THE PREPARATION OF CERTAIN DERIVATIVES OF CYCLOHEXANE.

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Many methods for the preparation of cyclohexane derivatives have previously been employed.[1] The method described herewith for the preparation of cyclohexane and cyclohexanol, embodying Ipatiew's principle of high pressure, offers a simple procedure for the manufacture of these materials on a large laboratory scale with easily accessible materials.

The substance to be reduced, together with a metal oxide catalyst, is placed in a suitably constructed bomb which can be filled at intervals with hydrogen under pressure of 115 to 120 atmospheres, and the whole subjected to a temperature of approximately 250° until reduction is complete. The higher temperature and pressure tend to counteract the decreased activity of a partially poisoned catalyst. The process requires very little attention other than periodic filling and emptying of the bomb. The reaction proceeds to completion with a catalyst much less reactive than that necessary to obtain any reduction by the Sabatier method. The high pressure needed is obtained by use of commercial hydrogen sold in tanks at a pressure of 1800 pounds per square inch. Without materially slowing up the reaction the hydrogen tanks may be used without replacement until the pressure is decreased to approximately 1000 pounds.

During the past year in connection with work on the production of hydroheterocyclic compounds it was necessary to prepare considerable quantities of cyclohexane, cyclohexanol, and some of their derivatives. These are not procurable on the market, although the first two mentioned have been articles of commerce.

In seeking a method which could be standardized for the preparation of cyclohexane and cyclohexanol, we have used that of Ipatiew, for reasons given above. By this process about 30 kg. of hexahydrophenol have been prepared, the method being found very satisfactory. Nothing new is offered in the preparation of these compounds, but as they are the necessary starting materials for the production of a series of new substances, the procedure found most satisfactory for the preparation of cyclohexane, cyclohexanol, cyclohexylamine, cyclohexene and the more simple, well-

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[1] Aschan, *Ber.*, **24**, 1864, 2617 (1891); Einhorn and Meyenberg, *ibid.*, **27**, 2466, 2829 (1894); Baeyer, *ibid.*, **19**, 1797 (1886); **26**, 229 (1893); *Ann.*, **278**, 88 (1894); Paal and Amberger, *Ber.*, **38**, 1406 (1905); **40**, 2201 (1907); Paal and Gerum, *ibid.*, **40**, 2209 (1907); **42**, 1553 (1909); Paal and Roth, *ibid.*, **42**, 1541 (1909); Sabatier and Mailhe, *Ann. chim. Phys.*, **10** (s. 8), 527 (1907); *ibid.*, **16** (s. 8), 70 (1909); Sabatier and Murat, *Compt. rend.*, **154**, 928 (1912); Sabatier and Senderens, *ibid.*, **133**, 321 (1901); *Ann. chim. phys.*, [8] **4**, 319 (1905); Skita, *Ber.*, **48**, 1486, 1685 (1915); Senderens, *Compt. rend.*, **154**, 1168 (1912); Ipatiew, *Ber.*, **37**, 2961, 2986 (1904); **40**, 1270, 1281 (1907); **41**, 991, 993 (1908); Ipatiew, Jakowlen and Rakitin, *ibid.*, **41**, 996 (1908).

known members of this series will be outlined, since even after a careful perusal of the literature one is in doubt as to which method to follow.

A study of *o*-disubstituted derivatives of cyclohexane offers many opportunities in determining the effects of one group on the activity of the other, since these compounds lie intermediate to aliphatic and aromatic substances. Studies of *o*-disubstituted derivatives of the cyclohexane series are relatively few and these are confined mainly to compounds in which the groups are similar, such as the dibromo and dichloro prepared from cyclohexene. A few compounds in which the *ortho* groups are dissimilar have brief mention in the literature, for example, *o*-iodochloro-cyclohexane,[1] *o*-iodo-cyclohexanol,[2] *o*-iodobromo-cyclohexane and *o*-cyano-iodo-cyclohexane.[3] In addition the preparation of *o*-amino-cyclohexanol, *o*-chloro-cyclohexylamine and *o*-bromo-cyclohexylamine, together with some of their derivatives, will be described.

Experimental.

Preparation of Catalyst.—Metallic nickel was used almost exclusively. Pure nickel nitrate is calcined at a dull red heat for an hour, cooled, and very finely ground. It may be heated again to a red heat to insure complete decomposition of the nitrate. The powdered nickel oxide is then reduced in a stream of hydrogen at 250° for several hours. It is allowed to cool overnight in an atmosphere of hydrogen and is placed in a tightly stoppered flask until used. This catalyst used in the proportion of one part catalyst to 10 of substance remains in an active state for 5 or 6 reductions. If the reduction is proceeding too slowly it is best to replace the old by fresh unused nickel.

Cyclohexane.—Three hundred g. of purified benzene free from thiophene by the isatin test and 30 g. of nickel catalyst are placed in the bomb and shaken well to obtain a good distribution of the nickel. The bomb is placed in an electrically heated hot air oven at 250° and filled with hydrogen at 1800 pounds pressure; at intervals of 2 hours during the day more hydrogen is introduced to replace that which has reacted. At night the bomb is not refilled but is allowed to remain in the oven. At the end of 48 hours the reaction is complete. The bomb is then removed, cooled, and the contents poured into a distilling flask and distilled. The fraction boiling between 80° and 85° is collected and is sufficiently pure for synthetic work. The nickel remaining in the flask is washed back into the bomb with the next run and used again. Yield of cyclohexane, 275 g. or 85% of the theoretical amount.

Cyclohexanol.—Three hundred g. of redistilled U. S. P. phenol is melted and poured into the bomb with 30 g. of nickel. The reduction is

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[1] Brunel, *Zentralbl.*, **1903**, pp. 233, 711.

[2] Brunel, *Compt. rend.*, **135**, 1055–1057 (1902).

[3] Brunel, *Zentralbl.*, **1905**, ii, 1337–1339.

carried out precisely as given for benzene. When completed the reaction product is fractionated, the fraction boiling at 158° at 730 mm. being practically pure cyclohexanol. A small amount of cyclohexane and water is formed and is collected in the lower fraction, boiling between 80° and 110°. If the reduction has not proceeded to completion a fraction boiling above 158° is obtained. This may be returned to the bomb with the next run and the reduction is completed. The nickel is also returned. Yield, 255 g. or 80%.

Cyclohexanone.—Baeyer[1] prepared this substance by the oxidation of cyclohexanol with Beckman's chromic acid mixture and proved its identity with the ketohexamethylene obtained by Perkin, Jr., from calcium pimelate.[2] Baeyer used a proportion of 2 g. of cyclohexanol to 27 g. of the chromic acid mixture. The method used by us is essentially the same, modified slightly to keep the volumes down when dealing with 100-g. portions.

One hundred g. of cyclohexanol and 150 cc. of water are placed in a one-liter flask and cooled in ice water. To this is added gradually 35 cc. of conc. sulfuric acid. One hundred g. of sodium dichromate ($Na_2Cr_2O_7$-$2H_2O$) is dissolved in a solution of 35 cc. of conc. sulfuric acid in 150 cc. of water. The chromic acid solution is added to the cyclohexanol mixture in 10 cc. portions over a period of 2 hours, and the solution is shaken well after each addition. To complete the reaction the mixture is heated in a water-bath for 2 hours, cooled, and ether extracted, the extract dried with potassium carbonate and the ether distilled off. The cyclohexanone boils constantly at 155°. Yield, 83 g. or 85%.

o-**Chloro-cyclohexanone.**—This may be prepared by a method similar to that used by Kotz[3] for the corresponding bromine compound. Chlorine is bubbled through a mixture of 20 g. of cyclohexanone, 15 g. of calcium carbonate, and 50 cc. of water in a flask immersed in cold water, until the reaction is complete. The oil is extracted with ether, dried, and the ether removed. The oil does not distil *in vacuo* without decomposition and is difficult to obtain pure and free from chlorine.

Attempts to form an aminoketone invariably led to condensation products, and secondary and tertiary amines.

Cyclohexanone Oxime.—Baeyer[4] obtained the oxime in theoretical yield, by allowing the ketone to react with hydroxylamine hydrochloride and excess sodium hydrogen carbonate in alcohol at water-bath temperature, extracting the residue with ether and recrystallizing the residue from petroleum ether. It may also be obtained with equal facility and in theoretical yield in water solution by the following method.

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[1] A. Baeyer, *Ann.*, **278**, 88–116 (1894).

[2] W. N. Perkin, Jr., *Ber.*, **18**, 3245–3252 (1885).

[3] Kotz, *Ann.*, **358**, 194–208 (1907).

[4] Baeyer, *ibid.*, **278**, 88–116 (1894).

Eight and four-tenths g. of hydroxylamine sulfate in 60 cc. of water is added in small portions to a mixture of 10 g. of cyclohexanone and 50 cc. of water containing 4.1 g. of sodium hydroxide or excess of bicarbonate. The reaction flask should be continually shaken and cooled under tap water. When nearly all the hydroxylamine has been added the oxime separates as a crystalline solid and is filtered immediately, washed with water, and dried. If the reaction mixture is not cooled a red color is developed and the yield decreased. The dried product recrystallized from boiling ligroin melts at 88°.

Cyclohexylamine.—Many attempts to prepare cyclohexylamine by direct catalytic reduction of aniline have at the best resulted in very poor yields. By Paal's method a yield of 10% has been obtained in 80 hours.[1] The use of Sabatier's and Senderens' method results in destruction and numerous side reactions. Ipatiew[2] reports a yield by his method of from 40 to 50%, with nickel oxide as a catalyst and a pressure of 115 to 120 atmospheres. We have attempted to use Ipatiew's method with a nickel catalyst, but it has invariably resulted in such great destruction and production of side reactions as to cause its abandonment.

Cyclohexylamine may be obtained in good yield by reduction of ketohexamethylene oxime by either the method of Sabatier and Senderens[3] or that of Baeyer.[4]

In Baeyer's method 5 g. of the oxime is dissolved in 200 cc. of absolute alcohol and added to 25 g. of sodium. It is best to dissolve all the oxime in a small amount of alcohol, and add the solution to the sodium. Additional alcohol is then poured through the reflux condenser. In this way all the oxime is present during the entire reaction.

Ten g. of cyclohexanone oxime in 30 cc. of absolute alcohol is added through a reflux condenser to 50 g. of sodium strips, followed by an additional 400 cc. of absolute alcohol. When the reaction is complete the alcohol is distilled from a water-bath, water is added, and the solution made acid with hydrochloric acid. The acid solution is evaporated to dryness on a water-bath with the help of an air blast. A small amount of water is added (20 cc.), and an excess of solid potassium hydroxide. The oil which separates is extracted with ether, dried, and distilled, after removal of the ether; b. p., 133°. It distills with some decomposition and takes up carbon dioxide very rapidly, and consequently is best distilled in a stream of hydrogen as Baeyer recommends. However, this is not necessary if the receiver is protected with a soda-lime tube. The melting point of the carbonate is 110°, the hydrobromide 195°, the hydrochloride 204°, the acetate 147°, and the acetyl derivative 99°.

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[1] Willstätter and Hatt, **45**, 1471–1481 (1912).

[2] Ipatiew, *Ber.*, **41**, 991–3 (1908).

[3] Amouroux, *Chem.-Ztg.*, **35**, 192 (1911).

[4] Baeyer, *Ann.*, **278**, 88–116 (1894).

Cyclohexene.—Many methods have been proposed for the production of cyclohexene from cyclohexanol, using various dehydrating agents. It is also frequently made by treating monohalide cyclohexanes with alkalies, such as calcium oxide[1] and quinoline. Among the dehydrating agents may be mentioned particularly oxalic acid,[2] iodine,[3] sulfuric acid,[4] dimethyl sulfate,[5] and potassium hydrogen sulfate.[6]

Zelinsky, using one part of cyclohexanol to 5 parts of anhydrous oxalic acid at 100° to 110°, obtained cyclohexene. In using this method it has been found that this proportion may be considerably increased and good yields obtained. The process may be made continuous by addition of cyclohexanol as the tetrahydrobenzene and water distil over, and with occasional addition of anhydrous oxalic acid to replace that which is destroyed or distils over as the ester of cyclohexanol.

The objection to using dimethyl sulfate is of course obvious; calcium oxide requires a temperature of 350° and special apparatus, and potassium hydrogen sulfate gives poor yields due to formation of cyclohexyl ether. The catalytic sulfuric acid method described by Senderens is easy of application and gives practically a 90% yield. The procedure followed is precisely that of Senderens.

One hundred g. of cyclohexanol and 2 cc. of conc. sulfuric acid are slowly distilled until white fumes are evolved and the odor of sulfur dioxide is apparent. The water and cyclohexene in the distillate are separated, the cyclohexene dried with potassium carbonate and redistilled. Sixty g. of pure cyclohexene, boiling 82° to 84°, is obtained, and 16 g. of a higher boiling fraction, consisting of a mixture of unacted-on cyclohexanol and cyclohexene. Yield of pure cyclohexene, 73%. This may be increased to approximately 90% by retreating the higher fraction with the next run.

In searching for other agents which would serve to dehydrate cyclohexanol to cyclohexene, phosphorus trichloride has been found to be fairly efficient. Its disadvantage lies in the amount of phosphorus trichloride necessary to be used and in the mechanical losses of cyclohexene which occur. About one kg. of cyclohexene has been prepared by the following method.

Two hundred and seventy-four g. of phosphorus trichloride is added slowly through a dropping funnel to 300 g. of cyclohexanol in a one-liter flask fitted with a reflux condenser. The temperature is maintained at

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[1] Schmidt, Hochschwender and Eichler, U. S. Patent 1,221,382. *C. A.* **11**, 1885 (1917).

[2] Zelinsky and Zelikow, *Ber.*, **34**, 3249–3256 (1901).

[3] Hibbert, Brit. Pat. 5,408; *C. A.* **9**, 2291 (1915); THIS JOURNAL, **38**, 1748 (1915).

[4] Senderens *Compt. rend.*, **154**, 1168–1170 (1912).

[5] Chavonne and van Roelen, *Bull. soc. belge. chim.*, **22**, 410–413 (1908).

[6] Brunel, *Bull. soc. chim.*, [3] **33**, 270–271 (1905).

70° by immersion in a water-bath. Addition of the first mole (137 g.) of phosphorus trichloride produces a vigorous reaction, but the second may be added more rapidly. When all the phosphorus trichloride has been added the product is refluxed for 4 hours and then distilled from the phosphorus oxide. One hundred and fifty cc. of water is added to the distillate through a reflux condenser and the mixture is refluxed for a short time to decompose all excess phosphorus trichloride. The cyclohexene is separated from the aqueous layer, dried, and distilled. Yield of cyclohexene, 65% of the theoretical amount, or 160 g. of tetrahydrobenzene boiling between 82° and 87°, and 30 g. of a fraction boiling between 87° and 160°.

It is necessary to have the cyclohexanol warm when the trichloride is added as otherwise considerable chloro-cyclohexane is formed, which is not broken down by subsequent treatment and may be obtained in the final distillation as the fraction boiling at 143°.

***o*-Chloro-cyclohexanol.**—This substance, described by Fortey,[1] was made by shaking tetrahydrobenzene with a dilute hypochlorous acid solution, the hypochlorous acid being made by passing chlorine into water containing freshly precipitated mercuric oxide. Fortey described it as a yellowish oil distilling with decomposition and having a characteristic odor. Prepared by the following method it is a water-white oil possessing a characteristic odor, distilling in atmospheric pressure with only slight decomposition.

One hundred cc. of cyclohexene (about 3 times the calculated quantity) is shaken with 1700 to 1800 cc. of a 2% hypochlorous acid solution; the acid is added in 200 cc. portions and the mixture shaken until it is decolorized before the addition of more. When all hypochlorous acid has been added the mixture is shaken until one cc. gives only a faint or no yellow color with potassium iodide solution. The hypochlorous acid has always been made by bubbling carbon dioxide through a suspension of bleaching powder in water and filtering off the calcium carbonate. The reaction product is saturated with salt and steam distilled. The distillate is saturated with salt, and the upper layer of cyclohexene and *o*-chloro-cyclohexanol removed and fractionated. The first fraction boiling below 90° at 20 mm. is a mixture of water, unacted-on cyclohexene and some *o*-chloro-cyclohexanol, which may be used again. The *o*-chloro-cyclohexanol boils, at 92° under pressure of 10 mm. Yield, 85 g.

Subs., 0.1236: AgCl, 0.1298.
Calc. for $C_6H_{11}OCl$: Cl, 26.35. Found: 25.99.

***o*-Amino-cyclohexanol.**—No mention of *o*-amino-cyclohexanol can be found in the literature although it is easily prepared from *o*-chloro-cyclohexanol and alcoholic ammonia, the chlorine being substituted by the

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[1] Fortey, *J. Chem. Soc.*, **23**, 948 (1898).

amino group. In aqueous solutions secondary and tertiary amines are the chief products, but if sufficient strength of alcohol is used to maintain a clear solution the primary amine is the chief product.

For the preparation of the free amine the following has been found to be the best procedure. 26.8 g. ($^1/_5$ mole) of *o*-chloro-cyclohexanol is placed in a pressure bottle (the ordinary citrate of magnesia bottle fitted with a rubber stopper which can be clamped down is satisfactory) and 100 cc. of a strong solution of ammonia in 50% alcohol is added. If the solution is not clear, a higher per cent. of alcohol is used. The bottle is shaken well and is then heated in a steam-bath for one hour. The contents of 5 such bottles after cooling are poured into a one-liter distilling flask, 60 g. of anhydrous sodium carbonate is added and the alcohol and water distilled off; the temperature should be allowed to rise to 110° and maintained there until the greater portion of water is removed. Two hundred cc. of alcohol is added. The salts are removed by filtering the hot solution with suction, washing the precipitate well with alcohol. The alcohol is removed by distillation and the residue fractionated *in vacuo*, using the side neck of the flask as a condenser and immersing the receiver flask in ice water.

The fraction distilling up to 120° at 7 mm. pressure is redistilled at atmospheric pressure. The pure *o*-amino-cyclohexanol boils at 104° at 7 mm. pressure and at 212° at atmospheric pressure. It crystallizes in the receiver in rosets which melt at 65°. Yield, 70 g.

Subs., 0.0100: Amino nitrogen, 2.19 cc. (21° and 734 mm.).
Calc. for $C_6H_{13}ON$: N, 12.17. Found: 12.00.

Melting point of salts made from the corresponding acid and an ether solution of the amine: hydrochloride, 175°; hydro-iodide, 187°; hydrobromide, 191°; carbonate, 139°; sulfate not melted at 250°.

***o*-Chloro-cyclohexylamine.**—In attempting to prepare an *ortho* halogen cyclohexylamine, *o*-amino-cyclohexanol was treated with fuming hydriodic acid in a sealed tube at temperatures from 100° to 150°. It was found that the iodine did not replace the hydroxy group at a temperature below 130°, while at a higher temperature there was a deep-seated decomposition, with the separation of ammonium iodide. Hydrobromic acid also failed to substitute. Thionyl chloride does not replace the hydroxy group even when refluxed at the boiling point. Phosphorus trichloride does not substitute the hydroxy group with chlorine, producing instead an ester of a phosphorus acid. The great resistance of the hydroxy group suggested the necessity of using phosphorus pentachloride. When this was tried in chloroform a very poor yield of *o*-chloro-cyclohexylamine was obtained. Further investigations showed that phosphorus oxychloride readily reacts with *o*-amino-cyclohexanol in chloroform even at a temperature of 0°, apparently forming the phosphoric acid ester. If, however, the hydrochloride of *o*-amino-cyclohexanol is suspended in chloroform the reaction with phosphorus oxychloride is practically suppressed. Phosphorus pentachloride, even at 0°, reacts vigorously with the hydrochloride of *o*-amino-cyclohexanol.

The reaction product dissolved in water after the treatment with phosphorus pentachloride in chloroform is made alkaline with sodium hydroxide, extracted with ether, the ether removed, and the residue consisting of *o*-chloro-cyclohexylamine distilled *in vacuo.* Boiling point 85°, at 15 mm. pressure.

Fifty-seven and one-half g. ($^1/_2$ mole) of *o*-amino-cyclohexanol is dissolved in 300 cc. of anhydrous and alcohol-free chloroform. The chloroform solution is placed in a one-liter Erlenmeyer flask, with side neck, and fitted with a one-hole rubber stopper. A few milligrams of methyl orange is added and dry hydrogen chloride led in through a glass tube until the reaction is distinctly acid, indicating complete formation of the hydrochloride. The flask is cooled in ice-water. One hundred and fifty g. of phosphorus pentachloride, ground in a dry mortar to a fine powder, and about 300 cc. of purified chloroform are placed in a one-quart Mason fruit jar, which is packed in an ice- and salt-mixture. To this suspension, which is stirred mechanically and maintained below 0°, is added the mixture of *o*-amino-cyclohexanol hydrochloride and chloroform. This will require approximately one hour. The solution may then be filtered. The hydrochloride of the *o*-chloro-cyclohexylamine is quite soluble in chloroform, but a considerable portion will separate at 0°. The chloroform solution is placed in a one-liter distilling flask. One hundred cc. of water is added and the flask placed under a reflux condenser. Occasional shaking will start the reaction, decomposing the phosphorus oxychloride. After the vigorous reaction has subsided it is refluxed in a water-bath for not less than 90 minutes in order to decompose the last traces of phosphorus oxychloride. The chloroform is then distilled and the residue placed in a tall jar. The volume of the residue should be between 100 and 200 cc. This is packed in ice and salt, and a saturated solution of sodium hydroxide in water is added. The solution is stirred with a mechanical stirrer until it becomes very thick. Ether is then added and sufficient sodium hydroxide to make the solution distinctly alkaline. Solid sodium hydroxide is now added, and about 500 to 600 cc. of ether. The salt separates in solid, dry form and is readily extracted with ether. Three extractions are generally sufficient. The ether is dried over solid sodium hydroxide, removed by distillation, and the *o*-chloro-cyclohexylamine distilled *in vacuo.* The yield depends on the extent to which water is excluded and may reach 70 to 80%. If water is not completely excluded the yield may drop as low as 50%. The *o*-chloro-cyclohexylamine is a colorless oil of characteristic odor, which does not solidify at —10°.

Subs., 0.1412: AgCl, 0.1510.
Calc. for $C_6H_{12}NCl$: Cl, 26.55. Found: 26.45.

Hydro-anilides from *o*-amino-cyclohexanol and *o*-chloro-cyclohexylamine may be quantitatively prepared by the usual methods in an indifferent solvent, such as chloroform. As examples, the preparation of the acetyl and chloro-acetyl derivatives is given.

Acetyl-*o*-chloro-cyclohexylamine, $\underline{CH_2CH_2CH_2CH_2CHClCH}.NHCO.CH_3$.—To 13.4 g. of *o*-chloro-cyclohexylamine dissolved in 50 cc. of anhydrous chloroform and immersed in ice-water is added a solution of 12 g. (1.5 times of the theoretical amount) of acetyl chloride in chloroform. When all is added the solution is refluxed for about 2 hours. A small amount of alcohol is added to decompose the excess acetyl chloride, and the chloroform distilled off on a water-bath. The residue may be recrystallized by dissolving it in 90% alcohol and diluting this solution with water; m. p. 88°.

Chloro-acetyl-*o*-chloro-cyclohexylamine, $\underline{CH_2CH_2CH_2CH_2CHClCH}.NH.CO.CH_2Cl$.—This is prepared by a procedure identical with that given for the acetyl, using 1.5 times the calculated amount of chloroacetyl chloride. It is recrystallized from the alcohol by the addition of water. It is soluble in hot water, one part in 220; in cold water, one part in 2,000. The chloro-acetyl-*o*-chloro-cyclohexylamine melts at 111°.

Subs., 0.0882: AgCl, 0.1192.
Calc. for $C_2H_{13}ONCl_2$: Cl, 33.76. Found: 33.43.

Cyano-acetyl-*o*-chloro-cyclohexylamine, $\underline{CH_2CH_2CH_2CH_2CHClCH}.NH.CO.CH_2CN$.—The chloro-acetyl-*o*-chloro-cyclohexylamine may be treated with large excesses of sodium cyanide in water at the boiling point for a short time with substitution taking place only on the side chain. The yield, however, is not particularly good, since boiling with alkalies decomposes the nitrile present to some extent.

A mixture of 4 g. of chloro-acetyl-*o*-chloro-cyclohexylamine and 4 g. sodium cyanide in 400 cc. of water is boiled for 10 minutes. The solution is then quickly made acid to methyl orange by addition of about 15 cc. of conc. hydrochloric acid diluted 1 : 1. The cyano-acetyl-*o*-chloro-cyclohexylamine crystallized on cooling. Yield, 2.3 g. It may be purified by recrystallizing from hot water; m. p. 139°.

Subs., 0.1357: AgCl, 0.0965.
Calc. for $C_9H_{13}ON_2Cl$: Cl, 17.59. Found: 17.59.

o-Chloro-hexahydro Anilide of Malonic Acid, $\underline{CH_2CH_2CH_2CH_2CHClC}$-

$CH.NH.CO.CH_2COOH$.—This may be obtained by converting the corresponding cyano compound first to the ester, and then hydrolyzing the ester to the sodium salt with an aqueous solution of sodium hydroxide.

Four g. of the cyano-acetyl-*o*-chloro-cyclohexylamine is dissolved in 75 cc. of alcohol, which is then saturated with dry hydrogen chloride. It is refluxed for one hour while passing a stream of dry hydrogen chloride through the solution. The solution is concentrated to $^1/_2$ the original volume, the ammonium chloride removed by filtering, and the remainder of the alcohol distilled off *in vacuo*. The residue is taken up in water, 5 cc. of 30% sodium hydroxide added, and the product shaken until the saponification is complete. The alkaline solution is then acidified with hydrochloric acid and allowed to stand. The free acid crystallizes slowly; m. p., 132°.

Subs., 0.1598: AgCl, 0.1046.
Calc. for $C_9H_{14}O_3NCl$: Cl, 16.14. Found: 16.17.

o-Bromo-cyclohexylamine, $\underbracket{CH_2CH_2CH_2CH_2CHBrCH}.NH_2$.—This may be obtained in a manner similar to that given for the *o*-chloro-cyclohexylamine. It is not necessary, however, to maintain as low a temperature during the reaction.

Fifty-seven and one-half g. of *o*-amino-cyclohexanol is precipitated as the hydrochloride salt in anhydrous chloroform, as described for the preparation of the corresponding chlorine derivative. This suspension is added to a suspension of phosphorus pentabromide in anhydrous chloroform. The phosphorus pentabromide is prepared by adding 70 cc. of dry bromine to 17 g. of yellow phosphorus in 150 cc. of chloroform, cooling the jar in ice-water, and stirring mechanically. During the addition of the *o*-amino-cyclohexanol hydrochloride it is not necessary to cool the reaction mixture as the temperature does not rise above 35° or 40°. When the mixture becomes clear the chloroform is removed by distillation on a water-bath. About 300 cc. of toluene is then added and the solution cooled. The crystals which separate are filtered off, washed well with toluene, and dried.

Purification is effected by dissolving the crystals in a small amount of water, making this solution strongly alkaline with a 30% solution of sodium hydroxide, and extracting this product a few times with toluene. The toluene is dried for not more than one hour over stick sodium hydroxide and the amine is then precipitated as the hydrochloride salt with hydrogen chloride, in the form of needles, melting at 168°. Yield, 75 g. or 70%.

Subs., 0.0732: AgHal., 0.1142.
Calc. for $C_6H_{12}NBrCl$: Halogen, 54.04. Found: 53.89.

Acetyl-*o*-bromo-cyclohexylamine, $\underbracket{CH_2CH_2CH_2CH_2CHBrCH}.NH.CO$-

CH_3.—To 21.4 g. of *o*-bromo-cyclohexylamine hydrochloride in toluene is added 10 cc. of acetyl chloride and the mixture is refluxed for several hours. When the reaction is completed the toluene is removed *in vacuo*. The solid residue is dissolved in a small amount of warm alcohol and ice-water added. An oil separates, which crystallizes in a short while. M. p. of the acetyl derivative, 103–104°. Yield, 13.5 g. or 61%.

Subs., 0.1516: AgBr, 0.1312.
Calc. for $C_8H_{14}ONBr$: Br, 36.32. Found: 36.81.

Attempts to prepare *o*-iodo-cyclohexylamine in a manner analogous to the preparation of the chlorine and bromine compounds, using phosphorus tri-iodide in chloroform, were unsuccessful. Invariably the main products were esters of *o*-amino-cyclohexanol.

Substitution of bromine for iodine in *o*-bromo-cyclohexylamine, using potassium iodide in aqueous or alcoholic solution, has given 50% substitution, but the product is too impure for definite identification.

Summary.

Methods for obtaining cyclohexane derivatives by direct reduction of the corresponding benzene compounds have been reviewed. The method of Ipatiew for the reduction of benzene and phenol has been particularly applied.

Methods, with some modifications which are most applicable for the laboratory production of cyclohexane, cyclohexanol, cyclohexanone and its oxime, cyclohexylamine, and cyclohexene, are described.

Methods for obtaining the following *ortho* substituted cyclohexane compounds in which the *ortho* groups are dissimilar, chloro-cyclohexanone, chloro-cyclohexanol, amino-cyclohexanol, chloro-cyclohexylamine and bromo-cyclohexylamine, with certain of their derivatives, are given.

Work in this series is being continued.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF HAWAII.]

FRACTIONATION OF CHAULMOOGRA OIL.

BY ARTHUR L. DEAN AND RICHARD WRENSHALL.

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The material known commercially as chaulmoogra oil has assumed considerable importance in recent years. For many years, perhaps for centuries, this oil has been used in India as a palliative in leprosy. In more recent times it has had more or less use in all countries where leprosy occurs. Taken by way of the mouth its administration is frequently attended by amelioration of the disease, although the intolerance exhibited by many persons limits its usefulness, and at best the action is slow.

New interest was aroused by the results obtained by intramuscular