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Synthesis of 1-Arylpiperazine-4-thiocarboxamides*

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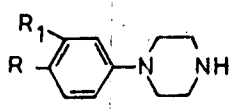
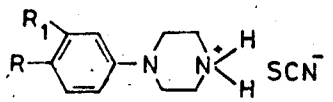
The reaction of 1-arylpiperazine salts with hot aqueous ammonium thiocyanate for a short time affords only the thiocyanate salts. 1-Arylpiperazine-4-thiocarboxamides have been obtained by prolonged heating of the aqueous solutions of the thiocyanate salts alone or in the presence of acetic acid. Acid or base hydrolysis of 1-aryl-4-benzoylthiocarbamoylpiperazines yields the same thiocarboxamides, which are formed also directly by the action of vinylisothiocyanate on 1-arylpiperazines.

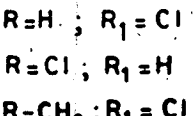
IN connection with some synthetic work, we were in need of 1-aryl-4-piperazinethiocarboxamides. A literature search showed that a few had been reported[1] in 1964 and that one of them, namely 1-(3-chloro-4-methylphenyl)piperazine-4-thiocarboxamide, possessed schistosomicidal properties[2]. We subjected the phenylpiperazines I-IV to reaction with thiocyanic acid under the reported[1] conditions and obtained crystalline products. The melting points of those from I, II and III agreed with those recorded[1]; the analytical values of all the four products were consistent with the thiocarboxamide structures. However, the presence of a strong absorption band in the IR spectra of the products (nujol) around 2200-2300 cm^{-1} and the deep red colour their aqueous solutions gave with ferric chloride indicated that the products were only the isomeric thiocyanate salts VI-IX. Likewise, the biologically important bases X and XI afforded only the thiocyanate salts under these conditions.



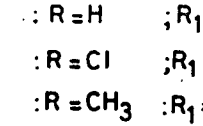
I : R=H ; R_1=Cl
II : R=Cl ; R_1=H
III : R=CH_3 ; R_1=Cl
IV : R=OCH_3 ; R_1=H



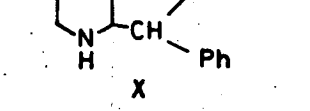
VI : R=H ; R_1=Cl
VII : R=Cl ; R_1=H
VIII : R=CH_3 ; R_1=Cl
IX : R=OCH_3 ; R_1=H



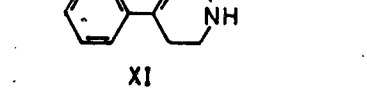
X



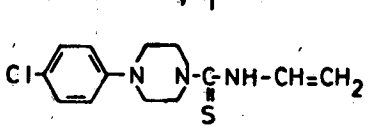
XI



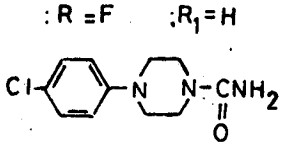
XII : R=H ; R_1=Cl
XIII : R=Cl ; R_1=H
XIV : R=CH_3 ; R_1=Cl
XV : R=OCH_3 ; R_1=H
XVI : R=F ; R_1=H



XVII : R=H ; R_1=Cl
XVIII : R=Cl ; R_1=H
XIX : R=CH_3 ; R_1=Cl
XX : R=OCH_3 ; R_1=H
XXI : R=F ; R_1=H



XXII



XXIII

*Contribution No. 158 from CIBA Research Centre, Goregaon, Bombay 63.

There are several reported syntheses of N-thiocarboxamides in the literature under very similar conditions. It was of interest to check this in one case and we chose 1,2,3,4-tetrahydroquinoline. It was found that the reaction of this base for a short time with thiocyanic acid gave the salt, while heating an aqueous solution at 100° for 4 hr led to the thioamide in 25% yield, in agreement with the literature report[3]. Under similar conditions, the thiocyanate salt VI was not converted to the thioamide to any appreciable extent. However, successive treatments with water and evaporation during 10 hr gave the thioamide XII in 25% yield. Alternatively, the piperazines I and IV could be treated with acetic acid and ammonium thiocyanate and then subjected to the afore-mentioned process for 15 hr to give 25-30% yield of the thioamides XII and XV respectively. Tetrahydroquinoline is a much weaker base than the phenylpiperazines and the piperidines X and XI; an aqueous solution of its thiocyanate salt can be expected to contain an appreciable concentration of the dissociated free base, which would react with thiocyanic acid irreversibly to form the thioamide. On the other hand, the salts VI-IX may dissociate less readily and to a lesser extent. The greater ease of conversion of tetrahydroquinoline to its N-thiocarboxamide compared to the phenylpiperazines I-IV and the piperidines X and XI is thus explained.

Treatment of an aqueous solution of the hydrochloride salt of II with potassium cyanate in the cold gave immediately the N-carboxamide (XXIII) as reported[1] (no band in IR for OCN^-; amide band at 1655 cm^{-1}). The difference between the behaviour of phenylpiperazines towards cyanic and thiocyanic acids can be attributed to the greater electrophilicity of the former.

As the previously described conversion of phenylpiperazines to N-thiocarboxamides was unsatisfactory, we explored another route, namely via the initial formation of the benzoylthioureas XVII-XXI. These were readily prepared in high yield from the piperazines and other bases using benzoylisothiocyanate. Hot acid hydrolysis of the derivative XVIII selectively removed the benzoyl group to give the thioamide (XIII) in 33% yield. The 3-chloro (XVII) and 4-methoxy (XX) analogues resisted hydrolysis under these conditions. It was possible in these cases to use alkaline conditions to remove the benzoyl group selectively to give the desired thioamides in about 40% yield. Likewise the 4-fluoro (XXI) and 3-chloro-4-methyl (XIX) derivatives were converted to the thioamides (XVI) and (XIV) in 22 and 85% yields respectively.

In another approach, 1-(4-chlorophenyl)piperazine (II) was treated with vinylisothiocyanate to give presumably the vinylthiourea (XXII), which in the process of working up, lost the moisture-sensitive vinyl group to afford the thioamide (XIII). Although the yield was reasonable (63%), this procedure required the use of chromatography.

While a number of the desired N-thiocarboxamides did thus become available, no single method was convenient for all. We have found that the formation of *t*-butylthioureas using *t*-butylisothiocyanate and their hydrolysis under mild conditions, a generally satisfactory procedure for the preparation of N-thiocarboxamides. A report on this will be published later.

Experimental Procedure

All melting points are uncorrected.

Formation of thiocyanate salts — To a solution of 1-(3-chlorophenyl)piperazine dihydrochloride (1 g, 4 mmoles) in water (5 ml) was added ammonium thiocyanate (0·38 g, 5 mmoles) and the solution heated at 80° for 15-90 min. Upon cooling, the thiocyanate salt crystallized out and was recrystallized from water; 0·4 g, m.p. 121-3°. The same salt was obtained when the dihydrochloride (1·15 g, 5 mmoles) in 1*N* HCl (10 ml) and ammonium thiocyanate (0·38 g, 5 mmoles) in water (2 ml) were heated under reflux for 15 min and cooled. Other salts were similarly obtained in yields ranging from 25 to 75%, and are recorded in Table 1.

Preparation of N-thiocarboxamides: (a) *From thiocyanate salts* — 1-(3-Chlorophenyl)piperazine thiocyanate (0·2 g) was dissolved in hot water (5 ml) and the solution evaporated to dryness on a water-bath. Addition of water (5 ml) and evaporation was repeated several times during 10 hr. The final residue was triturated with warm water and filtered. The precipitate was recrystallized from ethanol to give colourless crystals (50 mg) of the thiocarboxamide (XII); m.p. 174-6°, showing negative ferric reaction (Found: C, 51·52; H, 5·68; N, 16·22. $C_{11}H_{14}ClN_3S$ requires C, 51·66; H, 5·52; N, 16·44%). The same product was obtained when a solution

Table 1 — Thiocyanate Salts of Various Piperazines

Thiocyanate salt of	m.p. °C	Mol. formula	Calc. (%)			Found (%)		
			C	H	N	C	H	N
1-(3-Chlorophenyl)piperazine	121-3 (121-4·2)[1]	$C_{11}H_{14}ClN_3S$	51·66	5·52	16·44	51·57	5·39	16·35
1-(4-Chlorophenyl)piperazine	176-8 (172-6)[1]	$C_{11}H_{14}ClN_3S$	51·66	5·52	16·44	51·77	5·60	16·22
1-(4-Methoxyphenyl)piperazine (2HSCN)	139-41	$C_{13}H_{18}N_4OS_2$	50·31	5·85	—	50·82	5·95	—
1-(3-Chloro-4-methylphenyl)piperazine	136-7 (133·2-5·8)[1]	$C_{12}H_{16}ClN_3S$	53·43	5·98	15·58	53·63	6·17	15·79
1,1-Diphenyl-2-piperidylmethane	186-7	$C_{19}H_{22}N_2S$	73·52	7·14	9·03	73·52	7·24	8·78
4-Phenyl-1,2,5,6-tetrahydropyridine	120	$C_{12}H_{14}N_2S$	66·03	6·47	12·84	66·14	6·25	13·22
1,2,3,4-Tetrahydroquinoline	118-19 (120)[3]	$C_{10}H_{12}N_2S$	62·48	6·29	14·58	62·15	6·60	14·76

TABLE 2 — BENZOYLTHIOUREAS SYNTHESIZED

Benzoylthiourea from	m.p. °C	Mol. formula	Calc. (%)			Found (%)		
			C	H	N	C	H	N
1-(3-Chlorophenyl)piperazine	149-51	$C_{18}H_{18}ClN_3OS$	60·08	5·04	11·68	60·37	5·48	11·22
1-(4-Chlorophenyl)piperazine	174-6	$C_{18}H_{18}ClN_3OS$	60·08	5·04	11·68	59·65	4·93	11·62
1-(3-Chloro-4-methylphenyl)piperazine	165-6	$C_{19}H_{20}ClN_3OS$	61·05	5·39	11·24	61·29	5·14	11·57
1-(4-Methoxyphenyl)piperazine	158-9	$C_{19}H_{21}N_3O_2S$	64·21	5·96	11·83	64;31	6·12	11·53
1-(4-Fluorophenyl)piperazine	166-8	$C_{18}H_{18}FN_3OS$	62·96	5·28	12·24	62·97	5·42	12·44
1,2,3,4-Tetrahydroquinoline	144-5	$C_{17}H_{16}N_2OS$	68·90	5·44	9·45	69·02	5·63	9·08

of the piperazine base (2·8 g) and ammonium thiocyanate (1·2 g) in acetic acid (2 ml) was evaporated with repeated additions of water (15 ml) during 15 hr; yield 0·9 g; m.p. 176°. Similarly 1-(4-methoxyphenyl)piperazine was converted to its N-thiocarboxamide XV; m.p. 174° (Found: C, 57·44; H, 6·99; N, 16·51. $C_{12}H_{17}N_3OS$ requires C, 57·35; H, 6·82; N, 16·72%) and 1,2,3,4-tetrahydroquinoline to the thiocarbamoyl derivative (yield 25%), m.p. 140-41° (lit.[3] m.p. 141°) (Found: C, 62·89; H, 6·60; N, 14·51. $C_{10}H_{12}N_2S$ requires C, 62·48; H, 6·29; N, 14·58%).

(b) *From N-benzoylthiocarbamoyl derivatives*: (i) *Preparation of benzoylthioureas* — A solution of 1-(3-chlorophenyl)piperazine (4 g) in benzene (25 ml) was treated under stirring and cooling with benzoylisothiocyanate[4] (3·2 g). The solution was then heated under reflux for 1 hr. After concentration to half volume, hexane (10 ml) was added and the crystalline product filtered off. Recrystallization from acetone-ethanol afforded the benzoylthiourea (5·3 g, 74%), m.p. 149-51°. The benzoylthioureas are listed in Table 2.

(ii) *Alkaline hydrolysis of benzoylthioureas to thiocarboxamides* — 1-(3-Chloro-4-methylphenyl)-4-(N-benzoylthiocarbamoyl)piperazine (XIX) (3·74 g) in ethanol (50 ml) was mixed with sodium hydroxide (2 g) in water (5 ml). The mixture was heated under reflux for 6 hr. The resultant solution was evaporated to dryness, and the residue triturated with water. The insoluble part was recrystallized once from aq. isopropanol and then from methylene chloride-hexane to give 1-(3-chloro-4-methylphenyl)-4-thiocarbamoylpiperazine (XIV) (2·3 g, 85%); m.p. 173-5° (Found: C, 53·85; H, 6·11; N, 15·26. $C_{12}H_{16}ClN_3S$ requires C, 53·43; H, 5·98; N, 15·58%). Likewise were obtained 1-(4-fluorophenyl)-4-thiocarbamoylpiperazine (XVI) (yield 22%); m.p. 160° (from isopropanol) (Found: C, 55·08; H, 5·83; N, 17·38. $C_{11}H_{14}FN_3S$ requires C, 55·22; H, 5·90; N, 17·56%), 1-(3-chlorophenyl)-4-thiocarbamoylpiperazine (XII) (yield 35%), m.p. 175-8° (from alcohol), identical with the product obtained from thiocyanate salt; and 1-(4-methoxyphenyl)-4-thiocarbamoylpiperazine (XV) (yield 40%), m.p. 173-6° (from methanol), identical with the product obtained from thiocyanate salt.

(iii) *Acidic hydrolysis of benzoylthioureas to thiocarboxamides* — A solution of 1-(4-chlorophenyl)-4-(N-benzoylthiocarbamoyl)piperazine (XVIII) (0·5 g) in dioxane (10 ml) containing conc. HCl (5 ml) was heated under reflux for 2·5 hr. Upon cooling and basification with aq. sodium hydroxide, a crystalline precipitate separated. This was recrystallized from ethanol to afford the thiocarboxamide (XIII) (0·2 g, 33%); m.p. 171-2°; m.m.p. with starting material was depressed (Found: C, 51·62; H, 5·61; N, 16·20. $C_{11}H_{14}ClN_3S$ requires C, 51·66; H, 5·52; N, 16·44%).

(c) *Using vinylisothiocyanate* — A solution of 1-(4-chlorophenyl)piperazine (2·2 g) in ether (15 ml) was treated under stirring and cooling with vinylisothiocyanate[5] (1 g) in ether (10 ml) during 15 min. The mixture was stirred for 2·5 hr and then evaporated. The black residual solid was triturated with benzene and hexane and then filtered through a column of silica gel (35 g) in benzene. The clean product which thus resulted was recrystallized from acetone-ethanol to give the thiocarboxamide (XIII), (1·8 g, 63%); m.p. 174-6°, identical with the one obtained by the hydrolysis of benzoylthiourea.

Action of potassium cyanate on 1-(4-chlorophenyl)-piperazine — To a solution of 1-(4-chlorophenyl)-piperazine in water (10 ml) and conc. HCl (1 ml) was added potassium cyanate (0·81 g) with shaking. A white solid immediately separated; after cooling this was filtered and washed with water to give the urea (XXIII) (1·9 g); m.p. 198-200° (lit.[1] m.p. 198·2-202°).

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