[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF SOUTH CAROLINA]

Dichlorides of Cyclohexane

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Three dichlorides of cyclohexane, 1,1-, *cis*-1,2- and *trans*-1,2- have been prepared, the first two for the first time in pure form and their physical properties determined. The 1,1-dichloride was made by the action of phosphorus pentachloride on cyclohexanone without a solvent. The *cis*-1,2-dichloride was made by treating *trans*-2-chlorocyclohexanol with thionyl chloride in the presence of pyridine.

In conjunction with a study of the chlorination of chlorocyclohexane it became necessary to know the properties of the dichlorides of cyclohexane. Little information of value was found in the literature, a situation which has been remedied in part by the preparation and characterization of 1,1-, *trans*-1,2- and *cis*-1,2-dichlorocyclohexane.

The first of the pure isomers to be prepared in this investigation was the 1,1-dichlorocyclohexane. The substance has been alluded to by Markownikoff,[3] Favorskii and Boshovskii[4] and Mousseron and Jacquier,[5] but they gave no indication of its properties, merely assuming that it was present in a mixture obtained by the action of phosphorus pentachloride on cyclohexanone. Contrary to the conclusion of Mousseron,[5] we have found that the 1,1-dichloride can be isolated and is distillable at atmospheric pressure. Several experiments with the above reagents resulted in a procedure which gave a 21% yield of 1,1-dichlorocyclohexane, boiling at 169–173°. The use of a solvent or temperature above 65° was found to decrease the yield. This material was shown to be the 1,1-dichloride by hydrolyzing to cyclohexanone, identified by the 2,4-dinitrophenylhydrazone.

The first recorded preparation of a 1,2-dichlorocyclohexane, boiling point 187–189°, was by Markownikoff[3] who synthesized the compound by addition of free chlorine to cyclohexene. The same compound has since been made by other workers in a variety of ways. These include chlorination of cyclohexane,[6] treatment of cyclohexene with sulfuryl chloride,[7] addition of chlorine to cyclohexene,[8] reaction of cyclohexene chlorohydrin with phosphorus pentachloride,[8] addition of hydrogen chloride to 1-chlorocyclohexene in the presence of stannic chloride,[9] the action of phosphorus pentachloride on cyclohexene,[5] and also the reaction of chlorine with cyclohexene sulfide in carbon tetrachloride.[10] It was concluded by Mousseron[8] that the compound he obtained probably had the *trans* configuration, an assumption which is in accord with the observation that the addition of halogen to olefins is predominantly *trans*.[11,12] This is further borne out by the work of Winstein[13] on the structure of 1,2-dibromocyclohexane.

In order to get a very pure sample of the *trans*-1,2-dichlorocyclohexane for determination of properties, cyclohexene was treated with approximately one-half the theoretical amount of chlorine; the crude dichloride thus obtained was fractionated several times until successive fractions showed no change in boiling point and refractive index.

The only reference to a preparation of *cis*-1,2-dichlorocyclohexane is that of Komatsu and Kowamoto[14] who chlorinated cyclohexene in the presence of cuprous chloride. In the present work the pure *cis*-1,2-dichlorocyclohexane was prepared in the following manner: hypochlorous acid was added to cyclohexene to give *trans*-2-chlorocyclohexanol and this in turn reacted with thionyl chloride in the presence of pyridine. The latter reagents were selected because they have been found in the case of another chlorohydrin to give replacement of hydroxyl by chlorine with inversion.[15] The compound thus obtained analyzed correctly for a dichloride of cyclohexane and was found to boil at 206.9°, so that it is obviously not 1,1- or *trans*-1,2-dichlorocyclohexane. Furthermore this dichloride gave 1-chlorocyclohexene on boiling with quinoline whereas the dichloride boiling at 189°, presumed to

TABLE I

PHYSICAL PROPERTIES[a]

Isomer	F.p., °C.	B.p., °C.	B.p., Mm.	n^t_D	*t*, °C.	d^t_4	*t*, °C.
1,1-	−47 ± 0.5	62.0	20	1.4803	20	1.1559	20
		83.8	50	1.4780	25	1.1515	25
		101.0	100				
		171.0	758				
Trans-1,2-[b]	−6.3[c]	71.1	15	1.4902	20	1.1839	20
		78.1	20	1.4879	25	1.1787	25
		99.0	50				
		118.4	100				
		189.0	760				
Cis-1,2-[d]	−1.5[e]	91.0	20	1.4967	20	1.2021	20
		100.7	30	1.4945	25	1.1986	25
		114.4	50				
		134.2	100				
		206.9	763				

[a] All temperatures corrected. [b] Mousseron and Jacquier (ref. 5) give b.p. 71° (15 mm.), d^{20}_{20} 1.182, n^{20}_D 1.4902; Kharasch and Brown (ref. 7) give b.p. 79–80° (22 mm.), n^{20}_D 1.4903. [c] Freezing range 0.3°. [d] Komatsu and Kowamoto (ref. 14) give b.p. 92–94° (30 mm.), n^{25}_D 1.4902, d^{25}_4 1.1186. [e] Freezing range 0.6°.

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(1) Part of the work described herein was included in a thesis submitted by Ben Carroll to the University of South Carolina in partial fulfillment of the requirements for the degree of Master of Science.

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(8) M. Mousseron, R. Granger and J. Valette, *Bull. soc. chim.*, 244 (1946).

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be the *trans*, did not. This is the expected result if the above structure assignments are correct and if dehydrohalogenation is a *trans*-elimination, as is usually the case.[16] Since the physical properties reported by Komatsu and Kowamoto,[14] differ greatly from those of the above compound, some doubt is cast on the identity of their material.

Experimental

1,1-Dichlorocyclohexane.—Twenty moles (4,165 g.) of phosphorus pentachloride was placed in a 5-liter three-neck flask equipped with a dropping funnel, reflux condenser, mechanical stirrer and thermometer. Ten moles (1,030 ml.) of cyclohexanone was added dropwise at a rate of one to two drops per second. After about one-half the ketone was added the mixture became slushy and was stirred during the remainder of the addition, the temperature being kept below 65° throughout the process. The reaction mixture was then steam distilled by dropping it into boiling water contained in a three-neck flask properly equipped. The organic layer was separated, dried and fractionated to give first 536 g. (4.6 moles, 46% of theoretical) of 1-chlorocyclohexene, boiling range 141–143° and then 321 g. (2.1 moles, 21% of theoretical) of 1,1-dichlorocyclohexane, boiling range 169–173° which was purified by further fractionation.

Anal. Calcd. for $C_6H_{10}Cl_2$: Cl, 46.33; molecular refraction, 37.44. Found: Cl, 46.16; molecular refraction, 37.63.

The structure of this dichloride was proven by conversion to cyclohexanone. Ten grams of 1,1-dichlorocyclohexane, prepared as above, was stirred with 100 ml. of concd. sulfuric acid at 40° for one hour, at which time hydrogen chloride evolution had ceased and only one phase was present. The solution was poured onto ice and extracted several times with ether. Evaporation of the ether left about five grams of impure cyclohexanone which provided a 2,4-dinitrophenylhydrazone melting at 161–162° (literature,[17] 162°) after recrystallization.

***d,l-trans*-1,2-Dichlorocyclohexane.**—Three moles (294 g.) of cyclohexene was chlorinated at 30–40° in the absence of light by passing in chlorine gas with stirring until the gain in weight was 106 g. (50% of theoretical). The crude product was distilled, the dichloride being collected at 186–190°. Repeated fractionation gave a series of fractions having identical boiling points and indices.

Anal. Calcd. for $C_6H_{10}Cl_2$: Cl, 46.33; molecular refraction, 37.44. Found: Cl, 46.44; molecular refraction, 37.39.

***cis*-1,2-Dichlorocyclohexane.**—*d,l-trans*-2-Chlorocyclohexanol was prepared by the method of Newman and VanderWerf.[18] The chlorohydrin (134 g., 1.4 moles, b.p. 84–85° (18 mm.), m.p. 29°, $n^{25}\mathrm{D}$ 1.4832) was mixed with 233 g. (2.95 moles) of freshly distilled pyridine in a one-liter dropping funnel. This mixture was dropped slowly onto 338 g. (2.8 moles) of thionyl chloride (commercial grade) contained in a three-neck three-liter flask, fitted with a stirrer, thermometer and condenser, and maintained at 70–80° with a water-bath. Stirring and heating was continued for two hours after the addition was complete. Excess thionyl chloride was destroyed by dropwise addition of 500 ml. of ice-water and the organic layer separated and washed with 50-ml. portions of sodium carbonate solution. The product was then steam distilled, dried over calcium chloride and fractionated at reduced pressure. The yield of dichloride boiling at 114.4–114.5° (cor., 50 mm.) was 55 g. or 26%.

Anal. Calcd. for $C_6H_{10}Cl_2$: Cl, 46.33; molecular refraction, 37.44. Found: Cl, 46.49; molecular refraction, 37.24.

The above dichloride was dehydrochlorinated by refluxing 20 g. (0.13 mole) with 45 g. (0.35 mole) of freshly distilled quinoline. After the temperature of the vapor dropped to 155°, the mixture was distilled and material boiling up to 210° collected. Two distillations gave 4.0 g. of 1-chlorocyclohexene, b.p. 141–142°, $n^{25}\mathrm{D}$ 1.4780 (literature[5] b.p. 141–142°, $n^{25}\mathrm{D}$ 1.4772). A sample of *trans*-1,2-dichlorocyclohexane treated in a similar fashion produced no 1-chlorocyclohexene.

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[17] R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," 3rd. ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 262.

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Vitamin Activity of Lyxoflavin

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Synthetic lyxoflavin has been found to be devoid of riboflavin activity when tested in conventional assays using rats and *L. casei*. A rat assay for unidentified vitamins has been devised in which the diet contains the known vitamins including vitamins B_2 and B_{12}. The protein is supplied by soybean meal, and thyroid powder is added to enhance development of a deficiency state. The addition of liver and fish-meal components stimulated growth indicating the presence of new unidentified vitamins. Lyxoflavin has shown growth-promoting or vitamin activity in this rat assay.

Data from tests with synthetic lyxoflavin for vitamin activity have been described, and it was concluded that lyxoflavin showed growth-promoting or vitamin-like activity.[1] We now wish to describe further information and details about this investigation of lyxoflavin, and to give additional data from later vitamin tests.

In 1947, L-lyxose was reported[2] as being isolated from human myocardium by steps including hydrolysis with cobra venom. The manner in which the lyxose is combined with other chemical groups was not apparent to these investigators, and the object of a later paper by Sodi and Garza[3] was to describe the isolation of L-lyxoflavin from human myocardium, and its synthesis. Sodi and Garza concluded that lyxoflavin is the form in which lyxose is found in the human myocardium. A 5-mg. specimen of the flavin was recorded as the result of fractionation of 10 kg. of human heart muscle. This flavin and its tetraacetate were compared in composition and melting point behavior with synthetic L-lyxoflavin and its tetraacetate, and it was concluded that these properties are identical. Although this comparison of natural and synthetic materials is meager for the identification of flavins, the veracity of the conclusion is the significant point. It seems likely that additional evidence for or against the occurrence of lyxoflavin in nature will be forthcoming and, until then, a favorable interpretation seems to be propitious.

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