0.10 mole of m-substituted aniline (IV), and 8.0 g (0.25 mole) of sulfur was refluxed at 170° for 10 hrs; H_2S gas was vigorously evolved. The unchanged 2-picoline and IV were completely removed by vacuum distillation in an oil bath.[6] The residue was extracted with hot 3N NaOH solution (100 ml X 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.

IA: Anal. Calcd. for $C_{13}H_{12}N_2S$: C, 68.39; H, 5.30; N, 12.27.
Found: C, 67.98; H, 5.15; N, 12.22.

IB: Anal. Calcd. for $C_{13}H_{12}N_2OS$: C, 63.91; H, 4.95; N, 11.46.
Found: C, 63.83; H, 4.79; N, 11.02.

IC: Anal. Calcd. for $C_{14}H_{14}N_2OS$: C, 65.09; H, 5.46; N, 10.83.
Found: C, 65.00; H, 5.31; N, 10.41.

5-Substituted 2-(2-Pyridyl)benzothiazoles (IIA-C).— The alkali-insoluble residue from the above procedure exhibited only one spot on TLC (Kieselgel G; Benzene-MeOH 98:2). The crystals obtained were recrystallized three times from EtOH, giving IIA-C as colorless crystals.

IIA: Anal. Calcd. for $C_{13}H_{10}N_2S$: C, 69.00; H, 4.45; N, 12.38.
Found: C, 69.04; H, 4.33; N, 12.14.

IIB: Anal. Calcd. for $C_{13}H_{10}N_2OS$: C, 64.44; H, 4.16; N, 11.56.
Found: C, 64.13; H, 4.11; N, 11.56.

IIC: Anal. Calcd. for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72; N, 10.93.
Found: C, 65.32; H, 4.50; N, 10.96.

Oxidation of 2-Thiopicolinoyl-*m*-Substituted Anilides (I) with Potassium Ferricyanide.— To a stirred solution of 88 g of powdered $K_3Fe(CN)_6$ in 220 ml of water, a solution of 2.0 g of I and 22.4 g of NaOH in 350 ml of water was added dropwise at 60-70° during 2 hrs. After completion of the addition, the mixture was heated for an additional 2 hrs, and 60 g of K_2CO_3 was added to the reaction mixture; then the mixture was kept at 50-60° for another hour. After cooling and extraction with ether, the ethereal layer was dried over anhydrous Na_2SO_4 and filtered. Removal of the solvent left a residue[5] which 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, by mixture melting points and IR spectra, to be identical with the authentic samples of II. The other fraction is assumed to be VI.

VIA: Anal. Calcd. for $C_{13}H_{10}N_2S$: C, 69.00; H, 4.45; N, 12.38.
Found: C, 69.26; H, 4.18; N, 12.36.
VIB: Anal. Calcd. for $C_{13}H_{10}N_2OS$: C, 64.44; H, 4.16; N, 11.56.
Found: C, 64.74; H, 4.17; N, 11.49.
VIC: Anal. Calcd. for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72; N, 10.93.
Found: C, 65.60; H, 4.71; N, 10.53.

Synthesis of Authentic samples of 5-Substituted 2-(2-Pyridyl)-benzothiazoles.— Bis(4-substituted 2-nitrophenyl)disulfides (V) were prepared by the reported procedure[7] from 5-substituted 2-chloronitrobenzenes.

A mixture of 0.1 mole of V, 18.6 g (0.2 mole) of III, 16.0 g (0.5 mole) of sulfur, and 10 ml of dimethylformamide

(DMF) was heated at 160° for 10 hrs under reflux. The DMF and unchanged III were completely removed by vacuum distillation. The residue was recrystallized from EtOH. The yields of IIA-C were 47, 28, and 35% respectively.

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* To whom inquiries should be directed.

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5. A portion of this residue (mixture of benzothiazoles) was purified by three crystallizations from EtOH and submitted for elemental analysis. The results are given below.

Analysis of Mixture

IIA + VIA: Anal. Found: C, 69.26; H, 4.18; N, 12.36.
Calcd. for $C_{13}H_{10}N_2S$: C, 69.00; H, 4.45; N, 12.38.

IIB + VIB: Anal. Found: C, 64.74; H, 4.17; N, 11.49.
Calcd. for $C_{13}H_{10}N_2OS$: C, 64.44; H, 4.16; N, 11.56.

IIC + VIC: Anal. Found: C, 65.60; H, 4.71; N, 10.53.
Calcd. for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72; N, 10.93.

6. The amount of unreacted aniline was determined in the case of m-phenetidine (IVC). The fraction removed by vacuum distillation (see Experimental), bp. 110-150°/20mm amounting to 2.2 g, was treated with 2.2 g of phenylisocyanate. Upon standing overnight, this mixture deposited a crystalline solid which was washed with hot pet.ether and recrystallized from EtOH to give 3.6 g (0.014 mole) of N-phenyl-N'-m-ethoxyphenylurea, mp. 151-153°.[8] The low yields of thioanilides may be ascribed to partial decomposition to the corresponding anilides during the extraction with hot alkali, see ref. 9.

7. M. T. Bogert and A. Stull, "Organic Syntheses", Coll. Vol. I, 1948, p. 220.

8. Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.31; H, 6.25; N, 10.94.
Found: C, 70.15; H, 6.30; N, 10.68.

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