[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND PURDUE RESEARCH FOUNDATION, PURDUE UNIVERSITY]

Synthesis of Chloroalkyldialkylamines[1]

BY H. B. HASS AND H. C. HUFFMAN

Some time ago the attention of one of the writers was called[2] to the importance of rendering readily available 4-chloroamyldiethylamine for the synthesis of Plasmochin, Atabrine, and related antimalarial drugs. Hope was also expressed that the easy synthesis of other similar chloroamines could be developed in order to facilitate systematic investigation in this general field. The importance of this problem to the national defense has been stressed by Howe[3] in view of the possible interruption of the supply of quinine.

Previous work in this Laboratory has demonstrated that all of the isomeric monochlorides and dichlorides, conceivable as being formed without change in carbon skeleton, are always produced in the chlorination of a paraffin or of an alkyl chloride. Thus, from 1-chloropentane, the chlorination of which has not previously been reported, the following yields of isomers were obtained: 1,1- and 1,2-dichloropentanes (not separated), 20%; 1,3-dichloropentane, 30%; 1,4-dichloropentane, 31%; 1,5-dichloropentane, 19%. Conant and Kirner[4] have shown that primary chlorides react much more rapidly than do secondary or tertiary chlorides when treated with potassium iodide dissolved in anhydrous acetone. We have found that this difference in reactivity between the primary and secondary halogen atoms extends also to the dichlorides. Yields of 75 to 90% are obtainable in the conversion to chloroiodides if the dichloride contains a primary and a secondary chlorine atom which are not located on adjacent carbon atoms. Upon amination at room temperature with diethylamine or related compounds the iodine atom reacts rapidly and the chlorine atom sluggishly. It has thus proved possible to obtain good yields on the amination and to isolate the crystalline hydrochlorides of these chloroamines. This was particularly gratifying in view of the reported failure of Clemo and Hook[5] by other reactions to obtain the hydrochloride of 4-chloropentyldiethylamine in crystalline form.

Experimental

Chlorination of 1-Chloropentane.—The chlorination apparatus (Fig. 1) is a modification of the one described by Muskat and Northrup.[6] Normal amyl chloride from the Sharples Solvents Corporation was rectified in an all glass column having fifty theoretical plates. The fraction boiling from 107.8 to 108.4° at 749.7 mm., $n^{25}D$ 1.4121, was taken for chlorination. The 1-liter still pot (1) of the apparatus shown in Fig. 1 was charged with 1-chloropentane and heated until good reflux was maintained in the 76 cm. long, 32 mm. i. d. helix-packed Pyrex column (3). The rate of return of the liquid from the illuminated 3-liter reaction vessel (6) to the still pot was held to around 6 moles/hour. Chlorine was sent into the reaction chamber through inlet tube (7) at the rate of 0.5 mole/hour. Thus the mole ratio of monochloride to chlorine in the reactor was around 12 to 1. This was desirable since a high ratio of monochloride to chlorine lowers the amount of polychlorides produced in the reaction. The progress of the chlorination was followed by noting the temperatures in the still flask and column head. The latter temperature was kept very near the boiling point of the 1-chloropentane

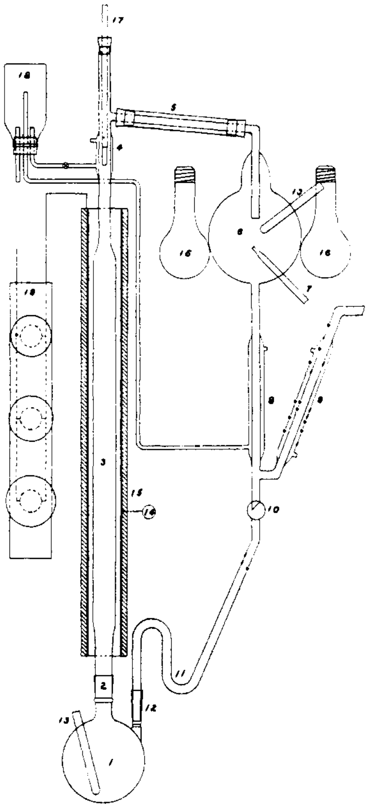

Fig. 1.—Chlorination apparatus.

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[1] Based upon a thesis submitted by H. C. Huffman to the faculty of Purdue University in partial fulfillment of requirements for the degree of Doctor of Philosophy, June, 1940.

[2] Private communication, Dr. Alfred Burger.

[3] Howe, *Ind. Eng. Chem.*, **32**, 886 (1940).

[4] Conant and Kirner, THIS JOURNAL, **46**, 232–252 (1924).

[5] Clemo and Hook, *J. Chem. Soc.*, 608–609 (1936).

[6] Muskat and Northrup, THIS JOURNAL, **52**, 4051 (1930).

by regulation of the amount of water sent through the partial condenser (4). As the chlorination progressed it was necessary to send increasingly colder water through to hold back the dichlorides. For example, in one of the three runs made, the temperature of the column head at the start was 105–107° and the temperature in the still pot was 107–108°, while after about fourteen hours of operation the column head temperature could not be held below 108° and still have any appreciable quantity of chloride coming over. The temperature in the still flask had risen to 148°. During the reaction the temperature in the chlorination vessel was 145–155°. The chlorides were washed with water, with sodium bicarbonate solution, again with water, then dried over anhydrous calcium chloride.

Analysis of the Dichloride Fraction.—A 332-g. portion of the chloride mixture was rectified in a modified Podbielniak column of 6 mm. o. d. Pyrex tubing containing a spiral of no. 20 Chromel wire. The packed section was 101 cm. long. With a reflux ratio of 12 to 1 the fractionation gave: 1,1- and 1,2-dichloropentanes (not separated), 20%; 1,3-dichloropentane, 30%; 1,4-dichloropentane, 31%; and 1,5-dichloropentane, 19%.

Rectification of Chlorinated Material.—The chlorides from the analysis by rectification were added to the main body of chlorinated product and the entire mixture was fractionated at 60 mm. pressure through a 50-plate glass helix-packed column. Rough cuts were taken. These were rerectified to give the compounds listed in Table I. The rectification of 2025 g. of a mixture of di- and polychlorides yielded only 4.4% of polychlorides.

TABLE I

PHYSICAL CONSTANTS OF PURIFIED DICHLOROPENTANES

Compound	B. p., °C., at 60 mm.	n^{20}_{D}	d^{20}_{4}
1,3-Dichloropentane	80.4	1.4485	1.0834
1,4-Dichloropentane[7]	88.1	1.4503	1.0840
1,5-Dichloropentane[8]	102.4	1.4563	1.1028

TABLE II

IODOCHLORIDES PREPARED

Compound	B. p., °C., of purified material	% Yield based on dichloride used	n^{20}_{D}	d^{20}
1-Iodo-3-chloropropane	60.8 at 15 mm.	53.1		
1-Iodo-3-chlorobutane	51.4 at 6.5 mm.	77.8	1.5267	1.7505
1-Iodo-3-chloropentane	50.5 at 2.5 mm.	90.4	1.5229	1.6611
1-Iodo-4-chloropentane	61.3 at 3.5 mm.	90.0	1.5248	1.6580
1-Iodo-5-chloropentane	75.8 at 4 mm.	61.6	1.5304	1.6731

Preparation of Iodochlorides.—The dichloride and sodium iodide were dissolved in anhydrous acetone and the resulting mixture refluxed for twenty-four hours. For the preparation of those compounds containing a secondary chlorine atom the mole ratio of sodium iodide to dichloride was generally 1.1 to 1 while for those containing two primary chlorines the ratio was 1 to 1. The reaction mixture was cooled and filtered from the sodium chloride. Acetone washings of the sodium chloride were added to the filtrate. Most of the acetone was removed from the halides by distillation at ordinary pressure. The residue was shaken with dilute sodium thiosulfate solution and finally the organic layer was dried over anhydrous calcium chloride. The iodochloride was obtained from the mixture of iodochloride, unreacted dichloride, and diiodide by rectification at reduced pressure. Yields of 75 to 90% based on the dichloride used were realized when the starting dichloride contained a primary and a secondary chlorine atom. Using this general procedure the compounds listed in Table II were prepared. The butane derivatives were obtained from 1,3-dichlorobutane furnished by Mr. H S. Barnaby of this Department, while the propane derivatives were made from Eastman Kodak Co. 1,3-dichloropropane.

The following diiodides were also obtained in the reactions: 1,3-diiodopropane, b. p. 78.5° at 5 mm.; 1,3-diiodobutane, b. r. 80–82° at 5 mm.; 1,3-diiodopentane, b. r. 80–82° at 2.5 mm.; 1,4-diiodopentane, b. p. 100° at 5 mm.; 1,5-diiodopentane, b. r. 101–102° at 3 mm.

Preparation of Chloroalkyldiethylamines (as hydrochlorides).—The dry iodochloride was added slowly at room temperature to three or four times the calculated quantity of well agitated dry diethylamine. A mushy solid, which probably consisted of a mixture of the hydroiodides of the chloroalkyldiethylamine and diethylamine, formed. The mixture was stirred for an hour after all of the iodochloride had been added. The contents of the reaction flask were shaken with three to four volumes of 5% sodium hydroxide solution. The upper layer, consisting of diethylamine, the chloroalkyldiethylamine, and unreacted iodochloride was washed with several portions of water to remove most of the diethylamine. The organic layer was taken up in ether, the ether solution was shaken with water, separated, and dried over Drierite. Dry hydrogen chloride was passed into the ice-cold, dry, filtered ether solution with immediate precipitation of the hydrochloride as a very fluffy solid. The crystals were washed on the filter with dry ether and dried in a vacuum desiccator. The hydrochlorides are very hygroscopic. Purification was effected by taking up the hydrochloride in a warm 1 to 1 (by volume) mixture of n-butanol and acetone, adding dry ether to the point of incipient clouding followed by cooling

TABLE III

DATA ON CHLOROALKYLDIETHYLAMINES (HYDROCHLORIDES)

Diethylamine hydrochlorides	M. p., °C., of pure material	% Yield based on iodochloride	% Ionizable Cl Found		% Ionizable Cl Calcd.	% Total Cl Found		% Total Cl Calcd.
3-Chloropropyl-	85.8–86.2	70	19.06	19.03	19.06			
3-Chlorobutyl-	83–84	68	17.90	17.93	17.72			
3-Chloropentyl-	98.5	74				33.21	33.30	33.12
4-Chloropentyl-	99.0	42				33.38	33.50	33.12
5-Chloropentyl-	80–81	44	16.56	16.58	16.56			

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(7) Beilstein, Vol. I, Syst. no. 10, p. 131.

(8) Servvy, *Bull. soc. chim. Belg.*, **42**, 485–501 (1933).

(9) Beilstein, Vol. I, Syst. no. 10, p. 114.

in an ice-bath to obtain crystallization. Two recrystallizations usually sufficed to give a product whose melting point did not change upon further recrystallization. Other combinations of solvents found suitable for recrystallization were *n*-butanol–ether and acetone–ether. Table III contains pertinent data on the compounds prepared. Attempts to prepare 4-chloropentyldiethylamine by heating 1,4-dichloropentane, sodium iodide, and diethylamine resulted in the formation of a mixture one of whose main components was the ethochloride of 1-ethyl-2-methylpyrrolidine.

Acknowledgment.—It is a pleasure to acknowledge the generosity of Mr. J. K. Lilly, who defrayed the cost of this investigation.

Summary

The vapor-phase photochemical chlorination of 1-chloropentane was carried out with the isolation by rectification of the 1,3-, 1,4-, and 1,5-dichloropentanes. The 1,1- and 1,2-isomers were not separated from each other.

A new synthesis of chloroalkyldialkylamines has been developed. The method consists of treating a chloroiodoalkane with diethylamine at room temperature. The iodochlorides were prepared by heating the corresponding dichlorides with sodium iodide in anhydrous acetone.

The amines prepared in good yields included: 3-chloropropyldiethylamine, 3-chlorobutyldiethylamine, 3-chloropentyldiethylamine, 4-chloropentyldiethylamine, and 5-chloropentyldiethylamine, all of which were isolated as the hydrochlorides.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NEW YORK UNIVERSITY]

Condensation of Diketones with Phenol[1]

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With the extension of the systematic study of the condensation of carbonyl compounds with phenols,[3] it was expected that the various phenomena encountered in monoketone–phenol condensations should be applicable also to the diketone condensations. This expectation was not always realized in the case of the di- and trihydroxyphenols[4] but in the case of phenol itself the expected condensation products were obtained. Thus when the γ-diketone, acetonylacetone, was condensed with phenol in the presence of dry hydrogen chloride in the ratio of 4 moles of phenol to 1 mole of diketone, the predicted double alkylidene-diphenol, 2,2,5,5-tetrakis-(4′-hydroxyphenyl)-hexane (I) was obtained. This tetraphenol was characterized by functional and nuclear substituted derivatives, such as esters [acetate (Ia) and propionate (Ib)], nitro (Ic) and mercury derivatives (Id).

When the α-diketone, benzil, was condensed with phenol, the reaction took a different course. These two compounds had been condensed by Liebig[5] under somewhat drastic conditions by fusing them at 180° in the presence of zinc chloride, yielding the lactone of *o*-hydroxytriphenylacetic acid, melting at 129°. Under the milder conditions of the present experiment, a crystalline compound was obtained, melting at 212° and analyzing for the combination of two moles of phenol and 1 mole of benzil with the loss of 1 mole of water (II). This compound formed a diacetate (IIa) and a dipropionate (IIb). Thus the present condensation product appears to be an entirely different substance and checks perfectly for benzoyl-4,4′-dihydroxy-tritan (II). This compound has been reported previously by Kempinski[6] who obtained it as a not further characterized red powder by fusing α,α-dichloro-α-phenylacetophenone with phenol in the presence of zinc chloride.

It suggests itself that the general reaction mechanism as advanced by McGreal and Niederl[7] for carbonyl compound–phenol condensations might be also applicable to the two types of condensations presented in this paper. In both cases, undoubtedly, also an intermediate "phenol–hydrin" type of a compound would form. This

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(1) The contents of this communication were part of a paper entitled "Diketone–Phenol Condensations" delivered before the Organic Division at the Cincinnati meeting of the American Chemical Society in April, 1940.

(2) Abstracted from a portion of the thesis submitted to the faculty of the Graduate School of New York University by Richard H. Nagel in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(3) J. B. Niederl and co-workers, THIS JOURNAL, **50**, 2230 (1928); **51**, 2426 (1929); **58**, 657 (1936); **59**, 1113 (1937); **61**, 345, 348, 1005, 1785 (1939); **62**, 320, 322, 324, 1157 (1940).

(4) Niederl and Nagel, *ibid.*, **62**, 3070 (1940); **63**, 307, 580 (1941).

(5) Liebig, *Ann.*, **350**, 206 (1908).

(6) Kempinski, *Bull. soc. chim.*, [3] **7**, 609 (1892).

(7) M. E. McGreal and J. B. Niederl, "Abstract of Papers, 97th Meeting, Am. Chem. Soc." Baltimore, Md., 1939, M, pp. 5–7.