Although cyclic ketals from 1,2- and 1,3-glycols are well known[2] only the unsubstituted and mono-2-substituted dioxepanes have been characterized.[3] These may be easily polymerized in the presence of acid, with a small amount of alcohol or diol to control molecular weights.[4] An attempt to open the ketal dioxepane with 0.025 mole per cent 1,4-butanediol and 0.085 weight per cent *d,l*-camphorsulfonic acid led to only the cracking products, acetone and tetrahydrofuran, in equimolar amounts (87%). Substitution of boron trifluoride etherate for the sulfonic acid caused much faster rearrangement to the same products.

While cyclization to the dioxepane is not remarkable in view of the *gem*-dimethyl substitution,[5] the acid catalyzed rearrangement is noteworthy. This phenomenon, which occurs under relatively mild conditions, is apparently intramolecular since no polytetramethylene oxide was obtained. Mechanistically, it is considered as induced by electron delocalization from one ketal oxygen, yielding a four atom SN_i type extrusion process.

EXPERIMENTAL

2,2-Dimethyl-1,3-dioxepane. 2,2-Dimethoxypropane, supplied by the Dow Chemical Co. (98%), was used as received. 1,4-Butanediol was distilled and stored over Linde 4A molecular sieves. Dry 1,4-butanediol (90 g., 1.0 mole) and 104 g. (1.0 mole) of the acetone dimethyl ketal were mixed with 300 ml. of anhydrous benzene. The two phase system became homogeneous upon addition of 0.02 g. of *d,l*-camphorsulfonic acid (Eastman Kodak Co.). The mixture was heated with stirring, and 198 ml. of distillate (mostly b.p. 59°) was collected; the final head temperature reading 80°. The distillate contained approximately the theoretical amount of methanol.

The reaction mixture was neutralized by stirring 3 hr. with 5 g. of sodium bicarbonate, then filtered. The clear benzene solution was distilled, yielding 95.5 g. of a fraction boiling at 136° (yield, 73.5%). A total of 11 g. of residue (nonviscous) was discarded. The clear, pleasant smelling liquid was tentatively assigned the structure of 2,2-dimethyl-1,3-dioxepane; redistillation gave b.p. 136–137° (uncorrected), n_D^{25} 1.4253, d_4^{25} 0.8934.

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.58; H, 10.78; mol. wt., 130.18. Found: C, 64.85; H, 10.95; mol. wt., 131.

Rearrangement of 2,2-dimethyl-1,3-dioxepane: A mixture of 51.73 g. of dimethyldioxepane, 1.186 g. of 1,4-butanediol, and 0.045 g. of *d,l*-camphorsulfonic acid was refluxed for 16 hr., during which time the pot temperature dropped from 137° to 111°. The reaction mixture was then distilled (55–68°), leaving a pot residue (oily) of 6.9 g. (13%). Gas chromatographic analysis showed that the distillate consisted principally of an equimolar mixture of acetone and tetrahydrofuran with about a 20% carry over of unrearranged dimethyldioxepane.

The experiment was repeated, using 3 drops of boron trifluoride etherate to 50 g. of 2,2-dimethyldioxepane, and no butanediol. As the pot temperature approached 125°, violent ebullition occurred and the temperature dropped to 100° within 10 min. After refluxing for 6 hr., the final pot temperature was 85°.

CONTRIBUTION NO. 210
RESEARCH AND DEVELOPMENT DEPARTMENT
UNITED STATES RUBBER CO.
WAYNE, N. J.

(2) (a) J. Boeseken and F. Tellegen, *Rec. trav. chim.*, **57**, 133 (1938). (b) E. J. Salmi, *Ber.*, **71**, 1803 (1938). (c) R. I. Meltzer, A. D. Lewis, J. Volpe, and D. M. Lustgarten, *J. Org. Chem.*, **25**, 712 (1960).

(3) D. B. Pattison, *J. Org. Chem.*, **22**, 662–664 (1957).

(4) (a) D. B. Pattison, U. S. Patent **2,870,097**, Jan. 20, 1959. (b) J. W. Hill and W. H. Carothers, *J. Am. Chem. Soc.*, **57**, 925 (1935).

(5) See N. L. Allinger and V. Zalkow, *J. Org. Chem.*, **25**, 701 (1960).

Solvolysis of Methylmaleic Anhydrides

OWEN H. WHEELER AND ELSIE E. GRANELL RODRÍGUEZ

Received May 29, 1961

While maleic and methylmaleic (citraconic) acids are known as both their acids and anhydrides, dimethylmaleic acid is only stable as its anhydride.[1] This anhydride usually crystallizes on acidification of solutions of salts of the corresponding acid. This evidence does not necessarily require that the acid cyclizes spontaneously to its anhydride, as if the anhydride were very much less soluble than the acid it would crystallize preferentially. However, Koskikallio[2] has recently prepared dimethylmaleic acid by careful neutralization at 0° of a solution of its sodium salt, and found that the acid was converted into its anhydride at immeasurably high rates in nonaqueous solvents, although at measurable rates in aqueous acetone and methanol. This publication describes a comparative study of the rates of solvolysis of maleic, citraconic and dimethylmaleic anhydrides in aqueous dioxane, to interrelate rate data of these three anhydrides.

The rates of solvolysis (Table I) were determined by measuring the change in conductivity with time.[3] The differences in rate found for maleic and citraconic anhydrides are of the same order as those found in water (11.5 and 7.65 $\times 10^{-3}$ sec.$^{-1}$, respectively.)[3] The rate of hydrolysis of dimethylmaleic anhydride is lower than those of the other two, although the differences are small and consistent with the inductive (−I) effect of the methyl groups which will decrease the positive charge on the carbonyl carbon atom. However whereas the solvolysis was essentially complete in the cases of maleic and citraconic anhydrides, the same final conductance being obtained with solutions of the same molar concentrations of the corresponding acids, the changes in conductance of solutions of dimethylmaleic anhydride were very small (less then 10% of the other two anhydrides). No further change

(1) *Cf.* P. D. Bartlett, *J. Chem. Ed.*, **30**, 22 (1953).

(2)(a) J. Koskikallio, *Ann. Acad. Sci. Fennicae*, **A II**, 57 (1954); (b) J. Koskikallio, *Suomen Kemistilehti*, **B29**, 5 (1955); (c) J. Koskikallio, *Acta Chem. Scand.*, **10**, 822 (1956).

(3) *Cf.* A. C. D. Rivett and N. V. Sidgwick, *J. Chem. Soc.*, **97**, 1677 (1910).

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.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF PUERTO RICO
MAYAGUEZ, P. R.

(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).

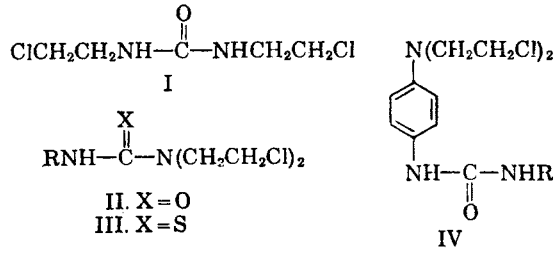
(6) *Chemistry of Carbon Compounds*, ed. Rodd, vol. IB, p. 994, Elsevier, New York, 1954.

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

FRANK D. POPP AND HERBERT SWARZ

Received May 29, 1961

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.



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*-$CH_3OC_6H_4$—).

(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).