

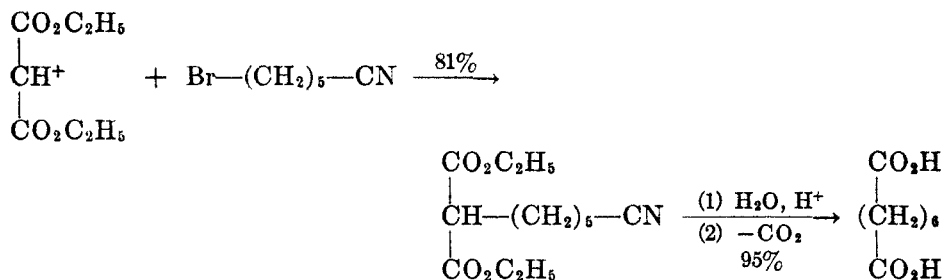
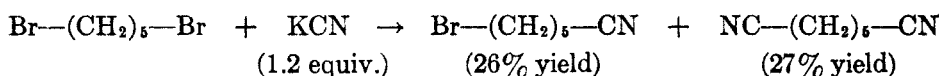
A CONVENIENT PREPARATION OF SUBERIC ACID. CONCERNING THE HOMOGENEITY AND USE IN SYNTHESIS OF POLY-METHYLENE CHLOROBROMIDE PREPARATIONS

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The dibasic acids have a variety of uses in synthesis, and have proved very valuable for extending the carbon chain in synthesis of branched-chain fatty acids, either by use of organocadmium reagents (1) or by acylation of β -keto esters (2). All the normal dibasic acids with ten or less carbons have been easily available, except for pimelic acid and suberic acid. Until recently, pimelic acid was obtained only by relatively tedious syntheses (3), but this acid is now easily obtained in high over-all yield from tetrahydropyran,¹ proceeding by way of the pentamethylene dihalide and the corresponding dinitrile. These reactions have been reported in the literature, but somewhat simplified experimental procedures are described in this paper.

A pentamethylene dihalide from tetrahydropyran may also serve as starting material for preparation of suberic acid, proceeding by way of the illustrated sequence of reactions.



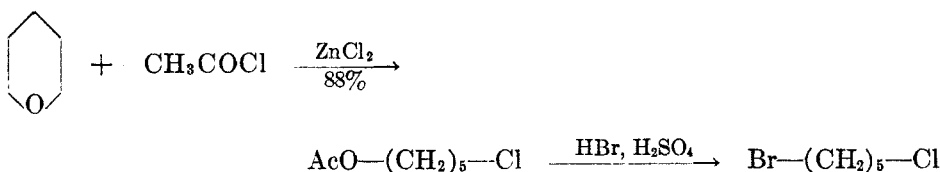
This sequence of reactions proceeds more favorably when pentamethylene dichloride¹ is used as starting material, if a small amount of potassium iodide is used as catalyst in each of the first two reactions. The alkyl chloride is converted to the more reactive iodide, and on reaction of the iodide with the other component the iodide ion is regenerated for further use in the same sequence of reactions. Using only four mole per cent of potassium iodide, the metathesis with cyanide proceeded as rapidly with pentamethylene dichloride as when pentamethylene dibromide was used. Alkylation of malonic ester with ω -chlorocapronitrile was complete in four hours when twenty-five mole per cent of

¹ We are indebted to the Electrochemicals Division, E. I. du Pont de Nemours and Co., for supplying us with the tetrahydropyran and pentamethylene dichloride used in this investigation.

potassium iodide was used. The dichloride has the advantage that the yield of halonitrile is appreciably greater than when the dibromide is used. Using 1.2 equivalent of potassium cyanide, there was obtained 37% yield of chloronitrile and 20% yield of dinitrile.

It is seen that the only poor yield in this process is in the first step, and this is offset by recovery of nearly 20% of the starting material and by the usefulness of pentamethylene dicyanide for making pimelic acid. If the yield in the first step is based on dichloride consumed the over-all yield of suberic acid from pentamethylene dichloride is about 35%. If desired, the ratio of recovered dichloride to dicyanide may be increased by reducing the equivalency of potassium cyanide to 1.1. This has only a small effect on the yield of halonitrile. Increasing the equivalency of potassium cyanide above about 1.2 lowers the yield of halonitrile.

Since the most attractive method for improving the yield of ω -halocapronitrile would seem to be its preparation from pentamethylene chlorobromide, this dihalide was prepared from tetrahydropyran by the following route:



Cyclic ethers have been opened with acetyl chloride by several investigators (1, 4), and the preparation of ω -acetoxyamyl chloride has recently been reported by Synerholm (5). A complication was encountered in the second step of this procedure, in that chlorine is replaced by bromine at an appreciable rate when the alkyl chloride is heated with hydrobromic and sulfuric acids. Table I shows the composition of the products obtained when 0.25 mole of ω -acetoxyamyl chloride was heated for various lengths of time with 0.5 mole of sulfuric acid and 0.5 mole of 48% hydrobromic acid. The figures in the fourth column represent the percentage of the total yield which was the chlorobromide, the remainder being dibromide. The last column gives the yield of chlorobromide, based on acetoxy chloride. Since the actual yield of chlorobromide remains constant from fifteen minutes up to two hours, it follows that conversion of chlorobromide to dibromide is compensated by conversion of acetoxy chloride to chlorobromide.

Composition of the mixture was determined by use of the specific gravity, after the specific gravities of pure pentamethylene dibromide and pure pentamethylene chlorobromide had been determined. By determining the values for known mixtures it was shown that linear extrapolation between these values is subject to less than 1% error. The validity of the analysis of reaction mixtures was also established by separating one reaction mixture by fractional distillation. A trace of pentamethylene dichloride was present, and the composition of small intermediate fractions was estimated, but the composition obtained by fractionation was within 4% of the value obtained by specific gravity determination.

The only previous report of pentamethylene chlorobromide is that of Magidson and Grigorowsky (6), who obtained it by the action of phosphorus tribromide and bromine on ω -benzoylaminoamyl chloride. Their product must have contained considerable quantities of the dibromide, for their density was 1.488, whereas the value obtained in the present investigation was 1.408. Also, the molecular refraction calculated from the values of the previous workers agrees rather poorly with the theoretical value.

Although the most obvious assumption is that the pentamethylene dibromide is formed by direct replacement of the chlorine by bromine (or, perhaps, *via* the hydroxy compound), it was thought possible that an intermediate is tetrahydropyran, for pentamethylene chlorohydrin has been reported (5) to lose halogen acid easily. This possibility was eliminated by treating trimethylene chlorohydrin with hydrobromic and sulfuric acids under similar conditions. This chlorohydrin gives a cyclic ether only on treatment with molten potassium hydroxide (6a); however, the halide obtained from the hydrobromic and sulfuric acid treatment contained considerable dibromide, and the rate of formation of dibromide was roughly parallel with that observed in the case of the pentameth-

TABLE I
COMPOSITION OF PENTAMETHYLENE DIHALIDE MIXTURES

REFLUX TIME, HRS.	YIELD, G.	SP. GR. $\frac{15}{25}$	MOLE % Br-(CH ₂) ₅ -Cl	% YIELD Br-(CH ₂) ₅ -Cl
0.25	34.5	1.440	91	66
0.5		1.454	86	
1.0	39.2	1.465	81	65.5
2.0	41.1	1.474	78	66
5.0 (2.6 eq. of HBr)		1.545	54	

ylene derivative. Although some investigators (7) have treated trimethylene chlorohydrin with hydrobromic and sulfuric acids and assumed the product to be the chlorobromide, it seems safe to say that all products so obtained from chlorohydrins contain significant quantities of dibromide. It has already been pointed out by Cloke and co-workers (8) that trimethylene chlorobromide obtained by the hydrobromic acid method "contains considerable quantities of trimethylene dibromide". These workers obtained nearly quantitative yields of trimethylene chlorobromide by use of phosphorus tribromide on the chlorohydrin. No attempt has been made by us to apply this procedure for preparation of the pentamethylene chlorobromide, on account of the ease of cyclization of the pentamethylene chlorohydrin.

When the mixture of pentamethylene chlorobromide and dibromide was treated with an amount of potassium cyanide slightly in excess of the total bromide present in the mixture, there was obtained a 52% yield of a mixture of chloro- and bromo-capronitriles. Thus, this process makes possible a yield of halonitrile somewhat greater than that obtained from the dichloride. Obviously, alkylation of malonic ester with this mixture leads to a single product. By this route, the over-all yield of suberic acid from tetrahydropyran is about 30%.

By use of the specific gravity method, the composition of the halonitrile mixture was determined. It was found that the yield of bromonitrile, based on dibromide present in the halide mixture, was 52%, double the yield of bromonitrile obtained when pure pentamethylene dibromide is treated with the most favorable ratio of potassium cyanide. Furthermore, the yield of chloronitrile, based on chlorobromide used, is also 52%; therefore, considerable bromonitrile must have been obtained directly or indirectly from chlorobromide. This very likely results from replacement of chlorine in chlorobromide or chloronitrile by bromine from potassium bromide. This would actually be expected on account of the much lower solubility of potassium chloride in the reaction medium. Whatever may be the route, it follows that even if pure chlorobromide is used as starting material the product is a mixture of chloro- and bromo-nitriles, and bromonitrile formed before the potassium cyanide is exhausted would be readily converted to dinitrile, thus partially defeating the effectiveness of chlorobromide in increasing the yield of halonitrile. In view of the mixtures obtained and the labor of obtaining the starting materials, the use of polymethylene chlorobromides for making halonitriles seems hardly superior to the use of the dichlorides.

EXPERIMENTAL

Microanalysis by C. W. Koch and V. H. Tashinian. Boiling points are uncorrected. Reduced pressures were measured with a Zimmerli gage, unless otherwise specified. Specific gravities were determined in a bulb of about 3 ml. capacity and are accurate to about ± 0.001 unit.

ω -Bromocapronitrile. Pentamethylene dibromide was prepared by the method of Wilson (9), using hydrobromic and sulfuric acids, in yields of 82–88%. A mixture of 230 g. (1 mole) of pentamethylene dibromide, 78 g. (1.2 mole²) of potassium cyanide, 160 ml. of water, and 650 ml. of 95% ethanol was heated under reflux for ten hours. The mixture was then distilled until about 550 ml. of distillate had been collected. After sufficient water had been added to the residue to dissolve precipitated salt, the oil phase was separated and the aqueous phase was extracted with three 35-ml. portions of benzene. After the oil and benzene extracts had been washed in sequence with 1 *N* sodium hydroxide they were combined and the solvent was flash-distilled. The residue was fractionally distilled through a 2-foot Vigreux column with heated jacket and total reflux head, collecting the products over ranges of about two degrees. Intermediate fractions were small (2–5 g.). The average yield of bromonitrile was 45 g. (26%), b.p. 133–135° (15 mm.). There was also obtained 27.5% yield of dinitrile and 17% recovery of dibromide. The bromonitrile fraction sometimes contained a trace of suspended white solid. This had no effect in the alkylation step. For the constant-boiling fraction of bromonitrile, b.p. 134.4° (15 mm.), n_D^{24} 1.4754, d^{24} 1.328, MR_D 37.41 (calc'd 37.35). Hauser and Breslow (10) reported b.p. 115–117° (6 mm.), for bromonitrile prepared from ω -bromocaproic acid.

ω -Chlorocapronitrile was prepared and isolated in the same manner as described for the bromonitrile except that four mole per cent of potassium iodide was added to the reaction mixture. In a 1.0-mole run, using 1.20 equivalent of potassium cyanide, the yield of chloronitrile was 49.3 g. (37.5%), b.p. 97–99° (5 mm.), and there was also obtained 24.8 g. (20%) of dinitrile, b.p. 141–144° (5 mm.). Recovery of dichloride was 26.5 g. (19%), b.p. 84–86° (26 mm.). For a constant-boiling fraction of chloronitrile, b.p. 121.0° (15 mm.), n_D^{23} 1.4488,

² Equivalencies of potassium cyanide in this paper are calculated on the basis of pure potassium cyanide, thus the values are a few per cent too high.

d^{25}_D 1.024, M_R , 34.51 (calc'd 34.46). This chloronitrile appears to have been reported previously only by Braun and Steindorff (11), who did not isolate it in a pure condition.

Pimelic acid. Pentamethylene dicyanide was prepared as described for the halonitriles, except that 2.1 equivalents of potassium cyanide were used and the product was distilled in a Claisen flask. Yields in several runs were 80–85%, b.p. 151–155° (3 mm.). For hydrolysis, 65 g. (0.53 mole) of the dinitrile was heated under reflux for three hours with 175 ml. of concentrated hydrochloric acid. The hot mixture was stirred vigorously in a beaker as it cooled, to prevent formation of an unworkable cake. After standing overnight, the semi-solid mass was pressed on a Büchner funnel, then stirred with 75 ml. of cold water. After collecting, washing with cold water, and drying there were obtained 91–94% yields of nearly white pimelic acid, m.p. 99–103°. This product is essentially pure but usually the melt is cloudy from traces of ammonium chloride, easily removed by recrystallization from water.

Diethyl ω -cyanoamylmalonate. To a solution of 5.7 g. (0.25 atom) of sodium in 200 ml. of absolute alcohol (distilled from sodium) was added 75 g. (0.47 mole) of diethyl malonate. After stirring this mixture for five minutes under reflux there was added during about five minutes 44 g. (0.25 mole) of ω -bromocapronitrile. This mixture was stirred under reflux until a test sample was no longer alkaline to phenolphthalein (1–2 hours). After most of the alcohol had been distilled from the mixture, with continued stirring to prevent bumping, the residue was shaken with water and benzene, and the aqueous phase was extracted again with benzene. The residue from the benzene extract was distilled in a Claisen flask at 2 mm. pressure. After a fore-run consisting largely of excess malonic ester, the cyanoester was collected at 155–165°, wt. 52.8 g. (81.5%, based on bromonitrile). Such material as this was used in the next step, but its homogeneity was checked by redistillation through a half-meter Podbielniak type column, measuring pressure with a McLeod gage. There was obtained 1.2 g. of fore-run, 49.0 g. of cyanoester of b.p. 161–162° (2 mm.), and 2.0 g. of distillation residue. For analysis, there was used a constant-boiling fraction of b.p. 161.9° (2 mm.), n_D^{25} 1.4425.

Anal. Calc'd for $C_{13}H_{21}NO_4$: C, 61.14; H, 8.29.

Found: C, 61.24, H, 7.95.

Alkylation with ω -chlorocapronitrile or the mixed halocapronitriles was carried out similarly and in essentially the same yields except that 25 mole per cent of potassium iodide was added to the reaction mixture, and alkylation was continued under reflux for about four hours. The composition of the mixed chloro- and bromo-capronitriles was determined by the density, and this value was used to determine the required equivalence of sodium.

Suberic acid. The cyanoester was hydrolyzed by heating under reflux with stirring for 3–4 hours with 7 *N* aqueous hydrochloric acid (5 ml. per g. of cyanoester). On cooling this mixture, 1,1,6-tricarboxyhexane crystallizes, but it is most convenient not to isolate this rather soluble intermediate. Water and acid were distilled from the reaction mixture and the residue was heated at 180–190° until carbon dioxide evolution had ceased (usually 60–90 minutes). The residue of suberic acid and ammonium chloride was heated with water under reflux with stirring for a few minutes, using 100 ml. of water per 0.2 mole of starting cyanoester. Suberic acid was filtered from the cooled solution and washed with cold water. The yield of slightly gray acid amounts to 90–95% of the theoretical amount, m.p. 138–141°. The melt is usually cloudy from ammonium chloride, which may be removed, if desired, by crystallization from a mixture of benzene and alcohol. Once-recrystallized acid melted at 139–141°.

ω -Acetoxyamyl chloride was prepared by a modification of the method of Synerholm (5). A mixture of 175 g. (2.03 moles) of tetrahydropyran, dried over sodium hydroxide, 8 g. of freshly-fused zinc chloride, and 159 g. (2.03 moles) of acetyl chloride, distilled from dimethylaniline, was heated under reflux for two hours. The cooled reaction mixture was filtered and directly distilled from a Claisen flask. After a fore-run of low-boiling material, the chloroester was collected at 109–112° (24 mm.), weight 294 g. (88%). From the literature (5), b.p. 104° (18 mm.) or 113–115° (34 mm.).

Mixed pentamethylene halides. A mixture of 56.6 ml. (0.5 mole) of 48% hydrobromic acid,

41.2 g. (0.25 mole) of ω -acetoxyamyl chloride, and 28 ml. (0.5 mole) of 96% sulfuric acid was heated under reflux for varying lengths of time. The crude product was washed with three 20-ml. portions of concentrated sulfuric acid, then with water, bicarbonate solution, and water, and finally dried over calcium chloride. On distillation at reduced pressure, the product was collected in the range 90–105° (15 mm.). Yields and compositions of the products are found in Table I. In a 1.8-mole run heated for two hours the yield of mixed halides was 87% of the theoretical number of moles, and the mixture contained 77 mole per cent of pentamethylene chlorobromide.

Data for analysis of pentamethylene dihalide mixtures. Pentamethylene dibromide, prepared by the method of Wilson (9) was washed repeatedly with sulfuric acid, and further purified as described for the mixed halides. On distillation, the total product was collected at 98–99° (15 mm.). The sp. gr.₂₅ for fractions taken near the beginning and end of the distillation were respectively 1.703 and 1.705. The value 1.704 was used for calculation of compositions of mixtures.

In order to obtain a sample of pure pentamethylene chlorobromide, a sample of mixed halides, sp. gr.₂₅ 1.471 was distilled through a 1-meter column packed with glass helices, at a pressure of 30 mm. Fractionation data are given in Table II. Fraction 2 was collected in six sub-fractions, and the sp. gr.₂₅ for the second, third, and fifth of these were determined, respectively, as 1.407, 1.408, 1.408. The latter value was used for calculating compositions. The value for n_D^{25} for Fraction 2 was 1.4838, thus MR_D was 37.71 (calc'd 37.92).

TABLE II
FRACTIONATION OF MIXED PENTAMETHYLENE DIHALIDES

FRACTION NO.	COMPONENTS	B. P. °C (30 MM.)	WT., G.
1	Dichloride and chlorobromide	90.5–102.4	3.6
2	Chlorobromide	102.4	82.1
3	Chlorobromide	102.4–103.2	8.0
4	Chlorobromide and dibromide	103.2–118.5	6.8
5	Dibromide	118.5–119	35.6

From the specific gravity of the mixture distilled, 1.471, its composition is calculated as 78.6 mole per cent pentamethylene chlorobromide. From the data in Table II, the chlorobromide content of the mixture is calculated as 74.4 mole per cent, if it is assumed that Fraction 1 is one third dichloride and two thirds chlorobromide, and Fraction 4 is equal amounts of chlorobromide and dibromide. This would seem adequate proof that no impurities in the reaction mixtures are rendering invalid the analyses based on specific gravity.

The validity of linear extrapolation between the respective specific gravities of the dibromide and chlorobromide was established by determination of the gravities of mixtures prepared from weighed amounts of the two pure components. The known dibromide contents of the mixtures, followed in parentheses by the values calculated from specific gravity determinations, were: 75.2% (75.0%), 56.4% (57.1%), 35.1% (35.8%). Thus, within the limits of our experimental accuracy, the two dihalides form a perfect solution over the entire range of composition.

Mixed trimethylene dihalides were prepared from a sample of commercial trimethylene chlorohydrin, using the same procedure as described for the pentamethylene dihalides. The products obtained from runs which had been heated under reflux for one quarter hour and two hours, respectively, were found to have sp. gr.₂₅ of 1.673 and 1.717. Using literature values for densities of trimethylene dibromide, d^{16} 1.987, and the chlorobromide³, d^8 1.63,

³ Although trimethylene chlorobromide has been prepared by numerous investigators, the chief analytical interest has been analysis of mixtures of the 1,2- and 1,3-chloro-

approximate values for the chlorobromide content of these mixtures were calculated; after fifteen-minute reflux, 88%; after two-hour reflux, 74%. By reference to Table I, it may be seen that these values are in rather good agreement with the values obtained in the pentamethylene dihalide series.

Mixed ω -bromo- and ω -chloro-capronitriles were prepared by the procedure described for ω -bromocapronitrile, using 44.3 g. (0.68 mole) of potassium cyanide and 0.5 mole of mixed pentamethylene dihalides (97.9 g. of sp. gr.₂₅ 1.477; 0.385 mole of chlorobromide and 0.115 mole of dibromide). Fractionation of the product through the 2-foot Vigreux column at 2 mm. pressure gave the following: (a) fore-run, b.p. 46–88°, wt. 5.5 g.; (b) mixed halonitriles, b.p. 88–107°, wt. 37 g.; (c) intermediate, b.p. 107–134°, wt. 3.4 g.; (d) dinitrile, b.p. 134–135°, wt. 14.0 g. For the halonitrile fraction, sp. gr.₂₅ 1.094. From the specific gravities of the pure halonitriles, as reported under their preparation, the halonitrile mixture is calculated to be 23 mole per cent bromonitrile. Thus, the yield of chloronitrile is 0.202 mole (52% based on chlorobromide used), and the yield of bromonitrile is 0.0595 mole (52%, based on dibromide used). Thus, the conversion of chloronitrile to bromonitrile by reaction with potassium bromide is clearly indicated, unless it be assumed that reaction of chlorobromide with potassium cyanide can yield appreciable quantities of bromonitrile.

The validity of analysis of the halonitrile mixture by use of density depends on the absence of other products of different density, such as dibromide or dinitrile. Such materials were shown to be almost entirely absent by fractionation of the products of two runs through a 3-foot packed column at 15 mm. pressure. Fractions obtained were: (a) fore-run, b.p. 114–121°, wt. 1.5 g.; (b) chloronitrile, b.p. 121–122°, wt. 40.6 g.; (c) intermediate, b.p. 122–134°, wt. 3.4 g.; (d) bromonitrile, b.p. 134–134.5°, wt. 21.6 g.; (e) residue, less than 1 g.

In one of the runs used for fractionation, only 35.8 g. of potassium cyanide was used, but this was found to be inconvenient for synthesis of halonitriles, for some pentamethylene dibromide was recovered, and this is separated from the chloronitrile only by careful fractionation.

SUMMARY

There is described a convenient synthesis of suberic acid depending on alkylation of malonic ester with an ω -halocapronitrile, followed by hydrolysis and decarboxylation.

ω -Bromo- and ω -chloro-capronitriles were prepared by reaction of the appropriate pentamethylene dihalide with 1.2 equivalent of potassium cyanide.

Pentamethylene chlorobromide was prepared by reaction of hydrobromic acid with ω -acetoxyamyl chloride, but there was always obtained a considerable amount of pentamethylene dibromide. Pure polymethylene chlorobromides may be obtained by this method only if dibromide is separated by fractional distillation.

It is shown that reaction of pentamethylene chlorobromide with potassium cyanide yields ω -chlorocapronitrile admixed with ω -bromocapronitrile.

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bromides, and the only available value for the density of the 1,3-chlorobromide is that reported in early work by Reboul (12), but this value appears of about the expected magnitude. The value (sp. gr.₂₅ 1.4718) reported by Rossander and Marvel (13) is obviously in large error, as is evident from comparison with values for the dibromide (1.99) and the dichloride (1.20). The same workers reported a very low value for the dichloride.

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