These findings suggest a generalization to the effect that chlorine (unlike bromine) in the ring of benzyl chlorides is not favorable to ether formation.

Summary

Some monochloro, dichloro and trichloro derivatives of the benzylphenols and benzyl phenyl ethers were prepared.

No ethers were formed in the aluminum chloride condensations where chlorine was present in the nucleus of the benzyl chloride.

In the Claisen reaction the presence of chlorine in the nucleus of the benzyl chloride exerted a retarding influence on the yield of benzylated phenol and its corresponding ether, the greatest retarding effect being exhibited when the chlorine was in the meta position, the next when in the ortho and the least when in the para position.

The yields of the benzylated phenol by the Claisen reaction in case of meta substituted benzyl chloride was increased by adding the corresponding benzyl ether to the reaction mixture.

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Addition Reactions of Unsaturated Alpha-Ketonic Acids. III

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The reaction of bromine with benzalpyruvic acid and with its *p*-methoxy and *o*-methoxy substitution products has been described in earlier papers.[1] The reaction in every case was the same: addition of bromine to the ethylenic linkage of the side chain. The acids themselves, however, as well as their bromination products, differ in certain respects so strikingly that it seemed of value to continue the investigation of these compounds for the purpose of studying the effect of methoxyl groups in different positions in the benzene ring on the reactions of the molecule.

The present paper describes the preparation and reaction with bromine of benzalpyruvic acid in which a methoxyl group is in the meta position to the side chain. This is of interest not only for comparison with other unsaturated α-ketonic acids of this series but particularly in view of the behavior of *m*-methoxycinnamic acid on treatment with bromine. This is described by Davies and Davies[2] as substitution in the ring with no addition to the ethylenic linkage of the side chain. So unusual is this behavior of a cinnamic acid that one is justified in reading the conclusions of Davies and Davies with surprise and even with a certain measure of skepticism. We have repeated these experiments as described by Davies and Davies and also under other conditions of temperature and with several different

(1) Reimer, THIS JOURNAL, **48**, 2454 (1926); Reimer and Howard, *ibid.*, **50**, 2506 (1928).

(2) Davies and Davies, *J. Chem. Soc.*, 602 (1928).

solvents. Our results substantiate those of these authors in every particular. With one molecular proportion of bromine 6-bromo-3-methoxycinnamic acid is formed in quantitative yield. With an excess of bromine a mixture of products results: 6-bromo-3-methoxy-, 4-(or 2)-6-dibromo-3-methoxycinnamic acids and substituted cinnamic acids with bromine undoubtedly also in the side chain. We have been no more successful than Davies and Davies in separating this mixture completely but we have found it possible to prepare *m*-methoxycinnamic acids with bromine in the side chain readily and in quantity from corresponding benzalpyruvic acids. *m*-Methoxybenzalpyruvic acid reacts normally with bromine, a dibromide being formed by addition at the ethylenic linkage. The unsaturated bromo acid obtained from this product by loss of hydrogen bromide gives, on oxidation with hydrogen peroxide, α-bromo-*m*-methoxycinnamic acid. On bromination of this bromocinnamic acid substitution takes place in the ring, α-bromo-6-bromo-3-methoxycinnamic acid being formed. This same compound can be prepared by bromination of β-bromo-*m*-methoxybenzalpyruvic acid and subsequent oxidation of the β-bromo-6-bromo-3-methoxybenzalpyruvic acid thus formed.

In its reaction with bromine, then, *m*-methoxybenzalpyruvic acid differs from *m*-methoxycinnamic acid but is like the other ketonic acids of this series. It most closely resembles the *o*-methoxy isomer although it is not so deeply colored nor so sensitive to reagents nor to light. Like the *o*-methoxy derivative it does not combine with solvents of crystallization, a conspicuous property of benzalpyruvic and *p*-methoxybenzalpyruvic acids; its dibromide is unstable like that of the *o*-methoxy compound and it is somewhat sensitive to light.

Experimental Part

Preparation of *m*-Methoxybenzalpyruvic Acid.—The *m*-methoxybenzaldehyde needed for this preparation was at first prepared by methylation of *m*-hydroxybenzaldehyde according to the directions of Posner.[3] As poor yields were obtained the following modification of the method used by Hodgson and Beard[4] for methylation of bromo-*m*-hydroxy benzaldehydes was used. Fifty grams of *m*-hydroxybenzaldehyde (0.24 mole) was placed in a three-necked flask fitted with return condenser and dropping funnels, a solution of 11 g. of sodium hydroxide in 250 cc. of water was added, the solution brought to the boiling point and 67 g. (0.32 mole) of dimethyl sulfate added rapidly enough to keep the solution boiling. Small amounts of 50% solution of sodium hydroxide were dropped in at frequent intervals to keep the mixture alkaline. When all the dimethyl sulfate had been added the alkaline solution was boiled for one-half hour longer. The oily product was extracted with ether, washed and dried in the usual way. The oil remaining after evaporation of the ether distilled at 230–233° (757 mm.). A purer product was obtained by distillation under reduced pressure. The yields of *m*-methoxybenzaldehyde boiling at 129–130° (30 mm.) were about 70%. The condensation of this aldehyde and pyruvic acid was carried out exactly as described for the

(3) Posner, *J. prakt. Chem.*, [2] **82**, 431 (1910).

(4) Hodgson and Beard, *J. Chem. Soc.*, **127**, 878 (1925).

corresponding condensation with benzaldehyde.[5] The potassium salt, separating in more than 90% yields from the reaction mixture, was washed with methyl alcohol and analyzed.

Anal. Calcd. for $C_{11}H_9O_4K$: K, 15.97. Found: K, 16.18.

From a cooled concentrated solution of the potassium salt, iced dilute hydrochloric acid precipitated a brilliant yellow acid in more than 80% yield. As the compound first precipitates as an oil, it is well to seed the solution with a few crystals of the acid prepared from a small sample of carefully purified potassium salt. The acid is readily soluble in the usual organic solvents. It separates from boiling water in fine yellow needles. A purer product is obtained by using boiling benzene, from which it separates in rosets of fine needles melting at 116–117°.

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64.07; H, 4.85. Found: C, 64.22; H, 5.15.

Oxidation of this acid in sodium carbonate solution, with a slight excess of hydrogen peroxide, gave a 96% yield of *m*-methoxycinnamic acid. The yellow color of the original acid disappeared rapidly and the oxidation was complete in a few hours. From the potassium salt of *m*-methoxybenzalpyruvic acid, by the same procedure, yields of 87% of the cinnamic acid, calculated from the aldehyde used in the condensation, were obtained. This is a far better yield than could be obtained by either the Perkin or the Knoevenagel synthesis of this acid.

The methyl ester of *m*-methoxybenzalpyruvic acid was prepared by dissolving 5 g. of the finely ground pure acid in 30 cc. of methyl alcohol saturated with hydrogen chloride. After two to three minutes the methyl ester crystallized from the solution in long needles of a paler yellow than that of the acid. The same ester is obtained by action of diazomethane in an ethereal solution of the acid. It can be purified by crystallization from a small volume of methyl alcohol to which a few drops of water are added. It melts at 57°.

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65.45; H, 5.45. Found: C, 65.10; H, 5.78.

When 5 g. of acid was dissolved in 30 cc. of warm methyl alcohol saturated with hydrogen chloride and the mixture heated to boiling, no crystals separated from the solution on cooling. The reaction mixture was therefore poured into iced sodium carbonate solution. The heavy yellow oil which separated quickly solidified. The solid was dissolved in hot methyl alcohol and water added until the solution was faintly cloudy. The crystals that separated slowly were of two kinds, the yellow needles of the ester just described and large, clear, almost colorless, compact clumps. These were separated mechanically and repeatedly crystallized from a very small volume of methyl alcohol slightly diluted. The shining colorless crystals separate slowly in characteristic hexagonal prisms, melting at 72°. The compound is not affected by alkalies but is rapidly hydrolyzed to *m*-methoxybenzalpyruvic acid by boiling it in water to which a few drops of sulfuric acid have been added. It is the dimethyl acetal of the yellow ester just described, $CH_3OC_6H_4CH{=}CHC(OCH_3)_2COOCH_3$.

Anal. Calcd. for $C_{14}H_{18}O_5$: C, 63.15; H, 6.76. Found: C, 63.18; H, 7.09.

Repeated attempts to prepare this substance from the ester were futile. It is evidently formed by the action of methyl alcohol and acid at a raised temperature with the ketone group of the acid, the product then esterifying. The yellow ester is formed at the same time. A partial separation of the two compounds may be made by repeated extraction of the mixture with small quantities of cold methyl alcohol, in which the yellow ester is sightly more soluble than the acetal.

The acetal group blocks the reaction of the ethylenic linkage so that the compound does not decolorize an acetone solution of potassium permanganate. This behavior led

(5) Reimer, THIS JOURNAL, **53**, 3147 (1931).

to the expectation that bromine might replace hydrogen of the ring instead of adding to the ethylenic linkage. The product of bromination was a bright yellow oil from which no pure substance could be obtained. Oxidation of this product with a hot solution of potassium permanganate gave a mixture of about equal quantities of *m*-methoxybenzoic and 6-bromo-3-methoxybenzoic acids, showing that the reaction had proceeded to a considerable extent in the direction looked for.

The ethyl ester of *m*-methoxybenzalpyruvic acid was prepared by dissolving the acid in ethyl alcohol saturated with hydrogen chloride. After standing for several hours, the clear solution was poured into iced sodium carbonate solution. The oil formed was extracted with ether, the ethereal solution washed, dried over sodium sulfate and the ether evaporated. The residue was a clear bright yellow oil.

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.67; H, 6.00. Found: C, 66.39; H, 6.16.

No acetal was obtained in this reaction.

Reactions with Bromine

***m*-Methoxybenzalpyruvic Acid Dibromide**, m-$CH_3OC_6H_4CHBrCHBrCOCOOH$.—*m*-Methoxybenzalpyruvic acid was brominated in cooled chloroform solution. The decolorization was rapid and there was no evolution of hydrogen bromide until nearly the end of the reaction. The product separated from the chloroform in a thick paste if moist air was used, or in a semi-solid condition if the chloroform was evaporated in carefully dried air. The fact that this product is oily would seem to indicate a mixture of stereoisomers. The product lost hydrogen bromide so readily that all attempts at purification had to be abandoned.

β-Bromo-*m*-methoxybenzalpyruvic Acid, m-$CH_3OC_6H_4CH{=}CBrCOCOOH$, 166–167°.—This substance is prepared by shaking the oily product of the bromination reaction with cold water. A typical reaction was as follows: the colorless oily bromination product from 8.4 g. of pure *m*-methoxybenzalpyruvic acid was extracted, with vigorous shaking, with about 750-cc. portions of cold water. The liquid was filtered off and the residue further extracted until about 3 liters of water had been used. The clear filtrates gradually became cloudy and on standing overnight deposited a pure white crystalline compound. After another twenty-four hours further quantities of this substance separated from the filtrates. The reaction is evidently slow loss of hydrogen bromide from the dibromide in solution. From the solution were obtained in all about 90% yields of this substance, an unsaturated bromo acid. It is readily soluble in the usual organic solvents except ligroin. The purest samples are obtained from boiling benzene, from which it separates in stiff white needles melting at 166–167°.

Anal. Calcd. $C_{11}H_9O_4Br$: C, 46.31; H, 3.15. Found: C, 46.44; H, 3.43.

The acid dissolved in a small volume of 10% sodium carbonate solution from which, almost instantly, its shining sodium salt crystallized. When warmed or left standing in alkaline solution it slowly decomposed, a fragrant oil, probably a styrene derivative, being formed.

Oxidation of this acid in dilute sodium carbonate solution with potassium permanganate gave a nearly quantitative yield of *m*-methoxybenzoic acid, m. p. 105°, identified by a mixed melting point with this acid prepared by oxidation of *m*-methoxybenzaldehyde, thus proving the bromine to be in the side chain.

The methyl ester of β-bromo-*m*-methoxybenzalpyruvic acid was prepared by the action of an ethereal solution of diazomethane on the acid. It separates from methyl alcohol in fine, flattened needles melting at 95°.

Anal. Calcd. for $C_{12}H_{11}O_4Br$: C, 48.16; H, 3.68. Found: C, 47.83; H, 3.76.

Like the other β-bromobenzalpyruvic acids studied heretofore this ester could not be prepared by action of methyl alcohol saturated with hydrogen chloride.

α-Bromo-*m*-methoxycinnamic Acid, m-$CH_3OC_6H_4CH{=}CBrCOOH$, 122°.—This compound is prepared by oxidation of the bromobenzalpyruvic acid just described. Five grams of this acid was suspended in 100 cc. of water and sufficient 10% sodium carbonate solution added to bring the acid into solution with vigorous shaking. Forty cc. of hydrogen peroxide (13 volumes) was now added, the mixture frequently shaken and allowed to stand at room temperature overnight. A second portion of 40 cc. of hydrogen peroxide was then added and the solution left for twenty-four hours. This long standing was necessary as the oxidation was found to proceed with unusual slowness. A slight cloudiness, probably due to the corresponding styrene derivative, was removed by repeated filtration, the solution cooled to 0° and dilute hydrochloric acid added, drop by drop, with vigorous stirring. The milky oil precipitating gradually solidified. The acid is readily soluble in methyl and ethyl alcohols, glacial acetic acid and chloroform, less readily in benzene. It can be purified by repeated crystallization from petroleum ether (b. p. 80–100°). By means of this solvent it can be separated from any admixture of the benzalpyruvic acid which may have escaped oxidation. It separates from boiling water in stiff fine needles of a faint cream color, melting at 122°. An 84% yield was obtained.

Anal. Calcd. for $C_{10}H_9O_3Br$: C, 46.70; H, 3.50. Found: C, 47.04; H, 3.82.

The acid is interesting in that it is not possible to obtain it from *m*-methoxycinnamic acid nor by condensation reaction.

The methyl ester was prepared by treatment of an ethereal solution of the acid with diazomethane. It is a clear pale yellow oil.

Anal. Calcd. $C_{11}H_{11}O_3Br$: C, 48.71; H, 4.06. Found: C, 48.53; H, 4.15.

α-Bromo-6-bromo-3-methoxycinnamic Acid, $\begin{matrix}3\text{-}CH_3O\\6\text{-}Br\end{matrix}\!\!\rangle C_6H_3CH{=}CBrCOOH$, 167–169°.—This acid is prepared by treating the cinnamic acid just described with one molecular proportion of bromine in cooled chloroform solution. The decolorization of the bromine proceeded slowly with copious evolution of hydrogen bromide. When all the bromine had been added, the solution was shaken vigorously until decolorization was complete. A crystalline product separated, which with more of the same substance crystallizing on evaporation of the solvent gave a 93% yield of product. The compound separates from boiling benzene in fine brittle needles very faintly cream-colored. It softens slightly at 163° and melts at 167–169°. It is readily soluble in cold methyl and ethyl alcohols and acetone and in hot chloroform and benzene. It is strongly triboelectric.

Anal. Calcd. $C_{10}H_8O_3Br_2$: C, 35.71; H, 2.38. Found: C, 35.77; H, 2.53.

On oxidation of this acid with potassium permanganate 6-bromo-3-methoxybenzoic acid was obtained.

The methyl ester separates in quantitative yield when the acid is warmed with methyl alcohol saturated with hydrogen chloride. It crystallizes from a small volume of hot methyl alcohol to which a few drops of water have been added in stiff, colorless needles melting at 79°.

Anal. Calcd. for $C_{11}H_{10}O_3Br_2$: C, 37.72; H, 2.86. Found: C, 37.80; H, 3.08.

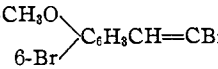
Reaction with Excess of Bromine

α-Bromo-6-bromo-3-methoxystyrene, $\begin{matrix}3\text{-}CH_3O\\6\text{-}Br\end{matrix}\!\!\rangle C_6H_3CH{=}CHBr$, 99°.—*m*-Methoxybenzalpyruvic acid was treated with one molecular proportion of bromine as previously described and then a second molecular proportion of bromine added slowly. After twenty-four hours the solution was practically colorless. On evaporation of the

solvent a yellowish, heavy oil was left. As no pure substance could be obtained from this it was dissolved in methyl alcohol, excess of potassium acetate added and the mixture boiled for one hour. The potassium bromide which had been separated was then filtered out, the alcohol distilled off, the product poured into water and the oily mixture extracted with ether. The clear yellow oil left on evaporation of the ether slowly deposited pale yellow crystals which were filtered out, washed with methyl alcohol and crystallized from a small volume of methyl alcohol. The substance separates in firm pale yellow stocky crystals melting at 99°. It is not soluble in sodium carbonate solution. It is readily soluble in benzene, acetone and ether, less readily in alcohol. Its acetone solution immediately decolorizes potassium permanganate solution. The properties are those of a styrene derivative.

Anal. Calcd. for $C_9H_8OBr_2$: C, 37.00; H, 2.75. Found: C, 37.24; H, 3.04.

From the yellow oil remaining no pure substance has been obtained.

β-Bromo-6-bromo-3-methoxybenzalpyruvic Acid, 

COOH.—Three grams of β-bromo-3-methoxybenzalpyruvic acid was added to 60 cc. of dry chloroform and 0.49 cc. of bromine added slowly. The bromine was decolorized with extreme slowness. After forty-eight hours of standing at room temperature and frequent shaking the solution was colorless. On evaporation of the solvent a colorless oil was left which gradually solidified. The oil was washed with small quantities of benzene. It was then dissolved in a small volume of cold chloroform to which an equal volume of low-boiling petroleum ether (30–60°) was added. The solution deposited colorless fine needles melting when pure at 137–139°. The substance is readily soluble in the usual organic solvents except low-boiling petroleum ether (30–60°). It may be crystallized from benzene. It readily decomposes on standing in solution.

Anal. Calcd. for $C_{11}H_8O_4Br_2$: C, 36.27; H, 2.20. Found: C, 36.33; H, 2.74.

On treatment in alkaline solution with excess of hydrogen peroxide the substance was very slowly oxidized to α-bromo-6-bromo-3-methoxycinnamic acid.

The methyl ester of this dibromomethoxybenzalpyruvic acid was prepared from an ethereal solution of the acid and diazomethane. It separates from ether in fine needles, from methyl alcohol in shining, stiff needles melting at 143°.

Anal. Calcd. for $C_{12}H_{10}O_4Br_2$: C, 38.10; H, 2.65. Found: C, 38.37; H, 2.31.

Reaction with Concentrated Sulfuric Acid.—When a sample of *m*-methoxybenzalpyruvic acid was stirred with a few drops of concentrated sulfuric acid, the yellow acid gave a dark reddish-brown solution changing rapidly to deep cherry-red. This color persists for many hours. The bromine derivatives of this acid gave none of the brilliant color reactions with sulfuric acid characteristic of the corresponding para- and ortho-methoxybromo compounds. The colors were pale yellow changing to brown with a faint pinkish tinge.

Summary

m-Methoxybenzalpyruvic acid and its reaction with bromine have been studied for the purpose of comparison with isomeric methoxybenzalpyruvic acids and with *m*-methoxycinnamic acid.

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