

took place at 0° and it was slow at room temperature. Refluxing was omitted. Diketone, b. p. 164–166°; copper salt, m. p. 172°. 2-Methyl-3,5-hexanedione boils at 160–170° and its copper salt melts at 171°. ¹⁰

Ethyl Isobutyrate + Acetone.—One-half mole of ester, ketone and sodium were used. The reaction was vigorous but only a small quantity of the copper salt melting at 171° was obtained. A mixture of this with that obtained in the preceding reaction also melted at 171°.

Summary

1. The Claisen condensation between several esters and ketones has been studied and the diketones resulting have been identified.
2. Modifications of proportions and conditions did not change the course of the reaction in the cases studied.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

BROMINE DERIVATIVES OF CERTAIN MIXED ETHERS AND SOME OF THEIR REACTIONS

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Previous work¹ in this Laboratory has shown that in the bromination of certain phenyl alkyl ethers the hydrogen bromide liberated may split them unless sodium acetate is present, and that the splitting is more pronounced when the alkyl radical is connected through a secondary or tertiary² carbon atom.

In cases where, as indicated below, the phenyl radical could not be further brominated under the conditions already described, and where, in consequence of this, no "nascent hydrogen bromide"³ was produced during attempts at bromination, splitting of these ethers was not observed. Nevertheless, it was a matter of interest to test the behavior of such ethers toward hydrogen bromide under several conditions.

Graebe and Martz⁴ found that heating trimethoxygallic acid with 48% hydrobromic acid in an open vessel surrounded by boiling water removed the methyl radical from position 4 to the extent of 90%. In the present work that method did not give satisfactory results. Refluxing 2,4,6-

¹⁰ Conrad and Gast, *Ber.*, **31**, 1339 (1898).

¹ Raiford and Birosel, *THIS JOURNAL*, **51**, 1776 (1929).

² In the tertiary butyl derivative splitting occurred although sodium acetate was present. This may be due to a tendency of the ether to split off the unsaturated hydrocarbon isobutylene. Konowalow [*Z. physik. Chem.*, **1**, 67 (1887)] observed such a change in the study of tertiary amyl acetate.

³ The small amount, if any, produced by the action of bromine on the alkyl radical of the ether was not detected and was disregarded.

⁴ Graebe and Martz, *Ann.*, **340**, 220 (1905).

tribromophenyl isobutyl and isoamyl ethers with constant boiling hydrobromic acid over a free flame for three and fourteen hours, respectively, caused splitting to the extent of 5 and 12%, while the pentabromo compounds were not affected. These low yields suggested the use of "nascent" hydrogen bromide. Its action was tested in different ways, and examination of Table II (see Experimental Part) will show that the most pronounced effect was obtained by the action of the bromide at an elevated temperature.

In the present work an attempt was made to brominate 2,4,6-tribromophenyl- β,γ -dibromo *n*-propyl ether⁵ with pure bromine, catalyzed by aluminum bromide,⁶ in order to secure the corresponding pentabromophenyl derivative. The ether was split and pentabromophenol was obtained. The action was found to be general⁷ for the ethers here studied, as indicated in tabular form below.

In previous work it was noted that treatment of phenyl allyl ether with an excess of bromine saturated the aliphatic radical and introduced but two atoms of bromine into the phenyl nucleus, and that these took positions 2 and 4. The structure of this tetrabromo derivative was proved by bromination of 2,4-dibromophenyl allyl ether which, in turn, had been prepared from 2,4-dibromophenol. In the present work this conclusion has been confirmed by further examination of the above indicated tetrabromo compound, and by the study of other similar cases. Thus, the 2,4-dichloro, 2,6- and 3,5-dibromophenyl allyl ethers were treated at 0° in the presence of sodium acetate with a chloroform solution of bromine (1:1 by volume), in excess of that required to saturate the allyl radical and to substitute all available positions in the phenyl group, after which the mixture was allowed to stand at room temperature for about a week. In the first two cases the side chain only reacted, while in the last one both side chain and nucleus were attacked, although the latter was substituted by only two bromine atoms. These results tend to show that in the phenyl allyl ethers when any two of the *o,o,p*-positions have been substituted by bromine no more can be introduced by the method here used.

Claisen⁸ found that the allyl ethers of many phenols were readily rearranged by heat, in almost quantitative yield, into the corresponding allylphenols, in which the allyl radical enters the ortho or para position. In subsequent work⁹ *p*-bromophenyl and 2,4-dichlorophenyl allyl ethers

⁵ Raiford and Birosel, *THIS JOURNAL*, **51**, 1778 (1929).

⁶ Pfeiffer and Haack [*Ann.*, **460**, 170 (1928)] found that certain aryl methyl ethers form addition products (molecular compounds) with aluminum bromide, and that these compounds were demethylated by heating for several hours in presence of benzene.

⁷ In many cases the pentabromophenol was mixed with a brown powder that could not be identified. The amount formed was greater at boiling point than at room temperature.

⁸ Claisen, *Ber.*, **45**, 3157 (1912).

⁹ Claisen, *Ann.*, **418**, 84 (1919)

were found to rearrange. In the present work a small yield of the phenol was obtained from the 2,4-dichlorophenyl derivative, but attempts to rearrange the dibromo compounds were unsuccessful. Likewise, the phenyl alkyl ethers failed to rearrange.

The β,γ -dihalogenated products show a number of interesting properties. All of them absorb moisture from the air so rapidly and to such an extent that samples for analyses cannot safely be weighed in open vessels. They also hold alcohol strongly, and those crystallized from this liquid were dried under reduced pressure at elevated temperatures over extra long periods of time to secure samples for analyses.¹⁰ The compounds were further characterized by a study of their behavior toward alcoholic potash. In each case the elements of hydrogen bromide were removed from the side chain, and the corresponding propargyl ether was obtained in nearly quantitative yield. These ethers showed the characteristic properties of acetylene derivatives in the formation of unstable cuprous, mercuric and silver salts, the latter of which were isolated in combination with one molecular proportion of silver nitrate.

Experimental Part

The phenyl alkyl ethers indicated below were prepared by Claisen's method,¹¹ from phenol and the required alkyl halide. The product was then extracted with a solution of caustic alkali to remove phenol, and the ether purified in a suitable way. The tribromo derivatives were obtained by treatment of the ethers with an excess of bromine in chloroform solution,¹² in the presence of sodium acetate. The behavior of these products toward hydrogen bromide is shown in tabular form below.

Preparation of Pentabromophenyl Ethers.—The pentabromophenol used as starting material was prepared by Bodroux's¹³ method, modified as follows. One molecular proportion of melted phenol was dropped slowly with stirring into 1.5 times the theoretical amount of bromine in which about 1% aluminum had been dissolved, and the mixture was allowed to stand for twenty-four hours. Unchanged bromine and aluminum salt were extracted by hydrochloric acid solution of potassium bromide, and the phenol by 10% solution of sodium hydroxide. The product was crystallized from benzene or carbon tetrachloride.

¹⁰ The tendency to absorb alcohol raised the question of the replacement of halogen by the alkoxy radical, as observed by Hell and Gunthert [*J. prakt. Chem.*, **52**, 195 (1895)]. The products of the present work were repeatedly boiled with alcohol without change in composition.

¹¹ Claisen and Eisleb, *Ann.*, **401**, 36 (1913).

¹² When a mixture of 2,4,6-tribromophenyl *n*-propyl ether and more than five times its weight of pure bromine was allowed to stand in an open Erlenmeyer flask for three days at room temperature, a small yield of tetrabromo derivative was obtained. Failure to lose bromine when treated with alcoholic potash indicated that the halogen was not in the alkyl group. *Anal.* Subs., 0.2708: AgBr, 0.4526. Calcd. for $C_9H_5OBr_4$: Br, 70.79. Found: Br, 71.02.

¹³ Bodroux, *Bull. soc. chim.*, [3] **19**, 756 (1898).

The alkyl ethers of pentabromophenol were prepared by Claisen's method⁹ (with the exceptions noted in the table) with the modification that excess of alkyl halide was used. No reaction was obtained with tertiary butyl nor with tertiary amyl halide.

TABLE I
PENTABROMOPHENYL ALKYL ETHERS^a

| Alkyl | Formula | Crystal form | Yield, % | M. p., ° C. | Halogen, % | |
|-----------------------------------|--|-----------------------------|---------------|-------------|------------|-------|
| | | | | | Calcd. | Found |
| 1 Isopropyl | C ₉ H ₇ OBr ₅ | Short needles ^d | Nearly quant. | 86 | 75.47 | 75.38 |
| 2 <i>n</i> -Butyl ^b | C ₁₀ H ₉ OBr ₅ | Irreg. plates ^d | Nearly quant. | 79-80 | 73.39 | 73.26 |
| 3 Isobutyl | C ₁₀ H ₉ OBr ₅ | Short needles ^d | 45 | 92-93 | 73.39 | 73.30 |
| 4 <i>Sec.</i> -butyl ^b | C ₁₀ H ₉ OBr ₅ | Fibrous masses ^d | 25 | 57-58 | 73.39 | 73.34 |
| 5 Isoamyl ^c | C ₁₁ H ₁₁ OBr ₅ | Fine needles ^d | Nearly quant. | 64-65 | 71.55 | 72.68 |

^a The methyl, ethyl and *n*-propyl ethers of this series were obtained by Bonneaud [*Bull. soc. chim.*, [4] 7, 777 (1910)] by the action of the potassium salt of pentabromophenol on the required alkyl halide. No higher yield than 22% was recorded and the ethyl compound contained 1.32% more bromine than calculated. Lucas and Kemp [*THIS JOURNAL*, 43, 1661 (1921)] reported an 80% yield of this product from the action of the moist pink silver salt of pentabromophenol on ethyl iodide. Derivatives containing tertiary alkyl radicals have not yet been obtained. ^b The Claisen method was here modified to the extent of adding sodium iodide as well as the required alkyl bromide. Cf. Raiford and Colbert, *ibid.*, 48, 2658 (1926). ^c Obtained by refluxing an aqueous potassium hydroxide solution of the phenol with the required alkyl halide. ^d Crystallized from ligroin (80-100°). ^e Brown and Beal, *THIS JOURNAL*, 45, 1291 (1923).

Methods of Splitting the Ethers

1. A glacial acetic acid solution of the ether and phosphorus tribromide to which the calculated amount of water was gradually added was heated under a return condenser.

2. The mixture indicated in 1 was heated in a sealed tube at 135-150° for twelve to fifteen hours. The phosphorus tribromide was contained in an inner tube and did not come in contact with the remainder of the mixture until after the outer tube was sealed.

3. Bromine was dropped into a benzene solution of the ether in which some iodine was present as a catalyst.

4. A mixture of the ether, excess of bromine and about 1% of aluminum in the form of bromide was allowed to stand at room temperature for two days.

The products isolated in these experiments were tribromo- and pentabromophenol, respectively. No attempt was made here to recover any aliphatic halogenated product that might have been formed.

TABLE II
SPLITTING OF TRI- AND PENTABROMOPHENYL ALKYL ETHERS TO GIVE PHENOLS

| Ether | Methods | | | Phenol, % |
|--------------------|----------------------|------------|------------|-----------|
| | 1 | 2 | 3 | |
| | Tribromo Derivatives | | | |
| Methyl | No reaction | Completely | | |
| Ethyl | No reaction | Completely | | |
| <i>n</i> -Propyl | No reaction | Completely | | |
| Isopropyl | Completely | | Completely | |
| <i>Sec.</i> -butyl | Completely | | Completely | |
| Isobutyl | No reaction | Completely | | |
| Isoamyl | No reaction | Completely | | |

TABLE II (Concluded)

| Ether | Methods | | | |
|---------------------------------|------------------------|------------|-------------|-----------------|
| | 1 | 2 | 3 | 4 Phenol, % |
| | Pentabromo derivatives | | | |
| Methyl | | Completely | No reaction | 80 ^a |
| Ethyl | | Completely | No reaction | 40 ^a |
| <i>n</i> -Propyl | | Completely | | 40 ^a |
| Isopropyl ^b | Completely | | No reaction | 60 ^a |
| <i>n</i> -butyl | | Completely | | 30 ^a |
| Isobutyl | | Completely | | 20 ^a |
| <i>Sec.</i> -butyl ^b | Completely | | | 70 ^a |
| Isoamyl | | Completely | | 30 ^a |

^a The pentabromophenol was mixed with a brown amorphous solid that was not identified. Treatment at the boiling point of the mixture gave a lower yield of phenol and in some cases a larger quantity of the brown solid, which possibly was formed from the phenol.

^b Split by boiling with bromine in the absence of aluminum bromide to give high yields of pentabromophenol and some resinous material.

Substituted Phenyl Allyl Ethers

2,4-Dichlorophenyl Allyl Ether.—This was obtained by treatment of the corresponding dichlorophenol in acetone solution with potassium carbonate and with excess of allyl bromide by Claisen's¹⁴ general method. The product distilled as an almost colorless oil at 144–145° and 25 mm.

Anal. Subs., 0.2821: AgCl, 0.3988. Calcd. for C₉H₇OCl₂: Cl, 34.97. Found: Cl, 34.95.

3,5-Dibromophenyl Allyl Ether.—When the required phenol¹⁵ was treated with allyl bromide as indicated above an almost quantitative yield of ether was obtained; b. p. 145° at 10 mm.

Anal. Subs., 0.2979: 20.4 cc. 0.1 *N* AgNO₃. Calcd. for C₉H₇OBr₂: Br, 54.79. Found: Br, 54.73.

2,6-Dibromophenyl Allyl Ether.—2,6-Dibromo-4-nitrophenol was reduced as directed by Möhlau and Uhlmann,¹⁶ and the amino group replaced by hydrogen as follows. One-third of a molecular proportion of the amino compound was dissolved in a mixture of 750 cc. of 95% alcohol and 100 cc. of benzene, after which 50 cc. of concentrated sulfuric acid was added slowly with shaking. This mixture was placed in a suitable flask bearing a Y-tube, one arm of which was connected to a reflux condenser, while the other served for the introduction of sodium nitrite. Fifty grams of the finely powdered salt was slowly added. After reaction was apparently over, the mixture was refluxed for two hours, and then allowed to stand in a warm place for several hours. The product obtained by steam distillation and crystallization from dilute alcohol agrees in properties with that described in the literature. By treatment with excess of allyl bromide it was converted into the ether, which distilled at 132–133° at 10 mm.

Anal. Subs., 0.3423: 23.44 cc. 0.1 *N* AgNO₃. Calcd. for C₉H₇OBr₂: Br, 54.79. Found: Br, 54.74.

¹⁴ Claisen and Eisleb, *Ann.*, **401**, 36 (1913).

¹⁵ This was prepared from pentabromophenol by Kohn and Fink's [*Monatsh.*, **44**, 188 (1923)] method.

¹⁶ Möhlau and Uhlmann, *Ann.*, **289**, 94 (1896).

Pentabromophenyl Allyl Ether.—Pentabromophenol was converted to the ether by treatment with a large excess of allyl bromide as described. Crystallization from petroleum ether (80–100°) gave short colorless needles; m. p. 167–168°.

Anal. Subs., 0.2016: 17.96 cc. 0.1 *N* AgNO₃. Calcd. for C₉H₅OBr₅: Br, 75.61. Found: Br, 75.57.

The β,γ -Dibromo Derivatives.—The above-mentioned compounds were next subjected to the action of excess of bromine as follows. The ether was dissolved in chloroform, finely powdered dried sodium acetate added, the flask placed in an ice-bath and the mixture stirred while there was added gradually slightly more bromine than was required to saturate the side chain and substitute all available positions on the nucleus. The mixture stood for several days, the solvent and excess of bromine were distilled off, water was added to dissolve salts, and the ether extracted with a suitable solvent. The physical constants and analytical data for these products are given in Table III.

TABLE III
PHENYL- β,γ -DIBROMOPROPYL ETHERS

| Substituted phenyl | Formula | Crystal form | Yield, % | M. p., ° C. | Halogen, % Calcd. | % Found |
|---------------------|--|--------------------------------------|----------|---------------------------|-------------------|---------|
| 2,4-Dichloro- | C ₉ H ₅ OCl ₂ Br ₂ | Oil | 95 | Distilled at 188 (10 mm.) | 63.59 | 63.3 |
| 2,3,4,5-Tetrabromo- | C ₉ H ₅ OBr ₆ | Nearly ^a colorless prisms | 97 | 123–124 | 78.68 | 78.68 |
| 2,6-Dibromo- | C ₉ H ₅ OBr ₄ | Colorless needles ^b | 96 | 48–49.5 | 70.77 | 70.60 |
| Pentabromo- | C ₉ H ₅ OBr ₇ | Colorless needles ^c | 94 | 122–123 | 81.27 | 81.29 |

^a Crystallized from acetic acid. ^b Purified with much difficulty, first by distillation and afterward by repeated crystallization from alcohol. ^c Crystallized from ligroin (80–100°). ^d Brown and Beal, *THIS JOURNAL*, 45, 1291 (1923).

Action of Alcoholic Potash on the Ethers.—Weighed portions of the β,γ -dibromopropyl ethers were dissolved in hot alcohol, and an alcoholic solution of potassium hydroxide added. After the first vigorous action was over the mixture was refluxed for one hour,¹⁷ the liquid cooled, acidified with nitric acid, and diluted to a measured volume. Duplicate samples of the solution were withdrawn, boiled with measured volumes of standard silver nitrate solution in excess of that required by the bromide ion present and the unchanged silver salt determined by titration. From the values so obtained the weight of bromine removed by alkali in each case was estimated, and the decomposition percentage calculated. The remainder of the acid liquid was extracted with ether, the extract dried with anhydrous sodium sulfate, the solvent distilled off, and the propargyl ether purified in a suitable way. The results are given in the accompanying table.

Salts of the Ethers.—The silver salts were precipitated as nearly colorless solids by mixing alcoholic solution of silver nitrate and the required ether, as directed by Béhal.¹⁸ The cuprous salts were obtained as yellow solids by pouring alcoholic solutions of the ethers into ammoniacal solution of cuprous chloride, while the mercuric salts were prepared as gray precipitates by the use of Nessler's reagent. Analytical data for these compounds are given in Table V.

¹⁷ When 2,3,4,5-tetrabromophenyl β,γ -dibromo-*n*-propyl ether, described above, was subjected to this treatment, the amount of bromine removed was greater than that corresponding to the loss of two molecular proportions of hydrogen bromide from the side chain, which suggested that some halogen had been lost from the phenyl nucleus, possibly from one of the meta positions. The product was not obtained in the pure form, but it was shown to be an ether, and found to give metallic derivatives.

¹⁸ Béhal, *Ann. chim.*, [6] 15, 423 (1888).

TABLE IV
 PHENYL PROPARGYL ETHERS

| Substituted phenyl | Formula | Crystal form | Yield, % | M. p., °C. | Halogen, ^{d,e} % | |
|-----------------------|---------------|--------------------------------|-------------|------------|---------------------------|-------|
| | | | | | Calcd. | Found |
| 2,4-Dichloro- | $C_6H_4OCl_2$ | ^a | 99 | Liq. | 35.32 | 35.14 |
| 2,4-Dibromo- | $C_6H_4OBr_2$ | Colorless ^b needles | 98 | 65 | 55.17 | 55.04 |
| 2,6-Dibromo- | $C_6H_4OBr_2$ | Colorless ^c needles | 98 | 58-60 | 55.17 | 55.33 |
| 2,4,6-Tribromo- | $C_6H_3OBr_3$ | Colorless ^c needles | 97 | 136-137 | 65.04 | 65.08 |

^a Not obtained in crystalline form. Attempts to distil under reduced pressure caused decomposition. ^b Many recrystallizations from dilute alcohol were required for purification. Attempts to distil under partial vacuum caused much decomposition with a distillate passing over at 135° and 10 mm. Contact with air caused the hot material to char instantly. ^c Crystallized from alcohol. ^d Brown and Beal, Ref. d, Table III. ^e Carius method.

 TABLE V
 SALTS OF PHENYL PROPARGYL ETHERS

| Substituted phenyl | Formula | Halogen, ^a % | |
|-----------------------|------------------------------|-------------------------|-------|
| | | Calcd. | Found |
| 2,4-Dichloro- | $C_6H_4OCl_2Ag \cdot AgNO_3$ | 14.86 | 14.85 |
| 2,4-Dibromo- | $C_6H_4OBr_2Ag \cdot AgNO_3$ | 28.23 | 28.02 |
| | $C_6H_4OBr_2Cu$ | 45.36 | 45.07 |
| | $C_{18}H_{10}O_2Br_4Hg$ | 41.13 | 40.81 |
| 2,6-Dibromo- | $C_6H_4OBr_2Ag \cdot AgNO_3$ | 28.23 | 28.00 |
| 2,4,6-Tribromo- | $C_6H_3OBr_3Ag \cdot AgNO_3$ | 37.16 | 37.14 |
| | $C_6H_3OBr_3Cu$ | 55.61 | 55.31 |
| | $C_{18}H_5O_2Br_6Hg$ | 51.28 | 51.15 |

^a Halogen determined by the Carius method.

Summary and Conclusions

1. The hydrogen bromide evolved in the bromination of phenyl alkyl ethers may split them unless sodium acetate is present. The splitting is most complete when the alkyl group is connected through a secondary or tertiary carbon atom.

2. Phenyl allyl ethers containing two or more bromine atoms in the nucleus could not be rearranged by heat.

3. Under most conditions studied in this work the action of bromine on phenyl allyl ether saturates the side chain and substituted two positions in the phenyl radical.

4. The ethers here studied which have bromine in the β, γ -positions in the side chain react with alcoholic potash and lose two molecular proportions of hydrogen bromide to give the corresponding propargyl compounds. The latter form cuprous, mercuric and silver salts.

5. Further work is in progress in this Laboratory.

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