following procedure. A mixture of 10 g. of ethyl β-methylaminopropionate and 8 g. of γ-chloropropyl benzoate was heated for one hour in an oil-bath at 140–150°. The mixture was allowed to cool and the upper layer of tertiary amine dissolved in 100 cc. of absolute ether. The ether layer was separated from the lower hydrochloride layer by decantation. The tertiary amine was precipitated as the hydrochloride from the ether solution with hydrogen chloride. The ether was poured off and the hydrochloride recrystallized twice from a mixture of alcohol and ether. It melted at 103–105°; yield, 6 g.

Analyses. Subs., 0.2068, 0.2144: AgCl, 0.0880, 0.0920. Calc. for $C_{16}H_{24}O_4NCl$: Cl, 10.77. Found: 10.52, 10.63.

Summary

1. The synthesis of some 1,3,4-trisubstituted piperidines has been effected and their properties have been reported.
2. 1-Methyl-3-carbo-ethoxy-4-piperidyl benzoate is of particular interest in that it has the structure of the piperidine portion of the cocaine molecule. It is equally as toxic as cocaine and less efficient in producing anesthesia.
3. The open-chain compound, γ-(methyl β-carbo-ethoxy-ethyl)aminopropyl benzoate, which represents the structure of the piperidine portion of the cocaine molecule with the ring opened between the carbons carrying the substituent groups, has been prepared. It has about one-third the toxicity of cocaine, but produces practically no anesthesia when applied to the rabbit's cornea.

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THE ADDITION OF METHYL HYPOBROMITE TO CERTAIN ETHYLENE DERIVATIVES

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Received May 1, 1924 Published July 7, 1924

As a result of several investigations of the last few years,[1] a very satisfactory method has been developed for adding hypochlorous and hypobromous acids to ethylene and ethylene derivatives. This method consists in rapidly stirring the organic compound with water into which a current of chlorine or bromine vapor is passed; the hypohalogen acid formed by the reaction of the halogen with the water rapidly adds to the double linkage of the unsaturated compound and forms the chloro- or bromohydrin. In connection with an attempt to synthesize certain substituted ethylene oxides, we tried to utilize this method for the preparation of bromohydrins from certain unsaturated compounds of high molecular weight which were practically insoluble in water. Probably because of the sparing solubility no satisfactory results could be obtained and we

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[1] Read and Williams, *J. Chem. Soc.*, **111**, 240 (1917); **117**, 359 (1920). Read and Hook, *ibid.*, **117**, 1214 (1920). Gomberg, This Journal, **41**, 1414 (1919).

decided therefore, to investigate the feasibility of using a mixture of methyl alcohol and water. In order to determine whether or not the reaction would proceed under these new conditions, a number of experiments were performed with cinnamic acid which readily adds hypobromous acid according to Read and Williams' procedure.[2] To our surprise, considerable amounts of β-methoxy-α-bromo-phenylpropionic acid were formed apparently by the addition of methyl hypobromite to the ethylene linkage; cinnamic acid dibromide was also produced as would be expected. Similar results were obtained with benzalacetophenone.

Only one case of the addition of an ester of hypobromous acid appears to be on record, although alkyl hypo-iodites have been frequently added to ethylene derivatives by treating the unsaturated compound with the appropriate alcohol, iodine and mercuric oxide.[3] By the action of bromine on methyl alcohol solutions of quinizarin and alizarin, Dimroth[4] obtained substances which were apparently formed by the addition of methyl hypobromite to the diquinone first produced by the oxidizing action of the bromine. Although this case is complicated by such oxidation, in all probability the reaction in this instance and in those cases recorded in the present paper is essentially as follows: $Br_2 + CH_3OH \rightleftharpoons CH_3OBr + HBr$; $>C = C< + CH_3OBr \longrightarrow >COCH_3CBr<$.

We operated at 0° and introduced the bromine vapor at such a rate that only a faint color was visible. The reaction is slow and the rate of decolorization of the bromine is within certain limits dependent on the amount of water present. In 90% or stronger alcohol the reaction is too slow to be practical, while in 60% alcohol it is very rapid; we confined our experiments to 85–88% alcohol and have not yet determined whether different products are obtained in a solvent containing more water.

Reaction with Cinnamic Acid

Eleven g. of cinnamic acid was dissolved in 234 cc. of methyl alcohol and 41 cc. of water (15%) added. The solution was stirred very vigorously and cooled in ice while a slow stream of air and bromine vapor was introduced. This was accomplished by placing the requisite quantity of bromine (13 g.) in a side-arm test-tube and blowing a slow current of air through an inlet tube extending to a position just above the level of the liquid bromine; a suitable delivery tube dipping into the alcoholic solution was connected with the side arm of the test-tube. The air was regulated so that the solution was slightly orange, indicating a slight excess of free bromine. The absorption of the bromine was very slow, especially towards the end of the reaction, many hours being required to complete the reaction. After all the bromine had been thus introduced and the solution was finally colorless, the methyl alcohol was distilled and the residue diluted with water. The oil that first separated soon solidified and was filtered off, washed with

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[2] Read and Andrews, *J. Chem. Soc.*, **119**, 1774 (1921).

[3] Brunel, *Ann. chim. phys.*, [8] **6**, 217 (1905). Tiffeneau, *Bull. soc. chim.*, [4] **1**, 1205 (1907); *Compt. rend.*, **145**, 811 (1907). Daufresne, *Compt. rend.*, **145**, 875 (1907). Beaufour, *Bull. soc. chim.*, [4] **13**, 354 (1913). Rességuier, *ibid.*, [4] **15**, 182 (1914).

[4] Dimroth, Schultze and Heinze, *Ber.*, **54**, 3035 (1921).

water and dried; it weighed 17 g. By extraction with petroleum ether and ether, 1.9 g. of oil resembling bromostyrene was obtained. The residue melted at 155–165° and was obviously a mixture. Several crystallizations from chloroform yielded a substance melting at 184–185°. We were unable to purify this material further by crystallization, but the analyses, including a methoxy determination, indicated that it was a mixture of a methoxybromo compound and the dibromide of cinnamic acid. The methoxybromo compound was finally obtained in a pure condition by dissolving the material in sodium carbonate and heating the solution to the boiling point for ten minutes. The dibromide was decomposed by this treatment forming bromostyrene which was removed with ether, the methoxybromo compound being then obtained by acidification of the alkaline solution. After recrystallization it melted at 182–183°; tests showed that it was not affected by heating with sodium carbonate solution for a short time.

Analyses. Calc. for $C_{10}H_{11}O_3Br$: C, 46.3; H, 4.3; Br, 30.9. Found: C, 46.1, 45.7; H, 4.9, 4.7; Br, 31.2.

Methoxyl Group (Zeisel method). Subs., 0.2445: AgI, 0.2201. Found: 0.2225.

Since the addition of hypobromous acid to cinnamic acid yields α-bromo-β-hydroxy-phenylpropionic acid one would expect that the methoxybromo compound formed in our reaction would be the β-methoxy compound, $C_6H_5CHOCH_3CHBrCOOH$. The two possible stereo-isomeric forms of this acid have recently been described by Schrauth[5] who gives the melting point as 165–170° and 126–127°. The first was obtained by the addition of mercuric acetate to cinnamic acid and the replacement of the mercury by bromine, the second by a similar reaction with cinnamic ester. The mode of addition of the mercury salt was established with a number of α,β-unsaturated acids by converting the bromomethoxy compound into the known β-hydroxy-α-amino acid. Although Schrauth's melting point of his high-melting isomer was considerably lower than that of our compound, it seemed possible that his compound might have been impure, in view of the fact that it melted over a range of 5°. We prepared, therefore, a bromomethoxy compound by adding mercuric acetate to cinnamic acid and treating the mercury compound with bromine. The product was identical with the substance prepared by the action of bromine and methyl alcohol on cinnamic acid. The substance is, therefore, α-bromo-β-methoxy-phenylpropionic acid and the melting point is 182–183°.

Seven g. of cinnamic acid was dissolved in 75 cc. of methyl alcohol and treated with a solution of 16.5 g. of mercuric acetate in 60 cc. of methyl alcohol. When the mercuric acetate was added to the cinnamic acid solution, a heavy colorless precipitate immediately separated. By warming the mixture on the water-bath a clear solution was obtained. After about 12 hours at room temperature, most of the material had separated from the solution as a colorless solid. The solid weighed 16 g. and melted at 208–210° with evolution of gas.

Three g. of this compound, melting at 208–210°, was suspended in 25 cc. of absolute methyl alcohol and to this was added 1.3 g. of bromine. The reaction mixture was shaken for about 15 minutes and then allowed to stand at room temperature until the bromine was decolorized. Practically all of the material finally dissolved. The solvent was evaporated, the residue dissolved in ether and the solution thoroughly extracted with

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[5] Schrauth and Geller, *Ber.*, **55**, 2783 (1922).

concd. aqueous potassium bromide and finally with water. Evaporation of the solvent yielded colorless crystals. Recrystallization from chloroform gave a substance melting at 182–183°. The yield was 0.3 g. of substance melting at 182–183°; 0.2 g. of material melting at 160–170°; and 0.8 g. of residue from the crystallization, which contained a considerable amount of crystals. A mixed melting point of the compound which melted at 182–183°, with that prepared from cinnamic acid, methyl alcohol and bromine as described above, showed that they were identical.

The addition of methyl hypobromite to benzalacetophenone was accomplished by using the same procedure that we had found successful with cinnamic acid. The product was identical with α-bromo-β-methoxy-β-phenylpropiophenone ($C_6H_5CHOCH_3CHBrCOC_6H_5$) prepared by Middleton[6] by the action of mercuric acetate on benzalacetophenone followed by treatment with bromine.

Reaction of Benzalacetophenone with Bromine and Methyl Alcohol

Four g. of benzalacetophenone was dissolved in 158 cc. of aqueous methyl alcohol, containing 140 cc. of absolute methyl alcohol and 18 cc. of water. Bromine vapor was passed into the solution, which was kept at 0–5°, at a rate sufficient to maintain a slight yellow color. After the solution had ceased to absorb bromine, the colorless solid, which had separated, was filtered off and dried. It weighed 2.3 g. and melted at 118–130°. The filtrate was concentrated by distillation to a volume of about 50 cc. and the oil which had separated soon crystallized. It weighed 2.1 g. and melted at 63–75°. The remainder of the solution was evaporated to a volume of about 25 cc. and then extracted with ether; 0.6 g. of oil containing some crystals was thus obtained.

The bromomethoxy derivative of benzalacetophenone was separated from the dibromide by a fractional crystallization from methyl alcohol; about 0.7 g. of material, principally the dibromide, and 0.8 g. of the methoxybromo compound, melting at 74–76°, were obtained. Some intermediate portions containing chiefly the methoxybromo compound also resulted and about 1.3 g. of an oil. The identity of the substance melting at 74–76° as α-bromo-β-methoxy-β-phenylpropiophenone was established by mixed-melting-point determinations with the compound synthesized by Middleton's procedure which melted at 75–76°.

We are planning to continue this investigation with special reference to determining whether or not the esters of hypochlorous acid may be added to ethylene derivatives by a similar procedure.

Summary

The action of bromine on a methyl alcohol solution of cinnamic acid, containing 15% of water, results in the formation of cinnamic acid dibromide and α-bromo-β-methoxy-phenylpropionic acid; from benzalacetophenone, α-bromo-β-methoxy-β-phenylpropiophenone can be prepared. The reaction apparently involves the formation of methyl hypobromite which adds to the double linkage of the unsaturated compound.

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[6] Middleton, This Journal, **45**, 2763 (1923).