N,N'-Thiocarbonylbis(Cyclic Nitrogen Heteroparaffins)

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A series of thioureas, in which the two amido nitrogens are incorporated into separate rings, are prepared by the action of thiophosgene on hetercyclic amines. The infrared spectra are studied and the data correlated with that of prior investigations. The results of preliminary pharmacological testing are reported.

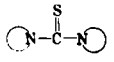
THIOUREA and its many derivatives have proven their therapeutic effectiveness in a variety of well-known pharmaceuticals (1). Incorporation of thiourea into cyclic structures tends to lower the toxicity of the parent compound (2). Though many of these cyclized thioureas are known, few attempts have been made to synthesize both of the amido-nitrogens of thiourea into separate rings (3). *N,N'*-Thiocarbonyldipiperidine was first synthesized from dipiperidyl thiuram disulfide (4); in 1924, a method for preparing symmetrically tetra-substituted thioureas was introduced by Dyson *et al.* (5). Rieds' recent synthesis of *N,N'*-thiocarbonylbis(3,5-dimethylpyrazole) and *N,N'*-thiocarbonyldiimidazole is the first preparation of *N,N'*-di-*N*-heteroaromatic thiocarbonyl compounds (6).

This investigation deals with the synthesis of a number of symmetrical *N,N'*-thiocarbonylbis-(cyclic *N*-heteroparaffins) such as Fromm prepared (4) by a modified version of the Dyson method (5).

Infrared Spectral Information.[1]—All the compounds show strong absorption at or near 1480 cm.$^{-1}$, and this band is assigned to the —N—C=S moiety. Weak absorption in the 660 to 667 cm.$^{-1}$ is also assigned to this moiety. A band in the region 1360 to 1370 cm.$^{-1}$ is believed due to the C=S group. Absorption in the 1280 to 1300 cm.$^{-1}$ region appears to be caused by the N—C group (7). Absorption for the Ried *N,N'*-thiocarbonylbis *N*-heteroaromatics is in the same regions for the major bands as the compounds used in this research (6).

Preliminary Pharmacology.—The investigation of *in vitro* anthelmintic, C.N.S., schistosomicidal, and trichomonacidal activity, as well as a broad antibacterial screening has led to negative expectations.

TABLE I.—*N,N'*-THIOCARBONYLBIS (CYCLIC NITROGEN HETEROPARAFFINS)



N,N'-Substituted Thiocarbonyls	% C[a] Calcd.	% C[a] Obs.	% H[a] Calcd.	% H[a] Obs.	% N[a] Calcd.	% N[a] Obs.	% S[a] Calcd.	% S[a] Obs.	M.p., ° C.
Dipyrrolidyl-	58.7	58.7	8.70	8.82	15.2	15.2	17.4	17.1	127–28
Dipiperidyl-	62.2	62.2	9.45	9.44	13.2	13.4	15.1	14.9	
Bis(2-ethylpiperidyl)-	67.2	67.2	10.5	10.6	...	...	...	...	150–160/2 mm.[b]
Bis(2-methylpiperidyl)-	64.9	65.2	10.0	10.1	11.7	11.1	...	...	146–154/2 mm.[b]
Bis(3-methylpiperidyl)-	65.0	65.0	10.0	9.97	11.7	11.7	13.3	13.2	148–158/4 mm.[b]
Bis(4-methylpiperazyl)-	54.5	54.9	9.10	9.49	23.1	22.3	13.2	13.1	82–4
Dimorpholyl-	50.0	50.3	7.40	7.89	13.0	12.9	14.8	14.6	89–90
Bis(1,2,3,4-tetrahydroisoquinolyl)-	74.0	73.4	6.49	6.49	9.09	8.84	10.4	10.3	173–75
Bis(1,2,3,4-tetrahydroquinolyl)-	74.0	73.7	6.49	6.49	9.09	8.93	10.4	10.0	168

[a] Duplicate C, H, N, and S by Dr. G. Weiler and Dr. F. B. Strauss, Microanalytical Laboratory, Oxford, England. [b] Yellow to brown oil.

EXPERIMENTAL

General Synthesis, Isolation, and Purification of the N,N' - Thiocarbonylbis(cyclic N - heteroparaffins).—Two-tenths mole of the corresponding cyclic amine is dissolved in 100 ml. of ether (or acetone), and placed in a three-necked reaction flask fitted with a separator, reflux condenser, and stirrer. The flask is placed in an ice bath; 0.05 mole of thiophosgene is dissolved in 50 ml. of ether or acetone and added dropwise from the separator to the reaction flask, stirring constantly. Reflux 1 hour past the addition of the last drop of thiophosgene solution. Heating will be necessary during this last hour of reflux. The reaction is violent at the start, so the thiophosgene addition must be made very slowly. The amine hydrochloride separates as an insoluble solid and is removed from the ethereal or acetone solution by filtration after the reaction is completed. The filtrate is decolorized with charcoal, dried over anhydrous sodium sulfate, and evaporated to either a thick viscous yellow-brown oil or a low-melting white or yellow solid, depending on the specific case. The product is vacuum distilled at low pressures (near 1 or 2 mm.). The oils are washed with ligroin repeatedly, and the solid products recrystallized from ethanol. Yields of about 50% are the rule. (See Table I.)

Received November 8, 1963, from the College of Pharmacy, University of Kentucky, Lexington.
Accepted for publication January 6, 1964.

[1] Beckman IR-8 spectrophotometer; 0.1 mm. path; chloroform solvent.

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