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The action of acid on 6-(*p*-tolylhydrazino)-2-thiouracil gives appreciable amounts of the stable Fischer intermediate, 5-(2'-amino-5'-tolyl)-6-amino-2-thiouracil. This compound undergoes intramolecular cyclization at high temperatures, and represents the first reported isolation of a diamine intermediate derived from a Fischer-type indolization reaction.

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6(Phenylhydrazino)uracils have been shown to undergo acid-catalyzed (1) and thermal (2) rearrangement to 9H-pyrimido[4,5-*b*]indole-2,4-diones. This Fischer-type indolization reaction is accompanied by side reactions which depend upon the acid reagent. With hydrochloric acid, hydrolysis of the starting material produces the phenylhydrazine and barbituric acid (1); in 98% formic acid a novel rearrangement occurs to yield 1-phenyl-3-carbox-amidomethyl-1,2,4-triazoles (1,3). We now report the effects of acid on a 2-thiouracil analog and compare these results with those obtained in the uracil series.

Reaction with Hydrochloric Acid.

After one hour at reflux in 1*N* hydrochloric acid, 6-(*p*-tolylhydrazino)-2-thiouracil (**1**) did not give a detectable amount of a pyrimidoindole. Two compounds were obtained under these conditions: *p*-tolylhydrazine hydrochloride (from hydrolysis of the starting compound) and the diamine **2**. Compound **2** presumably represents the intermediate formed from a [3,3] sigmatropic shift of **1**, the initial step in the Fischer rearrangement.

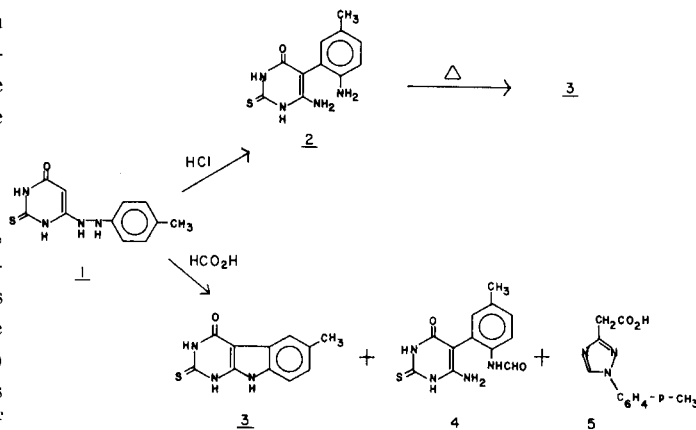
Evidence for the structure of **2** has been derived both from its nmr spectrum (see Experimental), and from its thermal conversion to pyrimidoindole. When **2** was heated in *N,N*-dimethylaniline at reflux for two hours, a 78% yield of a compound identified as 6-methyl-9H-pyrimido[4,5-*b*]indole-2-thio-4-one (**3**) was obtained. Methylation of **3** produced 2-methylmercapto-6-methyl-9H-pyrimido[4,5-*b*]indole-4-one, identical with an authentic sample. Thus, **2** represents a true intermediate in this rearrangement, although evidence has been obtained in other systems that the indolization step may occur *via* dienone-imine (**4**) or related (**5**) intermediates. Apparently, rapid tautomerization of a dienone-imine to **2** would precede cyclization in the acid-catalyzed rearrangement of **1**.

Reaction with Formic Acid.

A small (17%) yield of the pyrimidoindole, **3**, was obtained after heating **1** in 98% formic acid at reflux for one hour. The major product of this reaction, however, was a compound assigned the structure **4** based on its nmr spectrum. This compound is similar to the diamine intermediate isolated from the reaction of **1** with hydrochloric acid, but trapped as the formamido derivative. Compound **4** can, in fact, be hydrolyzed by sodium hydroxide to give the diamine, **2**.

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Rearrangement of **1** to the triazole gives minor yields (2-4%) of 1-(*p*-tolyl)-3-carboxymethyl-1,2,4-triazole (**5**). We do not know why the acid is obtained and not the corresponding amide as is the case in the uracil series, unless the proposed (1) intermediate acyl isothiocyanate is hydrolyzed directly to give **5**.

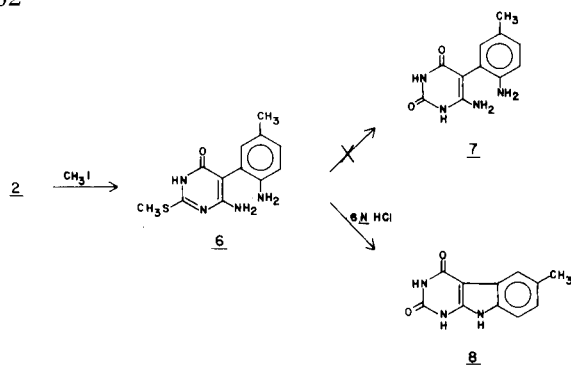


Discussion.

The observation that the Fischer-type cyclization of 6-(phenylhydrazino)-2-thiouracils produces primarily intermediates rather than pyrimidoindole products suggests differing reactivities of the 6-amino group in the presence of a 2-thio substituent compared to a 2-oxo substituent. We have generally found that displacement of the 6-amino group of 6-amino-2-thiouracil by nucleophiles, *e.g.*, phenylhydrazines, requires longer reaction times resulting in poorer yields compared with the analogous displacement in 6-aminouracil (reference 1 and unpublished observations). Decreased reactivity of the 6-amino group of **2** explains the ability to isolate it from these reactions; we have never found a trace of the 2-oxo analog, **7**, in similar reactions in the uracil series.

Attempts to prepare **7** have thus far failed. For example, reaction of **6** with 6*N* hydrochloric acid causes both hydrolysis of the 2-methylmercapto group and cyclization resulting in **8**. This was not surprising because prolonged (1 hour) reflux of 2-methylmercapto-6-(*p*-tolylhydrazino)-4-pyrimidone in *N* hydrochloric acid produced only **8**, and short (20 minutes) exposure to acid produced the methylmercapto pyrimidoindole where cyclization was effected without hydrolysis (1). It appears that cyclization of **6** occurs more readily than that of **2**.

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6-(Phenylhydrazino)uracils and -2-thiouracils represent "ene hydrazine" intermediates which have never been isolated during the Fischer reaction (6). Our ability to isolate the product of the [3,3] sigmatropic rearrangement step, *i.e.*, **2**, should permit detailed kinetic studies of the role of hydrogen ion concentration in its formation.

EXPERIMENTAL

Melting points were determined on a Mel-temp apparatus and are uncorrected. Nmr spectra were obtained with a Perkin-Elmer R-12B instrument equipped with a Nicolet TT7 Fourier Transform Accessory. Spectra were obtained in DMSO-*d*₆ solution and chemical shifts are reported in ppm (δ) from internal TMS. Elemental analyses were performed by HetChem Co., Harrisonville, MO, and by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

Reaction of **1** with Hydrochloric Acid.

A suspension of 6-(*p*-tolylhydrazino)-2-thiouracil, **1**, (1.0 g., 3.9 mmoles) in *N* hydrochloric acid (50 ml.) was heated at reflux for 1 hour. The reaction mixture was concentrated *in vacuo* to ca. 5 ml. and chilled. The resulting yellow solid was filtered and crystallized from *N* hydrochloric acid to give 388 mg. (35%) of 5-(2'-amino-5'-tolyl)-6-amino-2-thiouracil hydrochloride, m.p. > 350°; nmr: 12.02 δ (bd s, 2H, 1,3-H), 7.25 (m, 3H, 3', 4', 6'-H), 6.46 (bd s, 2H, 6-NH₂), 2.32 (s, 3H, CH₃).

Anal. Calcd. for C₁₁H₁₃ClN₄OS: C, 46.40; H, 4.60; N, 19.67. Found: C, 46.19; H, 4.67; N, 19.40.

The free base **2** was prepared by neutralizing an aqueous solution of the hydrochloride with sodium bicarbonate and crystallizing the resulting solid from water, m.p. > 350°; nmr: 11.71 δ (bd s, 2H, 1,3-H), 6.82 (d, 1H, 3'-H, *J* = 8.4 Hz), 6.67 (bd s, 3H, 6'-H and 6-NH₂), 6.60 (d, 1H, 4'-H, *J* = 8.4 Hz), 5.58 (bd s, 2H, 2'-NH₂), 2.11 (s, 3H, CH₃).

Reaction of **1** with Formic Acid.

A solution of 6-(*p*-tolylhydrazino)-2-thiouracil, **1**, (1.0 g., 3.9 mmoles) in 98% formic acid (40 ml.) was heated at reflux for 1 hour. The solution was poured into water (80 ml.), chilled and filtered yielding 150 mg. (17%) of 6-methyl-9H-pyrimido[4,5-*b*]indole-2-thio-4-one, **3**, m.p. > 350° (crystallized from 50% ethanol); nmr: 13.45 δ (bd s, 1H, 1-H), 12.04 (bd s, 1H, 9-H), 11.50 (bd s, 1H, 3-H), 7.62 (s, 1H, 5-H), 7.38 (d, 1H, 8-H, *J* = 8.1 Hz), 7.04 (d, 1H, 7-H, *J* = 8.1 Hz), 2.40 (s, 2H, CH₃).

Anal. Calcd. for C₁₁H₉N₃OS·0.5H₂O: C, 54.98; H, 4.20; N, 17.49. Found: C, 55.22; H, 4.30; N, 17.10.

The filtrate was evaporated to dryness and the brown residue dissolved in boiling water. After chilling, 435 mg. of a mixture (nmr) of two compounds was obtained. This mixture was stirred

in 1*N* hydrochloric acid (10 ml.). The undissolved solid was filtered and washed with water giving 340 mg. (31%) of 5-(2'-formylamino-5'-tolyl)-6-amino-2-thiouracil, **4**, m.p. > 350° (crystallized from water); nmr: 11.80 δ (bd s, 1H, 3-H), 11.50 (bd s, 1H, 1-H), 9.12 (s, 1H, CHO), 8.16 (m, 2H, 2'-NH and 3'-H), 7.16 (s, 1H, 6'-H), 6.97 (d, 1H, 4'-H, *J* = 7.2 Hz), 5.77 (s, 2H, NH₂), 2.26 (s, 3H, CH₃).

Anal. Calcd. for C₁₂H₁₂N₄O₂S·H₂O: C, 48.97; H, 4.79; N, 19.03. Found: C, 49.32; H, 4.93; N, 18.76.

The filtrate was neutralized with sodium bicarbonate and chilled, giving a light yellow solid. This was filtered and washed with water to give 15 mg. (2%) of 1-(*p*-tolyl)-3-carboxymethyl-1,2,4-triazole, **5**, m.p. 151-153°, identical (nmr, mixed m.p.) with a sample obtained (**3**) by hydrolysis of the corresponding carboxamide; nmr: 12.5 δ (bd s, 1H, CO₂H), 9.14 (s, 1H, 5-H), 7.72 (d, 2H, 2',6'-H, *J* = 7.6 Hz), 7.35 (d, 2H, 3', 5'-H, *J* = 7.6 Hz), 3.75 (s, 2H, CH₂).

Methylation of **2**

A solution of 5-(2'-amino-5'-tolyl)-6-amino-2-thiouracil, **2**, (50 mg., 0.2 mmole) in 1*N* sodium hydroxide (1 ml.) was treated with iodomethane (ca. 45 mg.) and stirred for 1 hour at room temperature. The solution was neutralized with acetic acid and chilled, yielding 41 mg. (79%) of 2-methylmercapto-5-(2'-amino-5'-tolyl)-6-amino-4-pyrimidone, **6**, m.p. > 350° (crystallized from ethanol); nmr: 6.74 δ (m, 5H, 3',4',6'-H and 6-NH₂), 4.67 (bd s, 2H, 2'-NH₂), 2.45 (s, 3H, SCH₃), 2.15 (s, 3H, 5'-CH₃).

Anal. Calcd. for C₁₂H₁₄N₄O₂S·0.33C₂H₅OH: C, 54.79; H, 5.81; N, 20.18. Found: C, 54.66; H, 5.91; N, 20.16.

Methylation of **3**

A solution of 6-methyl-9H-pyrimido[4,5-*b*]indole-2-thio-4-one, **3**, (50 mg., 0.21 mmole) in 1*N* sodium hydroxide (3 ml.) was treated with iodomethane (ca. 45 mg.) and stirred for 1 hour at room temperature. The solution was neutralized with acetic acid and chilled, yielding 48 mg. (92%) of 2-methylmercapto-6-methyl-9H-pyrimido[4,5-*b*]indole-4-one, m.p. > 350°, identical (nmr) with an authentic sample.

Thermal cyclization of **2**

A suspension of 5-(2'-amino-5'-tolyl)-6-amino-2-thiouracil, **2**, (50 mg., 0.2 mmole) in *N,N*-dimethylaniline was heated at reflux for 2 hours. The solution was chilled and the precipitate filtered, giving 36 mg. (78%) of 6-methyl-9H-pyrimido[4,5-*b*]indole-2-thio-4-one, **3**, identical with that obtained by the action of formic acid on 6-(*p*-tolylhydrazino)-2-thiouracil (see above).

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