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Some Acyl Thioureas

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As a part of a program of preparing various sulfur compounds[1] from thiourea and N-alkylthioureas for the purpose of studying their pharmacological properties, it has seemed of interest to report the synthesis of a series of lower acyl derivatives of thiourea and N-methylthiourea.

A large number of amides and ureas have been prepared and tested for their probable use in medicine. Several of these have been found to possess distinct hypnotic activity and are used in medical practice. Recent studies[2,3] in this field have correlated much of the information on the hypnotic activity of the ureas and ureides. De Beer, Buck, Ide and Hjort[4] have prepared and studied the hypnotic effects of some aryl and unsymmetrical alkylaryl thioureas. A few acyl derivatives of thiourea have been prepared but their physiological properties were not reported. Dixon[5] prepared acetyl- and isovaleryl-thiourea by the reaction of ammonia with the necessary acyl isothiocyanate, and isobutyrylthiourea by heating S-isobutyrylisothiourea at its melting point.

The acyl derivatives were prepared by allowing the appropriate acyl halide to react, under suitable conditions, with thiourea or methylthiourea in the presence of toluene and then refluxing for several hours. If the reaction of an acyl halide with thiourea is carried out at room temperature in a solvent, the hydrochloride of S-acylisothiourea is obtained. However, if this is then refluxed in toluene for several hours the N-acyl product is formed.

$$RCOCl + NH_2CSNH_2 \longrightarrow RCOS{-}C(=NH){-}NH_2{\cdot}HCl \longrightarrow RCONHCSNH_2 + HCl$$

Preliminary studies of the toxicity and hypnotic activity of these compounds have been made on female albino mice. A suspension of the compounds in 0.5% gum tragacanth was given orally by means of a stomach tube. Although the results are approximate only, because of the small number of animals used, they are accurate enough to show that the compounds are relatively inactive as hypnotics. The toxicity data are recorded in Table I.

Experimental

Acyl Thioureas.—The procedure for the preparation of these compounds is illustrated by the synthesis of *n*-octanoylthiourea.

In a one-liter, 3-necked flask, equipped with a mechanical stirrer and a reflux condenser, connected with a water trap for collecting hydrogen chloride, was placed a mixture of 19 g. (0.25 mole) of thiourea, and 40.6 g. (0.25 mole) of *n*-octanoyl chloride, in 250 ml. of toluene. The solution was stirred and refluxed for sixteen hours, or until hydrogen chloride was no longer evolved. The product, *n*-octanoylthiourea, was isolated and purified by evaporating the toluene on a steam-bath and recrystallizing the residue 3 times from boiling anhydrous alcohol, yield 35 g., 69%

(1) (a) Miller, Munch and Crossley, *Science*, **81**, 615 (1935); THIS JOURNAL, **58**, 1090 (1936). (b) Crossley, Miller, Hartung and Moore, *J. Org. Chem.*, **5**, 238 (1940).

(2) Volwiler and Tabern, THIS JOURNAL, **58**, 1352 (1936).

(3) Buck, *ibid.*, **56**, 1607 (1934); de Beer and Hjort, *J. Pharmacol.*, **52**, 211 (1934); Buck, Hjort, de Beer, Ferry and Ide, *ibid.*, **60**, 369 (1937).

(4) De Beer, Buck, Ide and Hjort, *ibid.*, **57**, 19 (1936).

(5) Dixon, *J. Chem. Soc.*, **117**, 720 (1920).

TABLE I

Acyl group	Formula	Yield, %	M. p., °C.[a]	Crystal form	Nitrogen, % Calcd.	Nitrogen, % Found	Toxicity data on mice,[b] MLD, mg./kg.
			ACYL THIOUREAS				
Acetyl	$C_3H_6ON_2S$	34	165	Rhombic			200
Propionyl	$C_4H_8ON_2S$	60	148	Prismatic needles	21.21	21.09	95
Valeryl	$C_6H_{12}ON_2S$	65	139	Rhombic plates	17.50	17.36	1625
Hexanoyl	$C_7H_{14}ON_2S$	68	138	Rhombic plates	16.09	16.05	>5000
Heptanoyl	$C_8H_{16}ON_2S$	43	133	Rhombic plates	14.89	14.75	>5000
Octanoyl	$C_9H_{18}ON_2S$	40	138	Rhombic plates	13.86	13.80	>5000
Undecanoyl	$C_{12}H_{24}ON_2S$	65	136.5	Needles	11.48	11.49	>5000
Isobutyryl[c]	$C_5H_{10}ON_2S$	47	114.5	Rhombic plates	19.18	18.99	50
Isovaleryl[c]	$C_6H_{12}ON_2S$	40	157.5	Prismatic needles	17.50	17.59	140
Isohexanoyl	$C_7H_{14}ON_2S$	46	155	Rhombic plates	16.09	16.07	1000
Ethyl-iso-amylacetyl	$C_{10}H_{20}ON_2S$	..	89.5	.....	12.96	12.85	135
			ACYL METHYLTHIOUREAS				
Acetyl	$C_4H_8ON_2S$	45	170.5	Rhombic	21.21	21.17	70
Propionyl	$C_5H_{10}ON_2S$	68	127.5	Rhombic	19.18	19.18	225
Valeryl	$C_7H_{14}ON_2S$	57	93	Thick needles	16.09	16.10	4600
Hexanoyl	$C_8H_{16}ON_2S$	70	85	Rhombic plates	14.89	14.85	>5000
Heptanoyl	$C_9H_{18}ON_2S$	69	76	Prismatic needles	13.86	13.73	>5000
Octanoyl	$C_{10}H_{20}ON_2S$	65	81.5	Rhombic	12.95	12.87	>5000
Undecanoyl	$C_{13}H_{26}ON_2S$	31	80.5	Plates	10.85	10.65	>5000
Isobutyryl	$C_6H_{12}ON_2S$	50	121.5	Rhombic plates	17.50	17.34	110
Isovaleryl	$C_7H_{14}ON_2S$	57	156	Rhombic	16.09	15.96	140
Isohexanoyl	$C_8H_{16}ON_2S$	64	78.5	Plates	14.89	14.78	....

[a] All melting points are uncorrected. [b] We are indebted to Mr. G. W. Webster for the pharmacological testing of these compounds. [c] Prepared by Dixon, *J. Chem. Soc.*, **117**, 720 (1920).

melting at 138°.[6] The acyl thioureas are insoluble in water, sodium bicarbonate solution and sodium hydroxide. They are readily soluble in alcohol, acetone, etc.

Acyl Methylthioureas.—These compounds were prepared in the same manner as the corresponding thiourea derivatives, using methylthiourea in place of thiourea.

Rearrangement of Acetylisothiourea.—S-Acetylisothiourea hydrochloride,[5] m. p. 98–100°, was prepared by the reaction of acetyl chloride with thiourea in acetone at room temperature. This material was refluxed about fourteen hours in toluene until the evolution of the hydrogen chloride gas had ceased. The product obtained, N-acetylthiourea, m. p. 164°, corresponds identically to the compound, m. p. 165°, prepared by refluxing acetyl chloride with thiourea in toluene for fourteen hours.

(6) All melting points are uncorrected.

Summary

A series of acyl thioureas and acyl N-methylthioureas has been prepared and identified. They may be prepared by refluxing the acyl chloride with thiourea or N-methylthiourea in toluene for several hours or by rearrangement of the acylisothiourea by refluxing in toluene for several hours.

A preliminary examination of the toxicity and hypnotic activity of the compounds has been made and they were found to be relatively inactive.

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