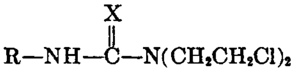
TABLE I. UREA AND THIOUREA MUSTARDS



$R{-}NH{-}C({=}X){-}N(CH_2CH_2Cl)_2$

R	X	Formula	Yield, %	M.P.[a]	Calcd., % C	Calcd., % H	Calcd., % N	Found, %[b] C	Found, %[b] H	Found, %[b] N
C_2H_5	O	$C_7H_{14}N_2OCl_2$	75	Oil			13.15			12.83
C_2H_5	S	$C_7H_{14}N_2SCl_2$	80	Oil	36.68	6.16		36.46	6.37	
n-C_4H_9	S	$C_9H_{18}N_2SCl_2$	95	Oil			10.89			10.38
C_6H_5	S	$C_{11}H_{14}N_2SCl_2$	63	76–80	47.48	5.07		47.61	5.21	
o-ClC_6H_4	O	$C_{11}H_{13}N_2OCl_3$	95	72–75	44.70	4.43		45.00	4.57	
m-ClC_6H_4	O	$C_{11}H_{13}N_2OCl_3$	70	94–95	44.69	4.43	9.48	44.45	4.41	9.56
p-ClC_6H_4	O	$C_{11}H_{13}N_2OCl_3$	80	143–145			9.48			9.61
p-$NO_2C_6H_4$	O	$C_{11}H_{13}N_3O_3Cl_2$	99	150–152	42.95	4.26	13.73	43.18	4.34	13.65
p-$CH_3C_6H_4$	O	$C_{12}H_{16}N_2OCl_2$	60	88–90			10.18			9.78
o-$CH_3OC_6H_4$	O	$C_{12}H_{16}N_2O_2Cl_2$	50	99–101			9.62			9.98
p-$CH_3OC_6H_4$	O	$C_{12}H_{16}N_2O_2Cl_2$	80	144–145	49.50	5.54		49.53	5.49	
n-C_7H_{15}	S	$C_{12}H_{24}N_2SCl_2$	70	Oil			9.36			9.15
[c]	O	$C_{17}H_{24}N_4O_2Cl_4$	91	85–87			12.23			12.18
[d]	O	$C_{23}H_{28}N_4O_2Cl_4$	92	107–110	52.70	5.28		52.52	5.54	

[a] Melting points are uncorrected, oils were not distilled. [b] Analysis by Spang Microanalytical Laboratory, Ann Arbor, Mich., and Drs. Weiler and Strauss, Oxford, England. [c] 3-[$(ClCH_2CH_2)_2NCONH$]-4-(CH_3)C_6H_3. [d] p-[p-$(ClCH_2CH_2)_2$-$NCONHC_6H_4CH_2$]C_6H_4.

Preliminary screening results against the Dunning leukemia in rats indicates only moderate activity for the thiourea mustards and little or no activity for the urea mustards.[4]

EXPERIMENTAL

Reagents. The isocyanates and isothiocyanates were obtained commercially and used without further purification

Preparation of ureas and thioureas. A solution of 8.9 g. (0.05 mole) of *N,N*-bis(2-chloroethyl)amine hydrochloride in a minimum of water was added to an aqueous solution of 2 g. (0.05 mole) of sodium hydroxide, and the mixture was immediately extracted 3 times with 20-ml. portions of benzene. After drying over sodium sulfate for a short time, the benzene solution was added to 0.05 mole of the isocyanate or isothiocyanate in a minimum of benzene. If a solid appeared after standing at room temperature for up to 24 hr., this was filtered, washed with benzene, and dried *in vacuo.* If an oil had separated, this was washed with benzene several times and dried *in vacuo.* The results are presented in Table I.

N,N-Bis(2-chloroethyl)-N'-(p-methoxyphenyl)urea. A benzene solution of *N,N*-bis(2-chloroethyl)-*p*-phenylenediamine[1] (from *N,N*-bis(2-chloroethyl)-*p*-nitrosoaniline[5]) was added to an equimolar amount of *p*-methoxyphenyl isocyanate to give, after treatment as described above, an 80% yield of the urea, m.p. 142–145°.

Anal. Calcd. for $C_{18}H_{21}N_3O_2Cl_2$: C, 56.55; H, 5.54. Found: C, 56.20; H, 5.24.

Acknowledgment. The authors wish to thank the Ott Chemical Co. for generous sample of the chlorophenyl isocyanates, and Dr. R. B. Ross, of the C.C.N.S.C., for a sample of *N,N*-bis(2-chloroethyl)amine hydrochloride.

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[4] R. Jones, Jr., and L. Rane, private communication. Complete screening results will be published elsewhere at a later date.

[5] J. L. Everett and W. C. J. Ross, *J. Chem. Soc.*, 1972 (1949).

Fluorine-Containing Nitrogen Compounds. IV. Hexafluoro-1,3,5-trichloro-1,3,5-triazacyclohexane[1]

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As a part of general study of the fluorinating properties of halogen fluorides, the action of chlorine mono- and trifluorides on symmetrically substituted triazines was investigated. Chlorine fluoride and mixtures of chlorine fluoride with chlorine trifluoride reacted with cyanuric chloride to yield hexafluoro-1,3,5-trichloro-1,3,5-triazacyclohexane (I)[4] and cyanuric fluoride (II). Hexachloromelamine also reacted with the chlorine fluorides to yield I and II, but melamine yielded only small amounts of II. The reaction is very exothermic and results largely in fragmentation of the triazine unless it is suitably moderated. Moderation was successfully accomplished by using a large mass of metal as a heat sink. The effect of varying the ratio of mono- to trifluoride on the yield of I and II is shown in Table I for one arbitrary set of conditions. The effect of varying the amount of moderator and the total amount of fluorinating agent (70/30 chlorine fluoride/chlorine trifluoride) is shown in Table II.

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[1] This work was performed under the auspices of the U. S. Atomic Energy Commission.

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[3] To whom inquiries should be sent.

[4] The possible existence of this compound was first indicated during discussion with the research staff of the Redstone Division of Rohm & Haas Chemical Corp.

TABLE I

YIELD OF I AND II AS A FUNCTION OF ClF-ClF$_3$ RATIO[a]

% ClF in the Fluorinating Agent	Yield as % of Theoretical[b]	
	I	II
100	17	43
80	51	22
75	57	4
70	63	2
65	40	32
50	34	43
25	0	43

[a] One gram of cyanuric chloride, 70 g. of 1/16- to 1/8-in. bronze balls, 0.51 l.-atm. (STP) of chlorine fluoride–chlorine trifluoride. [b] Based on cyanuric chloride.

TABLE II

YIELD OF I AND II AS A FUNCTION OF AMOUNT OF FLUORINATING AGENT AND MODERATOR[a]

Amount of Fluorinating Agent[b] in L.-Atm. (STP)	Weight of Moderator in G.[c]	Yield as % of Theoretical[d]	
		I	II
1.04	140	34	32
1.04	120	40	32
1.04	100	68	5
1.28	100	40	22
1.29	100	34	44
0.75	100	9	38
1.04	80	46	27
0.75	80	20	27

[a] Two grams of cyanuric chloride. [b] 70% chlorine fluoride, 30% chlorine trifluoride. [c] No. 22 uncoated copper wire cut to 1/8-in. lengths. [d] Based on cyanuric chloride.

Hexafluoro-1,3,5-trichloro-1,3,5-triazacyclohexane is a colorless liquid which boils at 48° at 15 mm. It is readily soluble in benzene, but insoluble in water. Its F^{19} NMR spectrum showed a single sharp peak shifted to lower field by 143 ± 2 cycles relative to trifluoroacetic acid. Its infrared spectrum showed major bands at 8 (10),[5] 8.4 (6), 8.7 (6), 9.1 (8), 9.4 (3), 10 (6), 10.4 (7), 12 (6), and 13 (7) μ. Identification was confirmed by chlorine and fluorine analysis, by molecular weight, and by hydrolysis to trichloroisocyanuric acid. Cyanuric fluoride was identified by its melting point and vapor pressure, by hydrolysis to cyanuric acid, and by comparison of its infrared spectrum with published spectra.[6] Its F^{19} NMR spectrum showed a single sharp peak shifted to lower field by 1885 ± 10 cycles relative to trifluoroacetic acid.

EXPERIMENTAL

All reactions took place in manifolds constructed of copper, brass, and stainless steel with silver-soldered joints. Valves were Kerotest diaphragm type[7] modified by insertion of a 1/32-in. Teflon disk under the stainless steel diaphragm; valve seats and gaskets were also of Teflon. Extruded Kel-F rod was used for constructing the traps. Pressures were measured with a Monel Bourdon tube gauge or a Fischer-Porter Press-I-Cell.[8] All metal surfaces were carefully preconditioned wich chlorine trifluoride. When the manifold was not in use, the surfaces were kept dry by maintaining the pressure in the manifold below 1 μ.

Chlorine monofluoride. A 36-l. stainless steel tank was charged with 8.7 l.-atm. (STP) of chlorine trifluoride. Chlorine (6.5 l.-atm.) was rapidly expanded into the tank from a 325-ml. stainless steel cylinder. The mixture was passed, at 400° and a flow rate (STP) of 3 ml./min., through a 1/2-in. i.d. nickel tube 9 in. long and packed with 3/16-in. nickel shot. The reaction mixture was initially condensed by means of liquid nitrogen and then separated by distillation through traps cooled in an *n*-pentane slush bath, an isopentane slush bath, and liquid nitrogen. The traps held chlorine trifluoride, chlorine, and chlorine monofluoride, respectively. Conversion of trifluoride to monofluoride was 78%. The purity of the monofluoride was better than 90% as determined by molecular weight measurements and ultraviolet spectra.

Hexafluoro-1,3,5-trichloro-1,3,5-triazacyclohexane. A 70-ml. copper reaction tube containing an appropriate amount (see Tables I and II) of moderator was attached to a manifold, evacuated, and then filled to about 300 mm. pressure with chlorine trifluoride. After 1 to 2 hr. at ambient temperature, the chlorine trifluoride was replaced by an atmosphere of argon. Cyanuric chloride[9] was added and mixed with the moderator. This was done carefully to avoid damaging the fluoride coating on the reaction tube and moderator. The fluorinating agent was condensed in the evacuated reaction tube by means of a liquid nitrogen bath. The valve connecting the tube with the gas-handling manifold was then closed, and the liquid nitrogen bath was replaced with one of crushed ice and water contained in a stainless steel Dewar. The ice bath was positioned around the reaction chamber by means of a remote controlled elevator. The operation was performed behind a suitable barricade.

The temperature inside the chamber rose very rapidly from that of liquid nitrogen to 10 to 20° and then subsided to about 0°. After 1 hr. at 0°, the volatile materials were passed through a trap cooled in Dry Ice–acetone. Material from the Dry Ice trap was transferred to a 100-ml. glass bulb containing 20 to 25 ml. of mercury and stirred magnetically at room temperature for 1 to 2 hr. The remaining volatile material was then passed through traps cooled in chlorobenzene slush and in Dry Ice–acetone. Crude I was found in the chlorobenzene-cooled trap, and crude II in the trap cooled with Dry Ice. Vacuum fractionation yielded pure I which boiled at 48° at 15 mm., d_{27} 1.84, n_{D}^{27} 1.404.

Anal. Calcd. for $C_3Cl_3F_6N_3$: Electropositive chlorine, 35.6; F, 38.2; mol. wt., 298.5. Found: Electropositive chlorine, 35.1; F, 37.5; mol. wt., 292 (cryoscopically in benzene).

Shaking with water or with aqueous acetone for several hours resulted in complete hydrolysis to trichloroisocyanuric acid which was identified by comparison of its infrared spectrum with that of an authentic sample. The cyanuric fluoride melted at −40 to −41° (lit.[11] m.p. −38°) and had a vapor pressure of 81 mm. at 21.9° (lit.[10] vapor pressure

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(5) Numbers in parentheses are relative intensities based on 8 μ band.

(6) D. W. Grisley, Jr., E. W. Gluesenkamp, and S. A. Heininger, *J. Org. Chem.*, **23**, 1802 (1958).

(7) Kerotest Manufacturing Co., Pittsburgh, Pa.

(8) Fischer & Porter Co., Hatboro, Pa., Model No. 1221PC53.

(9) Commercial cyanuric chloride was recrystallized from carbon tetrachloride, dried under reduced pressure, and screened to 20–40 mesh.

(10) F. Seel and K. Ballreich, *Ber.*, **92**, 344 (1959).

(11) A. F. Maxwell, J. S. Fry, and L. A. Bigelow, *J. Am. Chem. Soc.*, **80**, 548 (1958).

67 mm.). Its infrared spectrum corresponded to that published by Grisley, Gluesenkamp, and Heininger.[6] It was readily hydrolyzed by water to cyanuric acid which was identified by comparison of its infrared spectrum with that of an authentic sample.

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Ismine[1]

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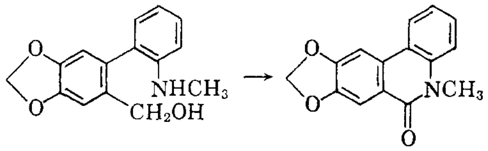
In the course of preparations of tazettine from extracts of an *Ismene* species,[2] it was observed that early eluates from alumina columns contained a compound characterized by twin peaks in the infrared spectrum centered about 6.3 μ. Further chromatography yielded a new optically inactive base, ismine, m.p. 99–100°.

Analytical data for ismine and its picrate correspond to an empirical formula for the free base of $C_{15}H_{15}NO_3$, and show the presence of an *N*-methyl group, two active hydrogens, and the absence of methoxyl groups. The formation of a neutral diacetate with infrared absorption at 1735 and 1650 cm.$^{-1}$ and without peaks attributable to OH or NH shows the functional groups to be a hydroxyl group and a secondary amine. The infrared spectrum of the base shows the presence of the methylenedioxyaromatic system,[3] while the ultraviolet spectrum in acid solution corresponds closely to that of 6-phenylpiperonyl alcohol, both spectra showing maxima near 255 and 293 mμ. It seemed likely that ismine was an aniline when it was observed that the free base absorbs more intensely in the ultraviolet than the salt and condenses with *p*-nitrobenzenediazonium chloride to form a red dye. Since the carbon system of 6-phenylpiperonyl alcohol is present, with a single exception,[4] in all the nuclei of *Amaryllis* alkaloids of known structure,[5] it was attractive to postulate that ismine retains this system, and in addition, retains the common orientation of the nitrogen atom on the second carbocyclic system *ortho* to the attachment to the piperonyl system. This orientation is supported by the appearance of a strong peak at 750 cm.$^{-1}$ in the infrared spectrum of the free base.[6] Thus, structure I represents ismine. Conversion to the known 8,9-methylenedioxy-5-methyl-6-phenanthridone (II) by treatment of ismine first by acid and then by basic potassium ferricyanide proved this hypothesis.



I II

The occurrence of an alkaloid without the central fifteen-carbon system common in the *Amaryllis* alkaloids is novel. Ismine may represent a natural degradation product of the haemanthamine-haemanthidine-tazettine series.[5] Further investigation has shown it to be present in *Sprekelia formosissima*, which contains alkaloids of this series,[7] and in *Crinum powellii*, which contains the closely related[4] crinamine and criwelline.[7,8]

EXPERIMENTAL[9]

Isolation of ismine. Bulbs of *Ismene* sp. (9000 g.) were extracted by a standard procedure[10] to provide a crude alkaloid fraction of 12.8 g. (0.14%). This material was chromatographed over alumina; elution by 25% ethyl acetate in benzene provided 0.7 g. of material with the infrared spectrum characteristic of ismine; repeated chromatography provided 0.45 g. (0.0042%) of crude ismine. A sample of this material (0.39 g.) was recrystallized from benzene-hexane to provide 0.22 g. (0.0024%) of m.p. 96°.

In chromatographing the extract from 23 kg. of *Sprekelia formosissima* bulbs the fractions were assayed by spotting approximately 0.1 mg. on filter paper and spraying with a 0.1*M* solution of diazotized *p*-nitroaniline. Control experiments showed that 0.025 mg. of ismine produced a vivid pink spot. Fractions giving a positive test were aggregated and rechromatographed until eventually 0.01 g. (0.00004%) of ismine, m.p. 99.5–100°, was isolated. Similar handling of

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[1] Paper XXII of a series on *Amaryllidaceae* alkaloids. Previous paper: H. M. Fales and W. C. Wildman, *J. Org. Chem.*, **26**, 1617 (1961).

[2] Tazettine was first isolated from *Ismene* species in these laboratories by Dr. H. M. Fales.

[3] L. H. Briggs, L. D. Colebrook, H. M. Fales, and W. C. Wildman, *Anal. Chem.*, **29**, 904 (1957).

[4] E. W. Warnhoff, *Chem. & Ind.* (*London*), 1385 (1957).

[5] A recent review of the alkaloids of this family has been reported by W. C. Wildman, *The Alkaloids*, Vol. 6, R. H. F. Manske, ed., Academic Press, Inc., New York, 1960, p. 289.

[6] L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd ed., John Wiley & Sons, Inc., New York, 1958, p. 77.

[7] H.-G. Boit and H. Ehmke, *Chem. Ber.*, **88**, 1590 (1955).

[8] H.-G. Boit and H. Ehmke, *Chem. Ber.*, **89**, 2093 (1956); cf., H. M. Fales, D. H. S. Horn, and W. C. Wildman, *Chem. & Ind.* (*London*), 1415 (1959).

[9] All melting points were observed on a Kofler microscope hot stage and are corrected. Ultraviolet spectra were obtained in absolute ethanol solution on a Cary Model 11 MS recording spectrophotometer. Infrared spectra were recorded on either a Perkin-Elmer Model 21 or a Beckman IR-7 double beam spectrophotometer. Identifications were confirmed by mixed melting points and comparison of infrared spectra (potassium bromide). Analyses were performed by Mr. J. F. Alicino, Metuchen, N. J.

[10] W. C. Wildman and C. J. Kaufman, *J. Am. Chem. Soc.*, **76**, 5815 (1954).