Acknowledgment.—The vapor phase chromatographic analysis was performed by Dr. R. C. Petersen and the benzyltriphenylphosphonium trifluoroacetate was prepared by Dr. S. D. Ross.

The Reaction of 2,3-Dichloro-*p*-dioxane with Phenyllithium

R. K. SUMMERBELL, WILLIAM M. SMEDLEY,[1]
DONALD M. JERINA,[2] AND DANIEL R. BERGER

Chemical Laboratories, Northwestern University, Evanston, Illinois

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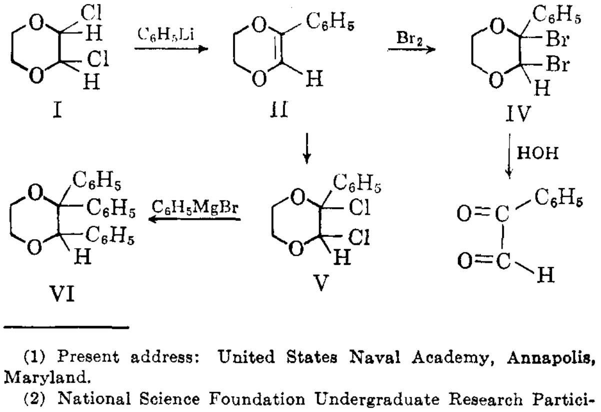
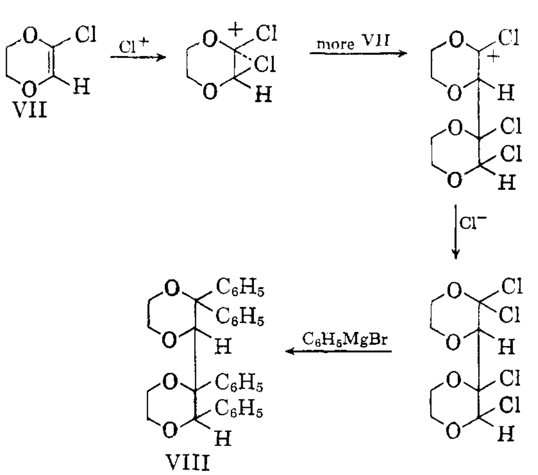
Organometallic compounds react with 2,3-dichloro-*p*-dioxane (I) in a variety of ways. Aryl Grignard reagents give mixtures of isomeric 2,3-diaryl-*p*-dioxanes in excellent yields.[3-5] The dominant isomer was assigned a *cis* structure by Stumpf,[5] but later strong evidence for a *trans* structure was presented.[6] The *trans* product predominates whether the starting material I is *cis* or *trans*.[7] The reaction of compound I with alkyl Grignard reagents is primarily one of dehalogenation,[4] dioxene and disproportionation products of the alkyl group resulting. The very small yields of mixtures of isomeric dialkyldioxanes produced from the alkylmagnesium halides can be markedly increased[8] by employing the Blaise[9] modification of the Grignard reagent utilising unisolated alkylzinc intermediates. Even better yields are obtained from similar alkylcadmium compounds, but dialkylmercury or alkylmercuric halide reagents are inert toward I. In the present study, phenyllithium has been found to react with I in yet another way, the product being 2-phenyl-*p*-dioxene (II).



The unsymmetrical 2-phenyl-*p*-dioxene is an extremely unstable and fugacious substance, in sharp contrast to the closely related, but symmetrical 2,3-diphenyl-*p*-dioxene (III).[6] Samples of III have now been kept for several years in ordinary shelf storage without modification, but II changes from a white crystalline solid to a light green liquid on standing at room temperature, often in a matter of hours. The nature of the change taking place in II is as yet obscure. Some sort of polymerization occurs, as the average molecular weight of a modified sample was found to be about 1400. That the reaction was not simply polymerization was indicated by the change in analysis, the percentages of carbon decreasing as modification proceeds. Addition of one oxygen atom for each phenyldioxene unit would account roughly for the change in composition. The infrared spectra indicate loss of double bond and a slight, but by no means proportional, formation of carbonyl during the transition.

Characterization and proof of structure of the 2-phenyl-*p*-dioxene were complicated by its unstable character but are quite definite. It adds one mole of bromine to yield 2-phenyl-2,3-dibromo-*p*-dioxane (IV). This readily undergoes hydrolysis to phenylglyoxal, which was isolated in the form of the osazone. The chlorine addition product, 2-phenyl-2,3-dichloro-*p*-dioxane (V), was converted by phenylmagnesium bromide to 2,2,3-triphenyl-*p*-dioxane (VI), which was also prepared by an independent synthesis from the known 2,2,3-trichloro-*p*-dioxane.[10]

When 2,2,3-trichloro-*p*-dioxane was treated with phenylmagnesium bromide, two products rather than the expected one were produced. Since the major one had the correct analysis and molecular weight for 2,2,3-triphenyl-*p*-dioxane, it was assigned that structure. The less soluble one, formed in minor amount, was reminiscent of by-products



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[1] Present address: United States Naval Academy, Annapolis, Maryland.

[2] National Science Foundation Undergraduate Research Participant, National Science Foundation Grant, 16238, Summer, 1961.

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observed when chloro-*p*-dioxane was treated with alkyl Grignard reagents, methyldioxanyldioxane and butyldioxanyldioxane.[11] A mechanism like that suggested by McElvain and Davie[12] in a similar situation would predict that in the present case a tetraphenyl-*p*-dioxanyl-*p*-dioxane of structure VIII would be expected to result from a byproduct formed when the intermediate 2,2,3-trichloro-*p*-dioxane was prepared. The analysis and molecular weight are consistent with this assignment of structure.

Our original work on 2-phenyl-*p*-dioxene was done a number of years ago, but publication was held up because several attempts to repeat or extend the work gave erratic results or were entirely unsuccessful. Even when the compound was obtained, carbon and hydrogen analyses were not satisfactory. Our present success seems to be due to a stringent avoidance of acid at any stage of the preparation or storage, all apparatus being rinsed with alkali carbonate or ammonia before contact with the product. Hydrolysis of the organometallic–chloro ether reaction mixture was with water, not with dilute acid. The traces of acid present in the atmospheres of desiccators charged with sulfuric acid or calcium chloride were sufficient to cause a noticeable increase in the rate of deterioration over that which took place in the open air of the laboratory. Obtaining a satisfactory analytical sample was achieved by Dry Ice temperature crystallization from pentane, followed by drying at room temperature in a desiccator charged with paraffin chips.

Experimental

2-Phenyl-*p*-dioxene (II).—Lithium (12.5 g., 1.8 g.-atoms) was cut into 300 ml. of absolute ethyl ether while the flask was continuously flushed with pure nitrogen. A solution of 141 g. (0.9 mole) of bromobenzene dissolved in 225 ml. of absolute ether was added dropwise at a rate to maintain ether reflux. A solution of 41.7 g. (0.3 mole) of *trans*-2,3-dichloro-*p*-dioxane (I) dissolved in 150 ml. of absolute ether was added, again at a rate to maintain ether reflux. The solution was heated to reflux, stirred for an additional 2 hr., and allowed to stand, with stirring, for 12 hr. It was then hydrolyzed with water and the ether collected and combined with two additional 100-ml. portions of ether used to extract the hydrolysis mixture. The ether was stripped and the resulting liquid distilled rapidly at 2 mm. through a 6-in. Vigreux column. The material, boiling at 97–103°, weighing 15.5 g., readily solidified on cooling. When crystallized from pentane, it melted sharply at 43°, yield 31%. An attempt was made to prepare an analytical sample by crystallization from ether and drying in a vacuum desiccator over sulfuric acid, but the sample (a) showed marked signs of deterioration in less than 0.5 hr. A second sample (b), recrystallized from pentane and dried in a vacuum desiccator over paraffin shavings, gave a satisfactory analysis.

Anal. Calcd. for $C_{10}H_{10}O_2$: C, 74.04; H, 6.21. Sample (a): C, 73.21; H, 5.81. Sample (b): C, 73.77; H, 6.04.

Mol. wt: Calcd.: 162. Found: 160, by micro-Rast method. Titrations in triplicate showed the addition of 0.96 mole of Br_2 per mole of phenyl-*p*-dioxene.[13]

2-Phenyl-2,3-dibromo-*p*-dioxane (IV).—Bromine dissolved in carbon tetrachloride was added in slight excess to a dilute carbon tetrachloride solution of II. After standing in the dark for 30 min., the solution was washed with a sodium thiosulfate solution, evaporated, and the residue recrystallized rapidly from methanol without prolonged heating, m.p. 118.5–119°.

Anal. Calcd. for $C_{10}H_{10}O_2Br_2$: Br, 49.64. Found: Br, 49.58.

A similar sample was prepared by adding bromine in chloroform solution to 1 g. of II, the solvent was removed, and the residue treated with 20 ml. of water containing 1 drop of conc. hydrochloric acid. Heating on the water bath for an hour produced a homogeneous solution which was allowed to react with a water solution of phenylhydrazine hydrochloride. The osazone, recrystallized from ethanol, melted at 150–151°. Lit. for osazone of phenylglyoxal: 152°.[14]

Properties of Modified 2-Phenyl-*p*-dioxene.—Crystals of 2-phenyl-*p*-dioxene could be kept indefinitely if stored at Dry Ice temperature; however, after standing at room temperature for a few hours, a coating of light green oil invariably formed, and the entire sample would liquefy in a matter of days. A sample of this oil (2 months old) was dried at 1-mm. pressure and 100° for 3 hr. and was then analyzed.

Anal. Found: C, 65.80; H, 6.46.

Infrared spectra differed from that of unmodified 2-phenyl-*p*-dioxene in that the prominent olefin band at 6.04 μ had almost disappeared, and new small probably carbonyl bands at 5.8 and 5.9 μ were evident. Molecular weight, cryoscopic, using benzene, was 1388, equivalent to about eight $C_{10}H_{10}O_3$ units.

2,2,3-Triphenyl-*p*-dioxane (V).—A solution of 1.62 g. (0.01 mole) of II in 50-ml. of pentane was cooled in ice and chlorine bubbled in until color persisted. It was added dropwise to 0.05 mole of phenylmagnesium bromide and the resulting mixture stirred and heated for 15 min. After hydrolysis, the residue which resisted crystallization was placed on an alumina column by means of hexane and eluted with a 25% solution of ether in hexane. After 0.1 g. of biphenyl, a single product, 1.71 g., m.p. 128°, identical in mixed melting point and infrared spectrum with 2,2,3-triphenyl-*p*-dioxane was obtained. Yield, 54%. The comparison sample which had been made earlier in connection with another study was prepared as described below.

To a solution of phenylmagnesium bromide prepared from 39.3 g. (0.25 mole) of bromobenzene and 6.1 g. (0.25 g.-atom) of magnesium in 150 ml. of dry ether was added, dropwise and with stirring, a solution of 10.1 g. (0.053 mole) of 2,2,3-trichloro-*p*-dioxane[7] in 50 ml. of ether. After refluxing for 15 min., the mixture was hydrolyzed by pouring onto ice–sulfuric acid, the layers separated, the aqueous layer washed with ether, and the combined ether solutions washed with dilute aqueous sodium bicarbonate and water. The ether was removed and the residual syrup was steam-distilled until no more biphenyl was present in the distillate. The residue was extracted in ether and dried over magnesium sulfate; crystallization gave 0.1 g. of a compound, m.p. 201°. The ether was removed and the residue taken up in hexane. Several evaporations of the hexane were done in order to remove the remaining traces of ether, and the hexane solution was separated into its components by chromatography, using a column of 80–200-mesh alumina packed in hexane. The column was eluted with a solution of one part ether and three parts pentane. A large amount of material was collected in the early fractions, melting, after recrystallization from ethanol, at 128°. The next compound isolated was the same compound, m.p. 201°, obtained above. The combined samples of the 201° compound were recrystallized from hexane.

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[12] S. M. McElvain and W. R. Davie, *J. Am. Chem. Soc.*, **74**, 1816 (1952).

[13] H. S. Davis, G. S. Crandall, and W. E. Higbee, *Ind. Eng. Chem., Anal. Ed.*, **3**, 108 (1931).

[14] R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," John Wiley & Sons, New York, N. Y., 1956, p. 284.

The major product, the compound melting at 128°, was assigned the structure of 2,2,3-triphenyl-*p*-dioxane on the basis of its analysis, molecular weight, and method of synthesis. The compound, m.p. 201°, has not been positively identified, but it is probably a tetraphenyl-*p*-dioxanyl-*p*-dioxane (VIII).

Compound, m.p. 201°. Yield: 0.3 g. *Anal.* Calcd. for $C_{32}H_{30}O_4$: C, 80.5; H, 6.3. Found: C, 80.86, 80.26; H, 6.30, 6.30. Compound, m.p. 128°. Yield: 2 g. Anal. Calcd. for $C_{22}H_{20}O_2$: C, 83.51; H, 6.37. Found: C, 83.51; H, 6.09. Molecular weight: Calcd.: 316. Found: 306 (Rast camphor).

The Structure of the Thiocytosine Analog of Nitrogen Mustard[1]

JOHN A. MONTGOMERY, ALAN L. FIKES, AND
THOMAS P. JOHNSTON

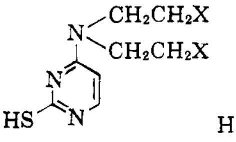
*Kettering-Meyer Laboratory, Southern Research Institute,
Birmingham 5, Alabama*

Received May 11, 1962

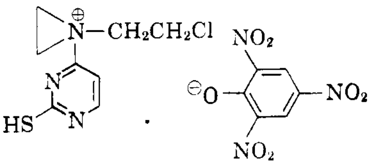
Recently the synthesis of 4-[bis(2-chloroethyl)-amino]-2-pyrimidinethiol (Ib, the thiocytosine analog of nitrogen mustard) by the chlorination of 2,2′-[(2-mercapto-4-pyrimidinyl)imino]diethanol (Ia) with thionyl chloride has been claimed[2] but no evidence was offered that both chlorine atoms of this compound are in fact covalent. Further, the conversion of Ib to 1-(2-chloroethyl)-1-(2-mercapto-4-pyrimidinyl)aziridinium picrate (II) by treatment with hot ethanolic picric acid is described. Since the true structure of a nitrogen mustard such as Ib is important to the evaluation of biological data obtained with it, and since it has been established that attempts to prepare the purin-6-yl analog of nitrogen mustard by thionyl chloride chlorination of the corresponding iminodiethanol gave only the tricyclic purine III,[3] we have studied the chlorination of Ia as recently described.[2] We have obtained conclusive evidence that the product of this reaction is actually the hydrochloride of the bicyclic 1-(2-chloroethyl)-2,3-dihydromidazo[1,2-*c*]-pyrimidine-5(1*H*)-thione (IV)[4] and, therefore, that the reported picrate is the picrate of the dihydromidazopyrimidine IV and not of the ethyleneimonium form of the nitrogen mustard.

Chlorination of Ia gave a material which resembled the reported compound,[2] but about half of its chlorine content was ionic. This material could, by careful neutralization, be converted to its free base whose ultraviolet spectrum is practically identical with that of the chloride and quite different from that of Ia (whose spectrum should be very similar to a structure such as Ib). The free base, which must have the structure IV, was then converted back to its hydrochloride by treatment with dry hydrogen chloride in chloroform. An anhydrous sample of the hydrochloride was thus obtained.

The rather low toxicity reported[2] for the chlorination product of Ia is more in keeping with the imidazo[1,2-*c*]pyrimidine (IV) than the nitrogen mustard (Ib) structure.

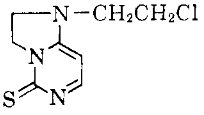


Ia. X = OH
Ib. X = Cl



II

III



IV

Experimental[5]

2-(2-Chloroethyl)-2,3-dihydroimidazo[1,2-*c*]pyrimidine-5(1*H*)-thione (IV). (a) Free Base.[6]—2,2′-[(2-Mercapto-4-pyrimidinyl)imino]diethanol (Ia)[2] (2.0 g., 9.3 mmoles) was added to a well stirred solution of 0.3 ml. of thionyl chloride and 0.5 ml. of ethyl alcohol in 22 ml. of bis(2-methoxyethyl) ether. Additional thionyl chloride (4.0 ml.) was slowly added to the mixture and the resulting white suspension stirred at room temperature overnight. The reaction mixture was then evaporated to dryness under reduced pressure to give a tan residue, which was dissolved in hot ethyl alcohol (100 ml.), treated with charcoal, and filtered. The clear filtrate was evaporated to dryness under reduced pressure to give the crude hydrochloride of IV; λ_{max} in mμ ($\epsilon \times 10^{-3}$): pH 1—247 (11.4), 273 (16.9), 320 (4.07); pH 7—232 (12.2), 266 (9.44), 336 (7.10); pH 13-232 (14.5), 266 (9.15), 338 (7.90); EtOH—245 (10.5), 278 (16.8), 326 (3.65).

Anal. Calcd. for $C_8H_{10}ClN_3S \cdot HCl$: Cl (total), 28.12; Cl (ionic), 14.06. Found: Cl (total), 27.0; Cl (ionic), 13.1 (by acid-base titration at 0°).

After several unsuccessful attempts to recrystallize the crude hydrochloride, it was dissolved in cold water and the pH carefully brought to 8 by the dropwise addition of 0.1 *N* sodium hydroxide solution. The free base precipitated as a yellow solid, which was recrystallized from methyl alcohol

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[1] This work was carried out at the suggestion of Dr. H. W. Bond and was supported by funds from the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. SA-43-ph-1740.

[2] H. Segal and C. G. Skinner, *J. Org. Chem.*, **27**, 199 (1962).

[3] T. P. Johnston, A. L. Fikes, and J. A. Montgomery, *ibid.*, **27**, 973 (1962).

[4] Many examples have been reported in which the chlorination of a 2-(4-pyrimidinylamino)ethanol has resulted in the formation of an imidazo[1,2-*c*]pyrimidine [G. R. Ramage and G. Trappe, *J. Chem. Soc.*, 4410 (1952); R. H. Martin and J. Mathieu, *Tetrahedron*, **1**, 75 (1957); J. Clark and G. R. Ramage, *J. Chem. Soc.*, 2821 (1958); J. H. Lister, *ibid.*, 899 (1960); P. R. Brook and G. R. Ramage, *ibid.*, 896 (1955)].

[5] Melting points were determined on a Kofler Heizbank and are corrected. The ultraviolet spectra were determined in alcoholic and aqueous solutions with a Cary Model 14 spectrophotometer. Paper chromatography was done by the descending technique on Whatman No. 1 paper; spots were viewed in ultraviolet light. R_{Ad} values were determined by locating spots relative to adenine arbitrarily assigned an R_f value of 1.00. Solvent systems: A, water-saturated butyl alcohol; B, butyl alcohol-acetic acid-water (5:2:3 by vol.); C, isopropyl alcohol-concentrated ammonium hydroxide-water (14:1:5 by vol.); D, acetate buffer (pH 6.1).

[6] The first part of this procedure is practically identical with that described by Segal and Skinner.[2]