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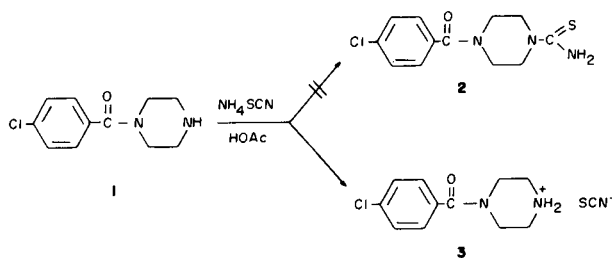
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1-(*p*-Chlorobenzoyl)piperazine failed to yield a thiocarbamoyl derivative when treated with ammonium thiocyanate; only a thiocyanate salt was formed. However, it reacted readily with benzoylisothiocyanate to form the expected 1-(*N*-benzoylthiocarbamoyl)-4-(*p*-chlorobenzoyl)piperazine. Benzoylisothiocyanate also produced an *N*-benzoylthiocarbamoyl derivative of 1-formylpiperazine.

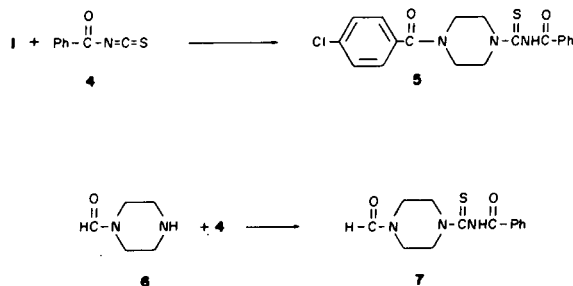
J. Heterocyclic Chem., **20**, 243 (1983).

In previous publications we reported a convenient preparation of monoaroylpiperazines (1) and the synthesis of 1-amidino-4-aryloperazines (2). This report describes efforts to prepare thiocarbamoyl derivatives of monoacyloperazines. New types of piperazine derivatives are of interest for their potential physiological activity (3).

1-Aryl-4-thiocarbamoylpiperazines had been prepared previously by Nagarajan, *et al.*, (4) who treated 1-aryloperazines with ammonium thiocyanate in aqueous acetic acid solutions. Evaporation of the mixtures to dryness yielded the desired thiocarbamoyl derivatives. When we applied this procedure to 1-*p*-chlorobenzoyl piperazine (1), however, the product obtained was a thiocyanate salt (3) rather than the intended thiocarbamoyl derivative (2). The substance gave the blood-red ferric chloride test characteristic of the thiocyanate ion and showed the thiocyanate infrared band at 4.75 μ . The striking contrast seen in behavior of the 1-acyloperazine 1 as compared with that of the 1-aryloperazines was surprising, but other unexpected failures of the ammonium thiocyanate reaction have been recorded; 1-adamantylamine, for example, also merely yielded the thiocyanate salt when treated with ammonium thiocyanate (5).



Benzoylisothiocyanate (4), formed *in situ* from benzoylchloride and ammonium thiocyanate (6), proved to have a higher reactivity, since it readily converted compound 1 into 1-(*N*-benzoylthiocarbamoyl)-4-(*p*-chlorobenzoyl)piperazine (5). Similarly, benzoylisothiocyanate (4) converted 1-formylpiperazine (6) into 1-formyl-4-(*N*-benzoylthiocarbamoyl)piperazine (7).



It is reported that the benzoyl group of *N*-benzoylthiocarbamoyl derivatives of amines can be removed by selective alkaline hydrolysis (6). Our attempts to remove the benzoyl groups from products 5 and 7 by the same means were unsuccessful. Compound 5 readily yielded a sodium salt in an initial neutralization reaction, but after it was heated with excess sodium hydroxide, *p*-chlorobenzoic acid was the only product easily separated (80% yield). Hydrolysis of 5 with hydrochloric acid also yielded only *p*-chlorobenzoic acid. Sodium hydroxide hydrolysis of the formyl derivative 7 yielded no well-defined product.

EXPERIMENTAL

Reaction of *p*-Chlorobenzoylpiperazine (1) With Ammonium Thiocyanate and Acetic Acid.

A mixture of *p*-chlorobenzoylpiperazine (1) (2.25 g, 0.01 mole) and ammonium thiocyanate (0.8 g, 0.01 mole) was dissolved in water (15 ml). Acetic acid (1.5 ml) was added and the solution was heated for 15 hours with repeated additions of water. The solution was then filtered to remove traces of a white solid (ca. 15 mg). The filtrate was evaporated to dryness to obtain a white solid which after washing with chloroform melted at 128-132°. The product was identified as a thiocyanate salt of *p*-chlorobenzoylpiperazine. The infrared spectrum displayed a SCN^- band at 4.75 μ and an aqueous solution of the solid gave a blood red color with ferric chloride. The nmr spectrum (δ 3.28-3.85 (br, 4, piperazine methylenes) and 3.85-4.43 (br, 4, piperazine methylenes), 7.45 (s, 4, aromatic)) taken in deuteriochloroform-trifluoroacetic acid corresponded to the same spectra obtained from aroyl piperazine hydrochlorides (1).

4-*p*-Chlorobenzoyl-1-(*N*-benzoylthiocarbamoyl)piperazine (5).

Ammonium thiocyanate (3.75 g, 0.0167 mole) was dissolved in acetone (25 ml) and benzoyl chloride (2.35 g, 0.0167 mole) was added dropwise. The mixture was boiled for 10 minutes. A solution of *p*-chlorobenzoylpiperazine (1) (3.75 g, 0.0167 mole) in acetone (25 ml) was then added.

The mixture was kept at room temperature for 30 minutes and then poured into five times its volume of water. The solid that precipitated was collected by filtration and crystallized from ethanol. The yield was

3.2 g, (49.5%), mp 161-162°; ir (Nujol): 3.10 (NH), 5.90, 6.10, 6.24, 6.52, 7.95, 8.06, 8.25, 8.38, 8.50, 9.20, 9.92, 11.70, 13.28, 13.98 μ ; nmr (deuteriochloroform-trifluoroacetic acid): δ 3.67-4.50 (m, 8, piperazine methylenes), 7.27-8.03 (m, 8, aromatic).

Anal. Calcd. for $C_{19}H_{18}ClN_3O_2S$: C, 58.84; H, 4.65; N, 10.84; S, 8.26. Found: C, 58.87; H, 4.85; N, 10.80; S, 8.12.

Hydrolysis of 4-(*p*-Chlorobenzoyl)-1-(*N*-benzoylthiocarbamoyl)piperazine (5).

(a) With an Equimolar Amount of Sodium Hydroxide.

4-(*p*-Chlorobenzoyl)-1-(*N*-benzoylthiocarbamoyl)piperazine (5) (1.06 g, 0.00275 mole) was added to a solution of sodium hydroxide prepared by dissolving 0.11 g, (0.00275 mole) of sodium hydroxide in 15 ml of ethanol. The mixture was refluxed overnight (ca. 18 hours). It was then cooled and the white solid product that precipitated was collected by filtration. The product (0.6 g, mp 210-212°) was the sodium salt of 5; an aqueous solution of it on acidification with dilute hydrochloric acid gave a white crystalline precipitate which was identified as 5 by mixed melting point and infrared spectrum.

(b) With Excess of Sodium Hydroxide.

4-(*p*-Chlorobenzoyl)-1-(*N*-benzoylthiocarbamoyl)piperazine (5) (1.94 g, 0.005 mole) was suspended in ethanol (25 ml). Sodium hydroxide (1.0 g) dissolved in 2.5 ml of water was added. The mixture was heated under reflux for 4.5 hours. The mixture was cooled and the white solid that precipitated was collected by filtration. The solid was dissolved in water and the solution so obtained was acidified with dilute hydrochloric acid. A thick white precipitate was formed. The solid was collected by filtration and identified as *p*-chlorobenzoic acid by mixed melting point (mp 241-242°) and infrared spectrum. The yield of *p*-chlorobenzoic acid was 0.64 g (82%).

Acid Hydrolysis of 5.

4-(*p*-Chlorobenzoyl)-1-(*N*-benzoylthiocarbamoyl)piperazine (5) (0.5 g, 0.0013 mole) was dissolved in tetrahydrofuran (10 ml). Concentrated hydrochloric acid (5 ml) was then added and the mixture was concentrated on a rotary evaporator and then basified with aqueous sodium hydroxide (20%). The aqueous layer was separated from the tetrahydrofuran layer and was acidified with dilute hydrochloric acid. A white solid was obtained. The product (0.12 g (60%), mp 241-242°) was identified as *p*-chlorobenzoic acid by mixed melting point and infrared spectrum.

Reaction of 1-formylpiperazine (6) With Benzoyl Chloride and Ammonium Thiocyanate.

Ammonium thiocyanate (3.2 g, 0.042 mole) was dissolved in acetone (60 ml) and benzoyl chloride (5.6 g, 0.04 mole) was added dropwise. The mixture was boiled for 10 minutes and then a solution of 1-formylpiperazine (6) (8) (4.56 g, 0.04 mole) in acetone (60 ml) was added slowly. The mixture was kept at room temperature for 30 minutes and then poured into 5 times its volume of water. A small amount of solid that precipitated immediately was collected by filtration. This product after crystallization from ethanol melted at 174-175° and analyzed for 1,4-bis-(*N*-benzoylthiocarbamoyl)piperazine solvated with one-half mole of ethanol. The yield was 0.6 g (3.5%); ir (Nujol): 3.00, 5.93, 6.00, 6.52, 7.75, 7.85, 8.10, 8.40, 8.70, 9.18, 9.80, 10.32, 10.60, 11.50, 14.16.

Anal. Calcd. for $C_{20}H_{20}N_4O_2S_2 \cdot \frac{1}{2} C_2H_5OH$: C, 57.93; H, 5.29; N, 12.87; S, 14.71. Found: C, 57.44; H, 5.02; N, 12.75; S, 14.67.

The filtrate on standing deposits 4-*N*-benzoylthiocarbamoyl-1-formylpiperazine (7) as a white crystalline solid which was collected by filtration. The yield of (7) was 5.65 g (51%), mp 142.5-143.5° (from methylene chloride-petroleum ether (bp 30-60°)); ir (Nujol): 5.90, 6.05, 6.54, 8.00, 8.50, 9.40, 9.72, 10.00, 11.64, 14.40; nmr (deuteriochloroform-trifluoroacetic acid): δ 3.67-4.43 (m, 8, piperazine methylenes), 7.47-8.03 (m, 5, aromatic), 8.30 (s, 1, -CHO).

Anal. Calcd. for $C_{13}H_{13}N_3O_2S$: C, 56.31; H, 5.45; N, 15.16; S, 11.54. Found: C, 56.07; H, 5.42; N, 14.92; S, 11.31.

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