was observed after one hour, while solutions of the other anhydrides continued to change in conductance up to ten hours.

The results show that while the differences in rates of hydrolysis of the three anhydrides are small, the rate of cyclization of dimethylmaleic acid must be greater than that of the other two acids. Koskikallio[2c] has shown that the energy and entropy of hydrolysis of dimethylmaleic anhydride are very similar to that of other anhydrides, whereas the entropy of cyclization of the acid is much greater. Free rotation of the methyl groups about the double bond in dimethylmaleic acid is impossible and its seems probable that their mutual repulsion brings the two carboxyl groups nearer together, facilitating ring closure. This will be primarily an entropy effect.[4]

Diethylmaleic acid has only been reported as its anhydride[5] and dichloro- and dibromomaleic acid readily lose water.[6] However cyclohex-1-ene-1,2-dicarboxylic anhydride is reported[3] to be less readily hydrolyzed but less readily formed, suggesting that the steric effect of the substituents is less when constrained in a ring.

EXPERIMENTAL

Maleic anhydride (Eastman Kodak White Label) and dimethylmaleic anhydride (Aldrich) were recrystallized before use and the citraconic anhydride (Eastman Kodak White Label) redistilled.

The anhydride (*ca.* 0.3 g.) in dioxane (5–25 ml.) was equilibrated in a constant temperature bath at 25.0 ± 0.1° and conductivity water (25–5 ml.) at the same temperature then added. Conductivity readings were taken with a dipping platinum electrode assembly and a Servass Bridge at intervals up to 10 hr. and again after 1–2 days. Rate constants were calculated from the formula $kt = \ln (k_0 - k_\infty)/(k_\infty - k_t)$, where k_0, k_∞, and k_t are the conductivities at zero and infinite time and at time t. The values reported in Table I are means of duplicate runs which differed by less than 5%. In the case of dimethylmaleic acid the rate constants were calculated from the slope of the tangents to the rate plots at zero time.

TABLE I

SOLVOLYSIS OF MALEIC ANHYDRIDES

$k \times 10^4$ sec.$^{-1}$

	Water		Aqueous Dioxane[c]		
	at 0°[a]	at 25°[b]	16.7%	50%	73.3%
Maleic anhydride	34.3	115	92.3	—	5.25
Citraconic anhydride	—	76.5	62.7	16.8	1.97
Dimethylmaleic anhydride	4.7	—	6.65	3.07	0.33

[a] Ref. 2a. [b] Ref. 3. [c] Present work, at 25.0 ± 0.1°, percentage dioxane vol./vol.

Acknowledgment. This work was supported by a grant from the National Science Foundation.

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[4] N. L. Allinger and V. Zalkow, *J. Org. Chem.*, **25**, 701 (1960).

[5] R. Anschutz and P. Volborth, *Ann.*, **461**, 177 (1928); E. Ott, *Ber.*, **61**, 2131 (1928).

[6] *Chemistry of Carbon Compounds*, ed. Rodd, vol. IB, p. 994, Elsevier, New York, 1954.

Synthesis of Potential Anticancer Agents. VI. Urea and Thiourea Mustards[1,2]

FRANK D. POPP AND HERBERT SWARZ

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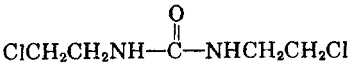
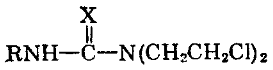
In spite of the wide interest in derivatives of bis-(2-chloroethyl)amine (nitrogen mustard) as potential anticancer agents, no reports of *N,N* bis-(2-chloroethyl)ureas have appeared in the literature. The only related compound reported was *N,N'*-bis(2-chloroethyl)urea (I).[3] Although one would not expect ureas and thioureas of the type II and III to exhibit alkylating action as such, it is entirely possible that they could be transformed in the body to an active mustard.



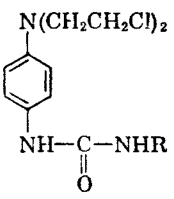
$\mathrm{ClCH_2CH_2NH{-}\overset{O}{\overset{\|}{C}}{-}NHCH_2CH_2Cl}$

I



$\mathrm{RNH{-}\overset{X}{\overset{\|}{C}}{-}N(CH_2CH_2Cl)_2}$

II. X=O
III. X=S



IV

The urea (II) and thiourea (III) mustards were conveniently prepared by the reaction, in benzene, of an isocyanate or an isothiocyanate and *N,N*-bis(2-chloroethyl)amine. In all the cases reported the product precipitated or oiled from the reaction mixture after standing for a short time at room temperature. In each case this product was analytically pure and did not require recrystallization or distillation. These results are tabulated in Table I.

In one case, *p*-methoxyphenylisocyanate reacted with *N,N*-bis(2-chloroethyl)-*p*-phenylenediamine to give the urea IV (R = *p*-$CH_3OC_6H_4$—).

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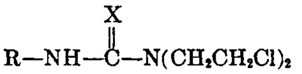
[1] Part V, F. D. Popp and W. Kirsch, *J. Org. Chem.*, **26**, 3858 (1961).

[2] This investigation was supported in part by Research Grants CY 4814 and CY 4814 Cl from the National Cancer Institute, U. S. Public Health Service. Presented in part before the Division of Medicinal Chemistry of the American Chemical Society, Chicago, Ill., September 1961. A preliminary report was presented at the Caribbean Chemical Symposium, U.C.W.I., Jamaica, April 1961.

[3] A. F. McKay, M. A. Weinberger, J. P. Picard, W. G. Hatton, M. Bedard, and H. E. Rooney, *J. Am. Chem. Soc.*, **76**, 6371 (1954).

TABLE I. UREA AND THIOUREA MUSTARDS



$R{-}NH{-}\overset{\overset{\displaystyle X}{\|}}{C}{-}N(CH_2CH_2Cl)_2$

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*-$(ClCH_2CH_2)_2NCONHC_6H_4CH_2$]$C_6H_4$.

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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Received June 2, 1961

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.