

6-*O*-ethyl-D-galactose. The vinyl ether does not polymerize easily with usual free radical initiators, but homopolymerizes readily with ionic initiators.

### Experimental

**1,2;3,4-Di-*O*-isopropylidene-D-galactopyranose.**—This compound was prepared from D-galactose according to the methods described by Ohle and Behrend<sup>9</sup> and by Levine and Meyer.<sup>10</sup> It had an optical rotation of  $[\alpha]^{25}_D -54.7^\circ$  (*c*, 3.5 in chloroform) and was chromatographically pure.

**6-*O*-Vinyl-1,2;3,4-di-*O*-isopropylidene-D-galactopyranose.**—For vinylation, 100 g. of the above product and 5 g. of dry powdered potassium hydroxide were placed in a cylindrical reaction vessel provided with a fritted glass bottom and with a gas inlet tube sealed beneath the fritted glass. The vessel was placed in an oil bath at 160°, and flushed with nitrogen. The nitrogen stream was discontinued, and acetylene was bubbled through the reaction mixture at 160–180° for a period of 16 hr. at a rate of approximately 0.2–0.3 l./min. Effluent gases were passed through a cool chamber before discard. The reaction mixture was extracted with chloroform and the extract was combined with material which condensed on the walls of the cooling chamber. After distillation of the chloroform, the resulting sirup was mixed with powdered potassium hydroxide and distilled at 12–15 mm. pressure without fractionation. It was distilled through a Vigreux column. The main fraction distilled at 154–156° and 10–11 mm; yield 64 g. (58% of theoretical).

The clear distillate produced a single spot when chromatographed on dimethylformamide treated paper irrigated with acetone–dimethylformamide (4:1 v./v.);  $[\alpha]^{25}_D -81.2^\circ$  (*c*, 1.90 in chloroform).

*Anal.* Calcd. for C<sub>14</sub>H<sub>22</sub>O<sub>6</sub>: C, 58.73; H, 7.74. Found: C, 58.89; H, 7.86.

**6-*O*-Ethyl-1,2;3,4-di-*O*-isopropylidene-D-galactopyranose.**—Five grams of 6-*O*-vinyl-1,2;3,4-di-*O*-isopropylidene-D-galactopyranose was dissolved in 50 ml. of 99% ethanol and mixed with 2 g. of Girdler nickel catalyst (Girdler 6–49A, 65.5% Ni)<sup>11</sup> in a 100-ml. rocking autoclave. Hydrogen was added to a pressure of 100 p.s.i.g. and the autoclave heated for 8 hr. at 80°. The reaction mixture was filtered and the filtrate concentrated to a sirup which was distilled in a micro distillation apparatus. The main fraction distilled at 89–93° at 0.2 mm. pressure; yield was 3.3 g. (66%) of a colorless liquid. The infrared spectra of this product showed no trace of the absorption bond characteristic of double bonds;  $[\alpha]^{25}_D -60.6^\circ$  (*c*, 1.45 in chloroform).

*Anal.* Calcd. for C<sub>14</sub>H<sub>24</sub>O<sub>6</sub>: C, 58.31; H, 8.38. Found: C, 58.17; H, 8.23.

**6-*O*-Ethyl-D-galactopyranose.**—6-*O*-Ethyl-1,2;3,4-di-*O*-isopropylidene-D-galactopyranose was hydrolyzed as described by McKeown and Hayward.<sup>12</sup> The product melted at 106°. Its X-ray diffraction pattern was identical to that of an authentic sample of 6-*O*-ethyl-D-galactopyranose.

**Homopolymerizations.**—6-*O*-Vinyl-1,2;3,4-di-*O*-isopropylidene-D-galactose did not polymerize with free radical initiators and was thus similar to other vinyl ethers. Initiators tested were 2,4-dichlorobenzoyl peroxide, benzoyl peroxide, and azobisisobutyronitrile. They were tested in concentrations up to 1% in methanol solutions of monomer at 3.5% concentration.

With ionic initiators polymerization took place rapidly at room temperature. Polymers were produced in 3.5% methanolic solution with trace addition of titanium tetra-

chloride, stannic chloride, and boron trifluoride etherate. Polymers precipitated immediately from the reaction mixture and were insoluble in methanol, ethanol, hexane, cyclohexane, ethylene dichloride, benzene, and pyridine.

**Copolymerizations.**—Copolymers of 6-*O*-vinyl-1,2;3,4-di-*O*-isopropylidene-D-galactopyranose were readily made with methyl methacrylate, vinyl acetate, and acrylonitrile in methanol solutions with the ionic initiators mentioned above.

Copolymers involving vinyl acetate could be produced with free radical initiators although the incorporation of the sugar derivative into the copolymer did not exceed 30% as estimated from infrared spectra (potassium bromide pellets). Limited incorporation of vinyl ethers had previously been observed in copolymerizations of various vinyl ethers and vinyl acetate.<sup>13</sup> 6-*O*-Vinyl-1,2;3,4-di-*O*-isopropylidene-D-galactopyranose did not copolymerize with methyl methacrylate in the presence of free radical initiators. Infrared patterns of the polymer products were identical with those of polymethylmethacrylate.

**Acknowledgment.**—The authors gratefully acknowledge a grant from the National Science Foundation which helped to support this work. Additional thanks is given to Dr. L. D. Hayward for a sample of 6-*O*-ethyl-D-galactose.

(13) A. M. Khomutov and M. F. Shostakovskii, *Izv. Akad. Nauk. SSSR, Otdel. Khim. Nauk.*, 2017 (1959); *Chem. Abstr.*, **54**, 8141g (1960).

## Antineoplastic Agents. VIII.

### Bis(2-chloroethyl)amine Condensation Reactions. Part A<sup>1,2</sup>

GEORGE R. PETTIT AND JOSEPH A. SETTEPANI

*Department of Chemistry University of Maine, Orono, Maine*

*Received March 20, 1962*

The facility with which bis(2-chloroethyl)amines will undergo certain intra- and intermolecular reactions under neutral or basic conditions is well established.<sup>3</sup> A detailed knowledge of these transformations, however, is essential both to developing efficient synthetic routes to nitrogen mustards, and to understanding their biological role in cancer chemotherapy.<sup>4</sup> While a number of investigations have dealt with various aspects of this problem, there remains a pressing need for additional basic information. For this reason, we have undertaken a study of intramolecular reactions involving nitrogen mustard.

(1) Part VII, G. R. Pettit and A. K. Das Gupta, *Chem. Ind. (London)*, in press.

(2) This investigation was aided by Grants No. T-79B and T-79C from the American Cancer Society.

(3) For example, refer to: O. M. Friedman, H. Sommer, and E. Boger, *J. Am. Chem. Soc.*, **82**, 5202 (1960); T. L. Fletcher and W. H. Wetzel, *J. Org. Chem.*, **25**, 1348 (1960); W. C. J. Ross and J. G. Wilson, *J. Chem. Soc.*, 3616 (1959); footnote 1; and a review by A. Streitwieser, Jr., *Chem. Rev.*, **56**, 571 (1956).

(4) A recent advance pertinent to the latter subject has been summarized by P. Brookes and P. D. Lawley, *Biochem. J.*, **80**, 496 (1961).

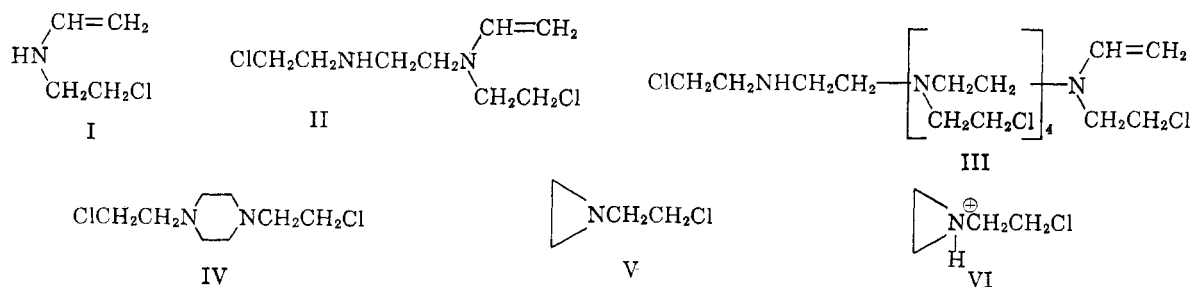
(9) H. Ohle and G. Behrend, *Ber.*, **58**, 2585 (1925).

(10) P. A. Levine and G. H. Meyer, *J. Biol. Chem.*, **92**, 257 (1931).

(11) Girdler Catalysts, Chemical Products Division, Chemetron Corp., Louisville 1, Kentucky.

(12) G. G. McKeown and L. D. Hayward, *Can. J. Chem.*, **38**, 174 (1960).

One of the first accounts of bis(2-chloroethyl)-amine self-condensation products was presented in 1949.<sup>5</sup> On standing, either alone or with a small quantity of methanol, nitrogen mustard was reported to yield its hydrochloride derivative and vinylamine I. The latter product was isolated as a dimer subsequently assigned an *N,N'*-bis(2-chloroethyl)-*N*-vinyl-1,2-diaminoethane (II) monohydrochloride (m.p. 322–325°) structure.<sup>5</sup> Evidence for this formulation was based on elemental analyses and isolation of formaldehyde (5% yield) following ozonization of the dimer (II) hydrochloride. Treating an ethereal extract of the oily product accompanying dimer II hydrochloride with picric acid was shown to yield a new substance (m.p. 215–216°) believed to be the pentapicrate derivative of a trimer (III) or related compound. Furthermore, the oily product (ca. 25% conversion) which separated upon making basic an aqueous solution of dimer II hydrochloride gave a picrate (m.p. 215–216°) identical with the "pentapicrate" and a hydrochloride (m.p. 311–312°) derivative.



We now wish to report that the "pentapicrate" and the hydrochloride salt melting (actually a decomposition point) at 311–312° are both derivatives of *N,N'*-bis(2-chloroethyl)piperazine (IV).<sup>6</sup> Unequivocal support for this observation was obtained as follows. The condensation experiments described previously<sup>5,7</sup> were repeated and essentially the same results were obtained. In addition, the hydrochloride (d.p. 310–311°) derivative of IV was also prepared from an ethereal extract of the crude reaction product. The hydrochloride (d.p. 310–311°) was identical with an authentic specimen of *N,N'*-bis(2-chloroethyl)piperazine dihydrochloride

(5) I. Langman, A. F. McKay, and G. R. Wright, *J. Org. Chem.*, **14**, 550 (1949).

(6) Interestingly, piperazine IV was rejected in the earlier study (ref. 5) as a possible structure for substance II as a result of the ozonization work.

(7) Dr. George F. Wright kindly informed us that the original specimens were no longer available.

(8) Cf., Y. Sakurai and M. Izumi, *Pharm. Bull. (Tokyo)*, **1**, 297 (1953); *Chem. Abstr.*, **49**, 8304 (1955). We were unable to obtain a dihydrochloride derivative of piperazine IV decomposing at 250° as described by E. Wilson and M. Tishler, *J. Am. Chem. Soc.*, **73**, 3635 (1951).

(9) The dihydrochloride derivative of piperazine IV was also identical with a sample prepared from bis(2-chloroethyl)amine in the presence of 1-butanol and paraformaldehyde as described by A. F. Childs, L. J. Goldswortey, G. F. Harding, F. E. King, A. W. Nineham, W. L. Morris, S. G. Plant, B. Selton, and A. L. L. Tompsett, *J. Chem. Soc.*, 2174 (1948). Further support for the piperazine formulation was provided by inspecting its infrared and proton magnetic resonance spectra.

(d.p. 316°) prepared<sup>8,9</sup> by chlorination of *N,N'*-bis(2-hydroxyethyl)piperazine<sup>10</sup> with thionyl chloride. Analogously, the picrate derivative (d.p. 220°) of piperazine IV was identical with the "pentapicrate."<sup>11</sup> The hydrochloride melting at 322–325° (originally considered to be a monohydrochloride derivative of vinylamine II) is therefore a mixture, composed partially of piperazine IV hydrochloride.<sup>12</sup>

Recently, self-condensation of bis(2-chloroethyl)-amine in methylene chloride solution has been reported to yield the corresponding hydrochloride derivative and *N*-(2-chloroethyl)ethyleneimine (V).<sup>13</sup> The imine (V) was characterized as monohydrochloride (m.p. 313–314°) and picrate (m.p. 213–214°) derivatives. Assignment of structure V was based on elemental and molecular weight determinations and synthesis of the picrate derivative (m.p. 210°) starting with ethylene imine and 1-bromo-2-chloroethane. Decolorization of aqueous potassium permanganate by both ethyleneimine and the hydrochloride, m.p. 313–314°, was also reported.<sup>14</sup>

As part of the present study, we were led to reinvestigate the reaction of nitrogen mustard in methylene chloride solution. While similar experimental results were obtained in our hands, reinterpretation of the structural assignments is now required. The hydrochloride (m.p. 313–314°) and picrate (m.p. 213–214°) are in fact derivatives of *N,N'*-bis(2-chloroethyl)piperazine (IV). Both the original<sup>15</sup> and specimens prepared in the present study were identical with authentic samples<sup>8</sup> of piperazine IV hydrochloride and picrate.

The piperazine formulation for these products is also consistent with the observed discolorization of aqueous potassium permanganate. Piperazine IV hydrochloride behaved similarly and other related

(10) D. E. Adelson, L. G. MacDowell, and C. B. Pollard, *J. Am. Chem. Soc.*, **57**, 1988 (1935).

(11) The respective parent amines were also compared and found to be identical.

(12) Following proton magnetic resonance and infrared spectral studies a vinylamine structure (II) was also excluded for the remaining product. The composition of this material will be discussed in a subsequent paper.

(13) F. D. Popp and E. Cullen, *Chem. Ind. (London)*, 1911 (1961).

(14) W. Marckwald, *Ber.*, **33**, 764 (1900), noted that ethyleneimine did not discolor aqueous potassium permanganate and we have reconfirmed his observation using a commercial sample of the imine.

(15) We wish to thank Dr. F. D. Popp for providing us with samples of the hydrochloride (d.p. 314–315°) and picrate (d.p. 218–218.5°) prepared in his laboratory.

examples of this oxidation reaction<sup>16</sup> are known.<sup>17</sup> Further, the hydrogen bromide generated during the condensation of ethyleneimine with 1-bromo-2-chloroethane may be expected to produce a transient ethyleneimmonium intermediate (*e.g.*, VI) which might then dimerize to the stable piperazine (IV).

In summary, under essentially neutral conditions N,N'-bis(2-chloroethyl)piperazine is one of the most important transformation products of bis(2-chloroethyl)amine. The facile production of this substance (IV) should now be considered when evaluating reactions of nitrogen mustard.

(16) Oxidative cleavage of vicinal amines by manganese dioxide has recently been described by E. F. Curragh, H. B. Henbest, and A. Thomas, *J. Chem. Soc.*, 3559 (1960). See also, H. S. Mosher, "Heterocyclic Compounds," Vol. 1, R. C. Elderfield, ed., John Wiley and Sons, Inc., New York, N. Y., 1950, p. 686.

(17) For example, see L. Knorr, *Ber.*, **37**, 3516 (1904).

## Symmetrical Tricyanobenzenes

CLAUS D. WEIS

*Explosives Department, Experimental Station Laboratory,  
E. I. du Pont de Nemours & Company,  
Wilmington, Delaware*

*Received April 9, 1962*

The cumbersome preparation of symmetrical tricyanotrimethylbenzene (I) (tricyanomesitylene) by a stepwise introduction of three cyano groups has been reported.<sup>1</sup> We deemed it of interest to attempt a more facile synthesis of this type of compound.

The Rosenmund-von Braun reaction generally proceeds well with halogen compounds bearing the halogen atoms on nonadjacent carbon atoms. The method is satisfactory even under sterically unfavorable conditions.<sup>2</sup> Therefore, simultaneous substitution of all three halogens in the 1, 3, 5-positions of substituted benzene derivatives appeared to be quite feasible.

It has now been prepared by the action of the pyridine-copper cyanide adduct on tribromomesitylene. Apparently the reaction proceeded stepwise, since at 170° a small yield (31%) of dicyanobromomesitylene (V) was formed and at 205° I was obtained in 46–56% yield. The crude reaction product could be readily separated from highly colored by-products by filtration of its solution in chloroform through a column of activated alumina. This procedure eliminated the yellow by-products which otherwise could only be removed by repeated recrystallizations involving considerable loss of material. Since the melting point was found to be slightly different from the reported one, the

structure was further supported by the n.m.r. spectrum.

Upon heating I in a mixture of concentrated sulfuric acid and fuming nitric acid symmetrical trinitromesitylene (III) was obtained. This was probably formed from I by successive saponification decarboxylation and subsequent nitration.

Symmetrical tricyanotriethylbenzene (IV) was similarly obtained in 81% yield from symmetrical tribromotriethylbenzene.<sup>3</sup>

### Experimental<sup>4</sup>

**Symmetrical Tricyanotrimethylbenzene (I).**—Copper cyanide (220 g., 2.46 moles) and pyridine (254 g., 3.30 moles; 260 ml.) were converted into the copper-pyridinium salt. The crude salt was thoroughly mixed with symmetrical tribromotrimethylbenzene (266 g., 0.74 mole) and the mixture in two equal portions heated in a steel autoclave to 205° for a period of 80 min.

The solid material was discharged and heated with hydrochloric acid to remove the pyridine. The mixture was filtered, and the residue heated in dilute nitric acid (1:5) for 5 hr. on a steam bath. After cooling, the black mixture was filtered and the residue dried and extracted with chloroform in a Soxhlet apparatus. The chloroform solution was concentrated and filtered through a column of neutral alumina (Woelm, 1500 mm. × 45 mm.).

Evaporation of the solution to dryness gave almost white crystals (82 g., 56%). Recrystallization from butanol yielded colorless crystals, m.p. 182° (lit. 165°), which started to sublime slowly at about 130°. The compound was soluble in most organic solvents except petroleum ether, hexane, and carbontetrachloride.

*Anal.* Calcd. for C<sub>12</sub>H<sub>6</sub>N<sub>3</sub>: C, 73.84; H, 4.65; N, 21.53. Found: C, 73.77; H, 4.60; N, 21.44.

Absorption in the nitrile band region occurred at 4.50 μ (KBr wafer).

**Dicyanobromomesitylene (II).**—A mixture of tribromomesitylene (5 g., 0.014 mole), copper cyanide (4.5 g., 0.5 mole), and pyridine (25 ml.) was heated in a sealed tube to 190° for a period of 45 min. The product was heated with an excess of dilute nitric acid (1:5) for 3 hr. on a steam bath. The black residue was filtered off and extracted with ethanol (25 ml.). Concentration and cooling of the solution yielded white crystals, m.p. 189–190° (from ethanol) (1.1 g., 31%).

*Anal.* Calcd. for C<sub>11</sub>H<sub>5</sub>N<sub>2</sub>Br: C, 53.03; H, 3.64; N, 11.24; Br, 32.09. Found: C, 53.24; H, 3.80; N, 11.09; Br, 32.18.

**Trinitromesitylene (III).**—Tricyanomesitylene (1.0 g., 0.005 mole) was dissolved in a mixture of fuming sulfuric acid (20% oleum) (25 ml.) and fuming nitric acid (30 ml.) and the mixture refluxed for 1 hr. It was then poured onto ice and the colorless crystals (0.71 g., 54.5%), m.p. 233–235° (from chloroform) identified by mixed melting point, m.p. 233–234°, with an authentic specimen of trinitromesitylene.

**Symmetrical Tricyanotriethylbenzene (IV).**—Tribromotriethylbenzene (142 g., 0.356 mole) was thoroughly mixed with pyridine-copper cyanide (255 g., 1.51 moles). The mixture was divided into two equal parts, pyridine (30 ml.) added to each one, and each heated in a steel autoclave for a period of 70 min.

The solid powdered reaction product was treated with an excess of dilute hydrochloric acid and the solid filtered off and heated with dilute nitric acid (1:5) on a steam bath for 5 hr. The mixture was then filtered and the residue washed with water and dried. The crystalline solid was dissolved

(1) F. W. Küster and A. Stallberg, *Ann.*, **278**, 207 (1887).

(2) R. C. Fuson *et al.*, *J. Am. Chem. Soc.*, **68**, 533 (1946).

(3) M. Markarian, Sydney D. Ross, and Mathew Nazzewska, U. S. Patent 2,695,900 (1954).

(4) All melting points are uncorrected.