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The Preparation of Some Fluorobenzothiazoles (1a)

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The seven possible monofluoro-2-phenylbenzothiazoles have been prepared. Each was prepared by potassium hexacyanoferrate(III) oxidation of the appropriately substituted thiobenzanilide. Several were also prepared *via* a benzyne intermediate through treatment of suitable thiobenzanilides with potassium amide and liquid ammonia.

In recent years a number of heterocyclic systems have been investigated with respect to the preparation and properties of their fluorine derivatives. Heterocyclic nuclei which have been studied include phenazine (2a), phenothiazine (2b, c), pyrazine (2d), pyridine (2e), pyrimidine (2d), quinoline (2f), isoquinoline (2g, h), quinoxaline (2d), and flavone (2i). Several fluorobenzothiazoles have been previously reported (3a-e) but no systematic investigation of their preparation is recorded. This paper reports the preparation of all seven possible monofluoro-2-phenylbenzothiazoles.

The many methods available for the preparation of benzothiazole and its derivatives are the subject of a review by Sprague and Land (4). Perhaps the most generally popular method has been that of Jacobson (5) who found the potassium hexacyanoferrate(III) oxidation of thiobenzanilide (I) to yield 2-phenylbenzothiazole (II). In 1958, Hrutfiord and Bunnett (6) reported a new general procedure for the synthesis of heterocyclic compounds by creating a benzyne intermediate which has a nucleophilic center so situated that it can add intramolecularly to the "triple bond" of the benzyne structure. This method is illustrated by the conversion of thiobenz-2-bromoanilide (III) to 2-phenylbenzothiazole (II) through the action of potassium amide in liquid ammonia.

Roberts (7), in studies on the order of halogen mobility, has previously demonstrated that both bromo- and chlorobenzene form benzyne when treated with potassium amide in liquid ammonia whereas fluorobenzene does not. Thus in the thiobenzanildes leading to fluorinated benzothiazoles, there should be no competition between the elimination of HCl (HBr) and HF.

The route to the fluoro-2-phenylbenzothiazoles *via* a benzyne intermediate was of special interest because of the specific direction of ring closure it affords. While the Jacobson and other methods of ring formation give rise to two cyclic products when the anilide ring is substituted in the *meta*-position, the benzyne intermediate can yield only a single product. For example, oxidation of the *meta*-substituted thioanilide (IV) can lead to benzothiazoles V and VI, whereas the thioanilide (VII) affords only product VI.

Preparation of Materials.

Many of the compounds required for this investigation have been prepared previously. The benzanilides were formed by standard methods (8) and their conversion to the sulfur analogs, the thioanilides, offered the only difficulty in the synthetic aspects of the present work. In most cases, the procedure suggested by Klingsberg and Papa (9) proved successful after slight modification. This method, involving treatment of the anilide with phosphorous pentasulfide in refluxing pyridine, was apparently too vigorous for anilides which had more than one halogen attached to the same aromatic ring. Such a thioanilide was prepared by treatment of the appropriate dithioester with an anilinomagnesium halide.

This procedure had previously been employed by Bodroux (10) and by Bassett and Thomas (11) to prepare anilides from simple esters but no report of its application to dithioesters is known. Data concerning the previously unknown anilides and thioanilides are given in Table I and Table II.

Formation of the Benzothiazoles. A. By Hexacyanoferrate(III) Oxidation.

The original method of Jacobson involved addition of potassium hexacyanoferrate(III) to a basic solution of the thiobenzanilide (5). More recently, Mizuno and Adachi (14) found that improved yields could be obtained by reverse addition of the reactants. The oxidation of fluorine-containing thiobenzanilides gave yields in the range of those usually reported for this reaction.

B. *Via* Benzyne Intermediate.

The experimental details for the ring closure *via* benzyne are similar to those used by Bunnett (15) and normally employed a 2.5 to 4.0 molar excess of potassium amide to thioanilide. Yields of benzothioazole ranged from 80% in the case of 2-(*o*-fluorophenyl)benzothiazole to 14% in the case of 2-(*m*-fluorophenyl)benzothiazole. The results of the ring closure experiments are summarized in Table III.

Where products were prepared by both the oxidative and benzyne methods they were shown to be

identical by mixture melting points and by comparison of their infrared spectra. Production of a single benzothiazole product *via* benzyne proved valuable in assigning structures to the products obtained from the sometimes unselective oxidative route.

TABLE I

Benzanilides (a)

Benzanilide	M. P., °C	Yield	Formula	Nitrogen, % Calcd.	Found
2-Fluorobenzanilide	98	93	$C_{13}H_{10}FNO$	6.50	6.27
3-Fluorobenzanilide	152-153	93	$C_{13}H_{10}FNO$	6.50	6.35
4-Fluorobenzanilide	184-185	96	$C_{13}H_{10}FNO$	6.50	6.57
2-Fluorobenz(2-chloro)anilide	80-80.5	88	$C_{13}H_9ClFNO$	5.65	5.52
3-Fluorobenz(2-chloro)anilide	118-120	85	$C_{13}H_9ClFNO$	5.65	5.49
4-Fluorobenz(2-chloro)anilide	106-107	96	$C_{13}H_9ClFNO$	5.65	5.45
Benz(2-fluoro)anilide (b)	111-112	94	$C_{13}H_{10}FNO$	6.50	6.54
Benz(3-fluoro)anilide	142-143	97	$C_{13}H_{10}FNO$	6.50	6.57
Benz(4-fluoro)anilide (c)	183-184	86	$C_{13}H_{10}FNO$	----	----
Benz(2-bromo-5-fluoro)anilide	75-77	94	$C_{13}H_9BrFNO$	4.76	4.88

(a) See ref. 21. (b) Lit. (12) m.p. 113°. (c) Lit. (13) m.p. 185°.

TABLE II

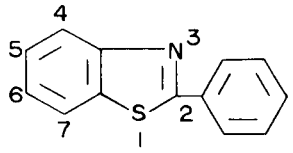
Thiobenzanilides (a, b)

Thiobenzanilide	M. P., °C	Yield	Formula	Nitrogen, % Calcd.	Found
2-Fluorothiobenzanilide	81-82	88	$C_{13}H_{10}FNS$	6.09	5.98
3-Fluorothiobenzanilide	104-105	61	$C_{13}H_{10}FNS$	6.09	6.11
4-Fluorothiobenzanilide	144-146	96	$C_{13}H_{10}FNS$	6.09	6.12
2-Fluorothiobenz(2-chloro)anilide	79-80	78	$C_{13}H_9ClFNS$	5.27	5.39
3-Fluorothiobenz(2-chloro)anilide	67-68	65	$C_{13}H_9ClFNS$	5.27	5.09
4-Fluorothiobenz(2-chloro)anilide	134-136	90	$C_{13}H_9ClFNS$	5.27	5.07
Thiobenz(2-fluoro)anilide	77-78	75	$C_{13}H_{10}FNS$	6.09	6.21
Thiobenz(3-fluoro)anilide	105-107	61	$C_{13}H_{10}FNS$	6.09	6.18
Thiobenz(4-fluoro)anilide	117-118	83	$C_{13}H_{10}FNS$	6.09	6.02
Thiobenz(2-bromo-5-fluoro)anilide (c)	78-80	31	$C_{13}H_9BrFNS$	4.51	4.40

(a) Except where otherwise noted, prepared according to Ref. 9. (b) Purified by crystallization from aqueous ethanol. (c) See Experimental section.

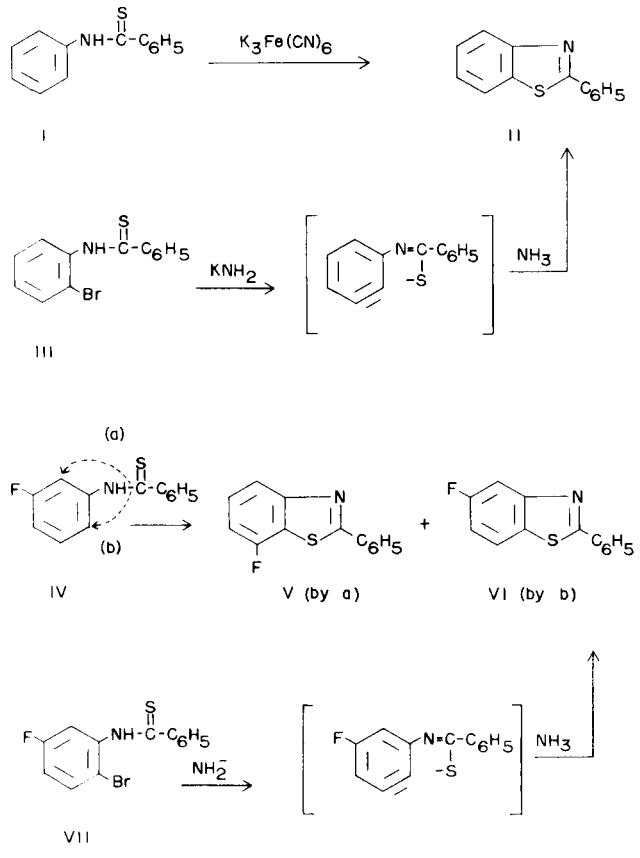
TABLE III

Benzothiazoles



	Method (a)	Molar Excess of KNH_2	Benzothiazole	M.p., °C	Yield	Analysis (b) C,%	H,%	N,%
4-Fluorothiobenzanilide	A (c)	---	2-(*p*-fluorophenyl)-	99-100	42	68.00	3.57	6.09
4-Fluorothiobenz-(2-chloro)anilide	B	2.5	2-(*p*-fluorophenyl)-	99.5-100	80			
3-Fluorothiobenzanilide	A (d)	---	2-(*m*-fluorophenyl)-	90-91	50	68.18	3.46	6.22
3-Fluorothiobenz-(2-chloro)anilide	B	4.	2-(*m*-fluorophenyl)-	90-91	14			
2-Fluorothiobenzanilide	A (d)	---	2-(*o*-fluorophenyl)-	77-77.5	50	68.31	3.20	6.12
2-Fluorothiobenz-(2-chloro)anilide	B	6. (e)	2-(*o*-fluorophenyl)-	76.5-77	23			
Thiobenz(2-fluoro)anilide	A (d)	---	2-phenyl-4-fluoro-	98-99	60	67.70	3.27	6.21
Thiobenz(3-fluoro)anilide	A (d)		2-phenyl-7-fluoro-	81-82	23 (f)	68.44	3.73	6.23
			2-phenyl-5-fluoro	117-118	43 (f)	68.23	3.74	6.09
Thiobenz(2-bromo-5-fluoro)anilide	B	3.3	2-phenyl-5-fluoro-	117-118	57			
Thiobenz(4-fluoro)anilide	A (c)		2-phenyl-6-fluoro-	134.5-136	47	68.18	3.29	6.15

(a) A, hexacyanoferrate(III), oxidation; B, *via* benzyne intermediate. (b) Calcd. for $C_{13}H_8FNS$: C, 68.10; H, 3.49; N, 6.11. (c) Original Jacobson method (5). (d) As modified by Mizuno and Adachi (14). (e) No product isolated with 3 and 4 molar excess of KNH_2. (f) Overall yield of benzothiazole, 66%.



EXPERIMENTAL (16)

2-Bromo-5-fluoroaniline.

To a cold solution of 75 g. (0.33 mole) of tin(II) chloride monohydrate in 75 ml. of concentrated hydrochloric acid was added 22 g. (0.1 mole) of 4-bromo-3-nitrofluorobenzene (17) in 50 ml. of glacial acetic acid. When the mixture was removed from the ice bath its temperature rose slowly to 35°, then very rapidly to 80°. At this point the solution was again cooled and then allowed to warm to 65° from which it cooled slowly to room temperature. Most of the acetic acid was removed by evaporation and the residue treated with 50 ml. of water and 120 ml. of 40% sodium hydroxide. The resulting solid was filtered, washed with water, and taken up in ether. After drying with magnesium sulfate, the ether was evaporated and the residue recrystallized from aqueous ethanol to give 15.1 g. (80%) of the desired product as white crystals, m.p. 47-49°.

Anal. Calcd. for C_6H_5BrFN: N, 7.32. Found: N, 7.36.

Benzanilides.

Benzanilides were prepared by reaction of the appropriate benzoyl chloride and aniline derivatives in pyridine and benzene (8) and were recrystallized from aqueous ethanol.

Thiobenzanilides.

With one exception the thiobenzanilides used in this investigation were prepared from their oxygen analogs by treatment with phosphorus pentasulfide in pyridine. The procedure described is essentially that of Klingsberg and Papa (9) but with slight modification.

A small molar excess of phosphorus pentasulfide was heated in 100-150 ml. of dry pyridine until solution was obtained. The benzanilide was added and the solution heated at reflux for 3-5 hours, then poured into 300 ml. of 15% hydrochloric acid and cooled. The yellow solid was filtered, washed with water, and purified by crystallization from aqueous ethanol or cyclohexane.

Thiobenz(2-bromo-5-fluoro)anilide.

In a reaction analogous to that described by Bassett and Thomas (11), 14.25 g. (0.075 mole) of 2-bromo-5-fluoroaniline was added slowly to

a molar equivalent of methylmagnesium iodide in 50 ml. of ether. After the reaction had subsided 12.60 g. (0.075 mole) of methyl dithiobenzoate (18) in 20 ml. of ether was added. The stirred mixture was refluxed for 60 hours, during which time the color changed from pink to light orange. Water was cautiously added to the cooled mixture followed by 50 ml. of 10% hydrochloric acid. The organic layer was separated, washed twice with dilute acid, dried with magnesium sulfate, and evaporated. The residue was dissolved in 15% aqueous sodium hydroxide, treated with charcoal and filtered. The filtrate was made acidic with concentrated hydrochloric acid and after cooling, the precipitated yellow solid was collected and recrystallized from aqueous ethanol. This procedure afforded 7.45 g. (31%) of bright yellow crystals, m.p. 78-80°.

Anal. Calcd. for $C_{13}H_9BrFNS$: N, 4.51. Found: N, 4.40.

Formation of the Benzothiazoles. A. Hexacyanoferrate(III) Oxidation.

The best results in the oxidative ring closure reactions were obtained by using modifications of the original Jacobson method (5) suggested by Mizuno and Adachi (14). The preparation of 2-(*m*-fluorophenyl)-benzothiazole is typical.

In a 300 ml. three-necked flask fitted with a thermometer, a dropping funnel, and a mechanical stirrer were placed 30.5 g. (0.092 mole) of potassium hexacyanoferrate(III) and 60 ml. of water. To this solution was added 6.93 g. (0.03 mole) of 3-fluorothiobenzanilide in 100 ml. of 8% sodium hydroxide over a period of 1.5 hours so that the temperature was maintained at 40°. After addition, the mixture was cooled and filtered. The yellow residue was extracted with warm concentrated hydrochloric acid and filtered. The filtrate was diluted to four times its volume and chilled overnight. The resulting yellow solid was collected, washed with water, and recrystallized twice from aqueous ethanol. In this manner, 3.42 g. (50%) of 2-(*m*-fluorophenyl)benzothiazole was obtained as white crystals, m.p. 90-91°.

Anal. Calcd. for $C_{13}H_8FNS$: C, 68.10; H, 3.49; N, 6.11. Found: C, 68.18; H, 3.46; N, 6.22.

By a similar procedure, thiobenz(3-fluoro)anilide furnished a mixture of 2-phenyl-5-fluoro- and 2-phenyl-7-fluorobenzothiazoles. The 5-fluoro isomer was separated by fractional crystallization from 95% ethanol. The 7-fluoro isomer was eluted from an alumina column with a benzene-petroleum ether mixture (2:1). An overall yield of 66% was achieved, two-thirds of which was the 5-fluoro isomer. (See Table III.)

B. *Via* Benzyne Intermediate.

The apparatus used for the formation of benzothiazoles *via* benzyne intermediates is described by Bunnett (15). A typical preparation is outlined below.

Reaction of 2-Fluorothiobenz(2-chloro)anilide with Potassium Amide in Liquid Ammonia.

The thiobenzanilide (10.60 g., 0.004 mole) was allowed to react for one hour with a six molar excess of potassium amide. To the residue after neutralization and evaporation of ammonia was added water and ether and the layers separated. The ether layer on evaporation yielded a dark oil which crystallized when treated with ammonium hydroxide. The solid was purified by two recrystallizations from aqueous ethanol and afforded 2.11 g. (23%) of 2-phenyl-7-fluorobenzothiazole as white crystals, m.p. 76.5-77°. (See Table III.)

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