EXPERIMENTAL[3]

2-Vinyl-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (I). A solution of 500 g. (4.7 moles) of 92% sulfuric acid was stirred at 6–7° during the addition of 56 g. (1.05 moles) of acrylonitrile over a 5-hr. period. The mixture was stirred at 8–10° and 118 g. (1.0 mole) of 2-methyl-2,4-pentanediol was added over a 4-hr. period. The reaction mixture was poured over 1000 g. of ice, treated with 470 g. (4.7 moles) of 40% sodium hydroxide, and washed 3 times with $^1/_3$ volumes of chloroform. The remaining aqueous layer was brought to *p*H 10 with additional 40% sodium hydroxide and extracted with diethyl ether. Distillation of the extract gave 72 g., a 47% yield, of I (b.p. 75°/24 mm.; n_D^{30} 1.4605; D_{20}^{20} 0.9192; infrared maxima: 3.24, 5.37 ($=CH_2$), 6.05 ($C=N-$), 6.22 ($C=C$ conugated), 7.22, 7.33 (*gem*-dimethyl), 8.5μ α,β-unsaturated ether).

Anal. Calcd. for $C_9H_{15}NO$: C, 70.7; H, 9.81; N, 9.16. Found: C, 70.4; H, 9.8; N, 9.12.

Copolymer of I with vinylidene chloride. Vinylidene chloride and I in a 7 to 3 mole ratio were agitated in a sealed glass tube at 50° in the presence of 1% azo-bisisobutyronitrile catalyst for 6 hr. A greenish pliable solid polymer was obtained which contained 70.5% of I. The yield was 17%.

2-Isopropenyl-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (II). The procedure was the same as that used for the preparation of I. II was obtained in 53% yield (b.p. 79°/20 mm.; n_D^{30} 1.4585).

Anal. Calcd. for $C_{10}H_{17}NO$: C, 71.9; H, 10.18; N, 8.38. Found: C, 71.54; H, 10.03; N, 8.71.

2-(2'-Cyanoethylidene)-4,6,6-trimethyltetrahydro-1,3-oxazine (III). A solution of 153 g. (1.0 mole) of I, 200 cm.^{3} of glacial acetic acid, 34 g. (1.25 moles) of hydrogen cyanide and 1 g. of 2,4-dinitrobenzene was refluxed for 1 hr. during which time the kettle temperature rose from 30° to 115°. Distillation gave a 45% yield of III (b.p. 87°/1.3 mm.; n_D^{30} 1.4542; infrared maxima: 3.00 ($-NH-$), 4.45 ($-C\equiv N$), 6.00 ($-C=C-$), 8.60 ($-C=C-O-$).

Anal. Calcd. for $C_{10}H_{16}N_2O$: C, 66.7; H, 8.80; N, 15.55. Found: C, 66.35; H, 8.60; N, 15.9.

Acknowledgment. The author is grateful to Mr. C. M. Lovell for infrared analyses and to Mr. Q. Quick for microanalyses.

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(3) All boiling points are uncorrected.

Potential Carcinostatic Agents. Benzimidazole Derivatives

WILLIAM S. GUMP AND EDWARD J. NIKAWITZ

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The need for larger amounts of 2-[bis(2-chloroethyl)aminomethyl]benzimidazole hydrochloride ("benzimidazole mustard")[1] for clinical trials and the intended synthesis of derivatives of this nitrogen mustard made it desirable to look for a more convenient method of preparation than the one previously employed by us[1] and other investigators.[2,3] We wished to eliminate the use of 2-chloromethylbenzimidazole or its hydrochloride as intermediates because these substances are very irritating and sensitizing on the skin and therefore difficult to handle. Substituted 2-chloromethylbenzimidazoles would be expected to have the same disadvantage.

Hughes and Lions[4] had shown that glycine could not be condensed with *o*-phenylenediamine in the presence of 4*N* hydrochloric acid at reflux temperature, according to Phillips' method.[5] Of substituted glycines in which the basicity of the amino group had been depressed by acylation, hippuric acid did not react, and phthalimidoacetic acid only poorly. We found, however, that *N,N*-bis(2-hydroxyethyl)-glycine and *o*-phenylenediamine, refluxed together in 4*N* hydrochloric acid solution, gave a fairly good yield of 2-[bis-(2-hydroxyethyl)aminomethyl]-benzimidazole dihydrochloride, the precursor of the benzimidazole mustard.

Similarly, the reaction of *N,N*-bis(2-hydroxyethyl)glycine with substituted *o*-phenylenediamines, such as 4-chloro-,4,5-dichloro and 4,5-dimethyl-1,2-phenylenediamine led to the desired substituted 2-[bis(2-hydroxyethyl)aminomethyl]benzimidazole dihydrochlorides which were converted into the corresponding bis(2-chloroethyl) compounds by means of thionyl chloride in the usual manner.

One of the benzimidazoles needed for testing, 1-methyl-2-[bis(2-chloroethyl)aminomethyl]benzimidazole hydrochloride, was prepared by the old method, starting from 1-methyl-2-chloromethylbenzimidazole hydrochloride. This substance which is irritating to the skin, but to a lesser degree than the unmethylated compound, was brought to reaction with diethanolamine. The resulting 1-methyl-2-[bis(2-hydroxyethyl)aminomethyl]benzimidazole was purified by means of its picrate and brought to reaction with thionyl chloride, yielding the "1-methylbenzimidazole mustard."

Preliminary studies[6] of the carcinostatic properties of the new compounds indicate that they are less effective against a number of experimental tumors in mice than the unsubstituted "benzimidazole mustard." The final results will be reported elsewhere.

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(2) A. R. Day, *Trans. N. Y. Acad. Sci.*, [2] **20**, No. 1, 3 (Nov. 1957).

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(4) G. K. Hughes and F. Lions, *J. Proc. Roy. Soc. N. S. Wales*, **71**, 209 (1938).

(5) M. A. Phillips, *J. Chem. Soc.*, 2393 (1928).

(6) We are indebted to Drs. A. Gellhorn and E. Hirschberg, Institute of Cancer Research, Columbia University College of Physicians and Surgeons, New York 32, N. Y., for evaluation of the antitumor activity of the compounds.

EXPERIMENTAL*

N,N-Bis(2-hydroxyethyl)glycine. This compound was prepared from diethanolamine and chloroacetic acid as described by Khromov-Borisov and Remizov.[7] In order to obtain satisfactory yields, refluxing of the mixture should be carried out for 24 hr. instead of 3 to 4 hr.

2-[Bis(2-hydroxyethyl)aminomethyl]benzimidazole dihydrochloride. A mixture of 400 g. of *N,N*-bis(2-hydroxyethyl)-glycine, 280 g. of *o*-phenylenediamine, and 2350 ml. of 4*N* hydrochloric acid was refluxed for 10 hr. in a nitrogen atmosphere. Darco decolorizing carbon (40 g.) was added and the mixture refluxed for 30 min. After filtration, the liquid was evaporated under reduced pressure. The distillation was stopped when some crystals had precipitated; they were removed by filtration after cooling. The light pink crystals (12 g.) which did not melt up to 260° consisted mainly of *o*-phenylenediamine dihydrochloride[8] (calcd. 39.4% Cl; found 40.2% Cl); *o*-phenylenediamine could be obtained on treating the salt with sodium hydroxide solution.

The filtrate was concentrated *in vacuo* almost to dryness and the residue recrystallized from 1500 ml. of 90% ethanol. Soft, light orange colored crystals (305 g.) of m.p. 190–192° were obtained; recrystallization from 90% ethanol yielded 251 g. of the pure substance, m.p. 194–195°. Concentration of the mother liquors resulted in a second crop (101 g.); m.p. 190–192°.

2-[Bis-(2-hydroxyethyl)aminomethyl]-5(or 6)-chlorobenzimidazole dihydrochloride. Commercial *p*-chloro-*o*-phenylenediamine was purified by recrystallization from toluene, but it still had a brown color.

p-Chloro-*o*-phenylenediamine (71 g.), *N,N*-bis(2-hydroxyethyl)glycine (82 g.), and 500 ml. of 4*N* hydrochloric acid were refluxed for 4 hr. in a nitrogen atmosphere, 15 g. of Darco carbon was added, and refluxing continued for 2 hr. After filtration, the liquid was evaporated to dryness under reduced pressure. The remaining dark orange resin was taken up in 350 ml. of absolute ethanol. Ether was added to the solution until an oil started to separate. The mixture was kept at −10° for 3 days; the reddish crystals which had formed were separated and recrystallized from 350 ml. of ethanol, some Darco being added. The solid obtained (55 g.) was still reddish; another crystallization from 400 ml. of ethanol gave 38 g. of slightly pinkish crystals; m.p. 171–172°.

Anal. Calcd. for $C_{12}H_{18}Cl_3N_3O_2$: Cl^-, 20.7; Cl (total), 31.1. Found: Cl^-, 21.0; Cl (total), 31.2.

2-[Bis(2-hydroxyethyl)aminomethyl]5,6-dichlorobenzimidazole dihydrochloride. 4,5-Dichloro-1,2-phenylenediamine (60.7 g.), prepared by catalytic reduction[9] of 4,5-dichloro-1,2-dinitrobenzene[10] or preferably of 4,5-dichloro-2-nitroaniline,[11] *N,N*-bis(2-hydroxyethyl)glycine (62 g.), and 450 ml. of 4*N* hydrochloric acid were agitated and refluxed for 10 hr. in a nitrogen atmosphere. The dark red solution was concentrated to dryness under reduced pressure. The remaining dark residue was refluxed for 30 min. with 500 ml. of absolute ethanol in the presence of about 10 g. of Darco carbon. Absolute ethanol (200 ml.) and ether (680 ml.) were added to the filtrate. The Darco and the filter were extracted with 300 ml. of boiling absolute ethanol, and 500 ml. of ether was added to the filtrate. The filtrates were combined and allowed to crystallize at −10°; the red solids were removed by filtration, washed with 40 ml. of ethanol and 140 ml. of ether, finally with ether. Yield: 71.7 g. The compound liquefied at 165° after a broad sintering range.

The product was then refluxed for 15 min. with 450 ml. water and 3 ml. of concentrated hydrochloric acid in the presence of 20 g. of Darco; the filtrate was again refluxed for 20 min. with 15 g. Darco. A slightly yellowish filtrate was obtained and concentrated to dryness at reduced pressure. The residue was dissolved in a refluxing mixture of 460 ml. of absolute ethanol and 20 ml. of water. Ether (480 ml.) was added to the warm filtrate. The whole was kept overnight at −10°. The crystals were separated by filtration, washed with ether and dried at 70° at 4 mm. Yield, 42.8 g. of a slightly yellowish solid; it softened at 160°, but did not form a clear melt when heated up to 178°. It was recrystallized from a mixture of 250 ml. of ethanol and 7 ml. of water. After standing overnight at −10°, the crystals were separated, washed with a little cold ethanol, and dried at 70° at 4 mm. Yield, 34.7 g.; m.p. 160–163° (turbid melt).

Anal. Calcd. for $C_{12}H_{17}Cl_4N_3O_2$: Cl^-, 18.8; Cl (total), 37.9. Found: Cl^-, 18.8; Cl (total), 37.7.

2-[Bis(2-hydroxyethyl)aminomethyl]5,6-dimethylbenzimidazole dihydrochloride. A mixture of 40.8 g. of 4,5-dimethyl-1,2-phenylenediamine,[12] 48 g. of *N,N*-bis(2-hydroxyethyl)-glycine and 294 ml. of 4*N* hydrochloric acid was refluxed for 10 hr. in a nitrogen atmosphere. A small amount of Darco was added to the solution and refluxing continued for 30 min. After filtration, the liquid was concentrated to dryness in vacuo. Ethanol (300 ml.) was added to the residue and the mixture refluxed for 30 min. Insoluble material was removed by filtration and the filtrate evaporated to dryness *in vacuo*. The brown resin was dissolved in 110 ml. of absolute ethanol and the solution kept at −10° overnight. The white solid isolated was twice recrystallized from ethanol. Yield: 17 g.; m.p. 190–192° (turbid melt).

Anal. Calcd. for $C_{14}H_{23}Cl_2N_3O_2$: C, 50.0; H, 6.9; Cl, 21.4. Found: C, 49.7; H, 6.7; Cl, 21.0.

2-[Bis(2-hydroxyethyl)aminomethyl]-1-methylbenzimidazole dihydrochloride. A mixture of 90 g. of 2-chloromethyl-1-methylbenzimidazole hydrochloride,[4] 44 g. of diethanolamine, 34 g. of anhydrous sodium acetate, and 600 ml. of acetone was refluxed for 2 hr. and allowed to cool. After addition of 25 g. of anhydrous sodium carbonate, refluxing was continued for 3 hr. The mixture was cooled again; after 35 g. of sodium bicarbonate had been added it was refluxed for another 2 hr. The salt was removed by filtration and the filtrate freed from acetone by distillation. The oily residue was dissolved in 250 ml. of hot water and poured slowly with stirring into a solution of 100 g. of picric acid in 2000 ml. of boiling water. Next morning the crystalline picrate was separated by filtration, washed with cold water, and recrystallized from 1100 ml. of water. Yield, 65 g.; m.p. 142–143°.

The picrate was finely ground and triturated with 260 ml. of concentrated hydrochloric acid. The mixture was extracted with 400 ml. of benzene; the aqueous layer was separated and washed six times with small amounts of benzene in order to remove the picric acid completely. The aqueous solution was decolorized with Darco and the filtrate evaporated to dryness in vacuo. Recrystallization of the semisolid residue from 150 ml. of alcohol gave 31.7 g. of white crystals, m.p. 172–174°.

Anal. Calcd. for $C_{13}H_{21}Cl_2N_3O_2$: C, 48.4; H, 6.5; Cl, 22.1. Found: C, 48.1; H, 6.6; Cl, 22.2.

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* After this note was submitted, we learned of the publication of W. Knobloch, *Chem. Ber.*, **91**, 2557 (1958) in which he reports the synthesis of some of the compounds described by us. It should be mentioned that most of the melting points shown by Knobloch are not in agreement with ours.

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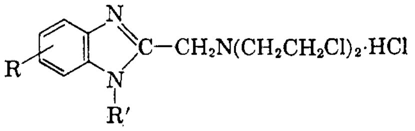
(12) We are grateful to Dr. Karl Folkers of Merck Sharp & Dohme Research Laboratories, Rahway, N. J., for a generous sample.

TABLE I

SUBSTITUTED 2-[BIS(2-CHLOROETHYL)AMINOMETHYL]BENZIMIDAZOLE HYDROCHLORIDES



R	R′	Yield, %	M.P., °C.	Analyses							
				Calculated				Found			
				C	H	N	Cl	C	H	N	Cl
5(or 6)-Chloro	H	45	146–147	41.97	4.37	12.24	41.40	41.86	4.23	12.07	41.52
5,6-Dichloro	H	49	171–173	38.17	3.73	11.13	46.95	38.24	3.85	11.26	47.01
5,6-Dimethyl	H	70	180–182	49.93	5.98	12.48	31.59	49.97	6.06	12.53	31.62
H	CH_3	61	137–138.5	48.37	5.58	13.03	33.03	48.47	5.60	13.12	32.8

2-[Bis(2-chloroethyl)aminomethyl]benzimidazole hydrochloride. This substance ("benzimidazole mustard") was obtained from the corresponding 2-hydroxyethyl compound by means of thionyl chloride, as had been described previously.[1] In order to obtain a pure product, several recrystallizations from ethanol are necessary in order to remove a lower melting by-product, which apparently is the dihydrochloride. It is less soluble in ethanol than the monohydrochloride and could be isolated from the first fractions of the ethanol recrystallization as a white crystalline substance, melting at 142–143° (after recrystallization from a small amount of ethanol).

Anal. Calcd. for $C_{12}H_{17}Cl_4N_3$: Cl, 41.2. Found: Cl, 41.4.

The substituted 2-[bis(2-chloroethyl)aminomethyl]benzimidazole hydrochlorides were prepared by the same general procedure from the alcohols and thionyl chloride. The crude products were twice recrystallized from absolute ethanol; usually, ether was added to the alcoholic solutions until cloudiness appeared.

The yields, physical properties, and analyses of the compounds are presented in Table I.

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Methyl 2-Nitro-3-ethoxyacrylate and Related Compounds

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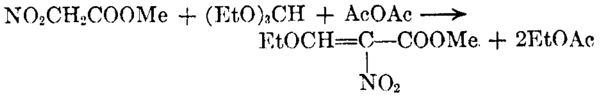
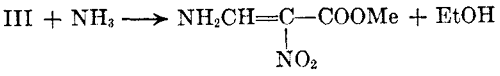
Active methylene compounds react with acetic anhydride and alkyl orthoformates to form alkoxymethylene derivatives.[1] The latter, in turn, readily undergo addition-elemination reactions with displacement of the alkoxyl group by nucleophilic agents. Thus, with ammonia ethoxymethylenemalononitrile, I, yields aminomethylenemalononitrile, II.[2] This note will serve to record the analogous synthesis of methyl 2-nitro-3-ethoxyacrylate, III, and methyl 2-nitro-3-aminoacrylate, IV, from methyl nitroacetate. Also described are methods of preparation and spectral data for several new derivatives of I.

$EtOCH{=}C(CN)_2$ I $\qquad$ $NH_2CH{=}C(CN)_2$ II



$$\mathrm{NO_2CH_2COOMe + (EtO)_3CH + AcOAc \longrightarrow EtOCH{=}\underset{\displaystyle NO_2}{\underset{|}{C}}{-}COOMe + 2EtOAc}$$

III



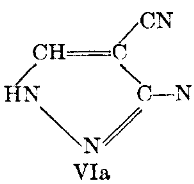
$$\mathrm{III + NH_3 \longrightarrow NH_2CH{=}\underset{\displaystyle NO_2}{\underset{|}{C}}{-}COOMe + EtOH}$$

IV

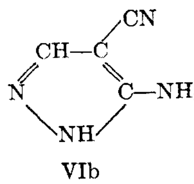
The structure of the compound derived from I with semicarbazide was assigned by comparison of its ultraviolet spectrum with those of I, II, and the product of I with hydrazine. I, II, and the semicarbazide product, V, all showed high intensity maxima between 248 and 267 mμ with minima below 215 mμ. The product of I with hydrazine which has been shown[3] to be the cyclized 3 (or 5)-amino-4-cyanopyrazole, IVa or b, exhibited only inflections at 214 and 240 mμ superimposed on a high intensity shorter wave length band. On this basis V was uncyclized semicarbazidomethylenemalononitrile.

$$\mathrm{H_2N\overset{\displaystyle O}{\overset{\|}{C}}NHNHCH{=}C(CN)_2}$$

V



VIa



VIb

The spectra of III and IV did not bear the expected resemblance to those of the corresponding dinitriles. IV exhibited medium-low intensity maxima at 235 and 312 mμ while III showed only a low intensity inflection at 252 mμ. Elemental analyses, the formation of a phenylurea from IV and

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(1) For leading references see R. G. Jones, *J. Am. Chem. Soc.*, **73**, 3684 (1951). A discussion of the mechanism is given by R. G. Jones, *J. Am. Chem. Soc.*, **74**, 4889 (1952).

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