The dimer (100 mg.) was dissolved in acetic acid (8 cc.) containing hydrobromic acid (8 cc., 48%), and the solution was boiled for twenty minutes. The mixture rapidly became dark and no pure product could be isolated from it.

Dithymoquinone (100 mg.) in ether (30 cc.) was shaken with a solution of sodium hydrosulfite (2 g.) in water (20 cc.) until the color was discharged (forty minutes). From the ether layer there was isolated thymohydroquinone (100 mg.), m. p., and mixed m. p., 138–141°. Reduction of thymoquinone (100 mg.) by exactly the same procedure was complete in thirty seconds; the hydroquinone melted at 142°.

A solution of ferric chloride hexahydrate (0.62 g.) in ethanol (20 cc.) was added to a solution of dithymoquinone (150 mg.) in ethanol (20 cc.). The mixture was heated (steam-bath) for thirty minutes and then poured into water. The yellow precipitate (140 mg.) was unchanged dimer, m. p., and mixed m. p., 196–199°.

Thymoquinone (1 g., m. p., 45–47°) was dissolved in warm ethanol (15 cc.) and two drops of aqueous potassium hydroxide (15%) was added. The solution immediately became dark; it was allowed to stand for four hours at room temperature. No precipitate formed, even when the solution was cooled to 0°. Water was added, the mixture was cooled, and thymoquinone (0.22 g.) was recovered. No other product could be isolated; no dimer was formed.

Summary

1. Dithymoquinone, the dimer of thymoquinone, is not a *p*-hydroxychroman analogous to diduroquinone.

2. The absorption spectra of thymoquinone and dithymoquinone have been measured.

3. Two structures for dithymoquinone merit consideration. One, V, represents the substance as a hexahydroanthracene derivative containing two tertiary hydroxyl groups and two carbonyl groups. The other structure, VI, represents the substance as a cyclobutane derivative containing four carbonyl groups and no hydroxyl groups, formed in a manner analogous to the dimerization of cinnamic acid and certain coumarins.

4. These two structures are discussed in the light of present chemical knowledge concerning dithymoquinone. Although neither structure is in accord with all of the known facts, structure VI is the more satisfactory of the two.

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[CONTRIBUTION FROM THE LABORATORIES OF W. J. BUSH & CO., LTD.]

A New Synthesis of α-Bromoaldehydes

BY PAUL Z. BEDOUKIAN

Methods of preparation of α-bromoaldehydes that have been reported involve protection of the carbonyl group followed by direct bromination. Some of these methods suffer from the disadvantage of low yields and limited applicability[1] and others from drastic and lengthy procedures.[2]

All are based upon a replacement reaction, and it was thought that if the bromination could be carried out as an addition reaction, a simpler method resulting in higher yields might be expected.

It is well known that enols add bromine very rapidly and although aldehydes do not exist in enolic form in appreciable quantities, it is possible to prepare stable enol acetates[3] by boiling aldehydes with acetic anhydride in the presence of a catalyst. It was expected that addition of bromine to the double bond of an enol acetate would take place rapidly and because of the presence of a halogen and an ester grouping on the same carbon atom, the resulting compound would undergo alcoholysis with great facility. Such compounds would yield bromoacetals on treatment with alcohol. Filachione[4] has reported the synthesis of bromoacetaldehyde acetal by brominating vinyl acetate in alcohol at low temperatures. It was realized that vinyl acetate is in effect the enol acetate of acetaldehyde. Since higher aldehydes containing an α-hydrogen are readily converted to enol acetates, it seemed desirable to determine whether they would react with bromine in a similar manner to give bromoaldehydes. The present paper is a report of the results of this work.

Isobutyraldehyde, heptaldehyde and phenylacetaldehyde were chosen for this work. The enol acetates were prepared in the usual manner by boiling with acetic anhydride and potassium acetate. The yields of enol acetates varied according to the nature of the aldehyde. The balance of the products consisted largely of the unreacted aldehyde and aldehyde diacetate which may be hydrolyzed to the original aldehyde by boiling with water or distilling at atmospheric pressure.[5]

It was found that addition of theoretical quantities of bromine to the enol acetate proceeded rapidly and smoothly in cold carbon tetrachloride solution. Upon adding excess methyl alcohol (99.5–100%) to the brominated mixture and allowing it to stand two or three days, dimethyl acetals of α-bromoaldehydes were obtained in 75–80% yields. When highly purified, these acetals were found to be stable, but slight impurities, especially traces of acids, caused decomposition and darkening. Hydrolysis of dimethyl acetals

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(1) Franke, *Ann.*, **351**, 423 (1907); Dworzak and Pfifferling, *Monatsh.*, **48**, 251 (1927); Dworzak and Enenkel, *ibid.*, **50**, 449 (1928); Dworzak and Pierri, *ibid.*, **52**, 141 (1929); Dworzak and Prodinger, *ibid.*, **53** to **54**, 588 (1929).

(2) Kirrmann, *Compt. rend.*, **184**, 525 (1927); *Ann. chim.*, [10] **11**, 223 (1929); Madinaveitia and Puyal, *Anal. soc. españ. fis. quim.*, **16**, 329 (1918); *C. A.*, **13**, 2677 (1919).

(3) Semmler, *Ber.*, **42**, 1161 (1909).

(4) Filachione, THIS JOURNAL, **61**, 1705 (1939). See also McElvain and Kundiger, "Organic Syntheses," **23**, 8 (1943).

(5) Wegscheider and Späth, *Monatsh.*, **30**, 825 (1909).

by boiling with acids gave α-bromoaldehydes in various yields (25–95%).

The reactions may be represented as follows

$$\begin{tikzcd}
\mathrm{RCH_2CHO + Ac_2O(KAc)} \arrow[r] & \mathrm{RCH{=}CHOCOCH_3 + CH_3COOH} \arrow[d, "\mathrm{Br_2}"', "\mathrm{(In\ CCl_4)}"] \\
\mathrm{CH_3OCOCH_3 + HBr + RCHBrCH(OMe)_2} & \mathrm{RCHBrCHBrOCOCH_3} \arrow[l, "\mathrm{MeOH}"']
\end{tikzcd}$$

Since the formation of enol acetates is a characteristic behavior of aldehydes having an α-hydrogen, the method developed constitutes a practical and efficient synthesis of saturated α-bromoaldehyde acetals. The procedures described have been tried and found to give excellent yields with the enol acetates of a low boiling aldehyde (acetaldehyde),[6] a branched chain aldehyde (isobutyraldehyde), a high boiling aldehyde (heptaldehyde) and the lowest aromatic aldehyde having an α-hydrogen (phenylacetaldehyde).

The possibility of the application of this method to the synthesis of α-bromoketones is being investigated at present.

Experimental Part

Isobutyraldehyde

Preparation of Enol Acetate.—Commercial isobutyraldehyde was distilled through a 20-cm. Vigreux column and the fraction boiling at 61–63° was considered to be pure isobutyraldehyde. A mixture of 72 g. (1 mole) of isobutyraldehyde, 153 g. (1.5 moles) of acetic anhydride, and 12 g. (0.125 mole) of crystalline potassium acetate was refluxed in an oil-bath for eight hours, using a long condenser to prevent the escape of isobutyraldehyde. The reaction mixture was then allowed to cool, excess acid washed out several times with water and finally with 5% sodium carbonate. The resultant oil was dried over sodium sulfate and distilled through the Vigreux column. The fraction boiling at 122–128° was taken as enol acetate of isobutyraldehyde; yield 40–45 g. (35–40%). Pure enol acetate of isobutyraldehyde b. p. 124–126°, $n^{25}\mathrm{D}$ 1.4178; d^{25}_4, 0.9297; saponification number 497, *i. e.*, ester content 101%.

Anal.[7] Calcd. for $C_6H_{10}O_2$: C, 63.11; H, 8.83. Found: C, 63.66; H, 8.51.

Bromination of Enol Acetate.—A solution of 57 g. (0.5 mole) of isobutyraldehyde enol acetate and 150 ml. of carbon tetrachloride was cooled in an ice-bath and bromine, diluted with an equal volume of carbon tetrachloride, was added slowly from a buret, with constant shaking, care being taken not to allow the temperature of the mixture to rise above 10°. The addition took about twenty minutes and the end-point reached when the theoretical amount was absorbed and bromine no longer decolorized.

Formation of Dimethyl Acetal.—To the above brominated mixture was added 200 ml. of methyl alcohol (99.5–100%), with shaking and cooling. The mixture was allowed to stand for two days with occasional shaking and then diluted with 600 ml. of water. The separated oil was dried and fractionated in the presence of a small amount of sodium carbonate. The fraction boiling at 52–54° (10 mm.) was taken as pure α-bromoisobutyraldehyde dimethyl acetal; yield 75 g. (76%), $n^{25}\mathrm{D}$ 1.4480; d^{25}_4 1.2792. Zeisel and Daniek[8] have reported preparation of α-bromoisobutyraldehyde dimethyl acetal but give no analyses or physical constants.

Anal. Calcd. for $C_6H_{13}O_2Br$: C, 36.54; H, 6.65; Br, 40.59. Found: C, 36.46; H, 6.58; Br, 40.20.

Hydrolysis of Acetal.—A mixture of 40 g. of bromoacetal and 40 ml. of concentrated hydrochloric acid was gently boiled in a distillation flask. Impure α-bromoisobutyraldehyde distilled along with water and methyl alcohol. Redistillation gave pure α-bromoisobutyraldehyde, b. p. 113–115°; $n^{25}\mathrm{D}$ 1.4518; d^{25}_4 1.383; yield, 18 g. (60%), 2,4-dinitrophenylhydrazone, m. p. 116°. Franke[9] reports α-bromoisobutyraldehyde b. p. 113° (750 mm.) and *d* 1.555.

Anal. of 2,4-dinitrophenylhydrazone, $C_{10}H_{11}O_4BrN_4$: Calcd. N, 16.92. Found: N, 17.10.

Heptaldehyde

Heptaldehyde Enol Acetate.—Commercial heptaldehyde was distilled through a 20-cm. Vigreux column and the fraction boiling at 151.5–153.5° was considered to be pure heptaldehyde. A mixture of 171 g. (1.5 moles) of heptaldehyde, 360 g. (3.5 moles) of acetic anhydride, and 24.5 g. (0.25 mole) of crystalline potassium acetate was refluxed in an oil-bath kept at 155–160° for one hour. The reaction mixture was then allowed to cool and excess acid washed out several times with water and finally with 5% sodium carbonate solution. The resultant oil was dried over sodium sulfate and fractionated through a three-foot Whitmore-Fenske column packed with glass helices. The fraction boiling at 88–90° (17 mm.) was taken as pure enol acetate, $n^{25}\mathrm{D}$ 1.4303; d^{25}_4 0.8826; yield, 111 g. (47%). Semmler[3] reports 50% yield and gives the following constants for this enol acetate: b. p. 76–79° (10 mm.), d_{20} 0.888, n_D 1.43258.

Bromination of Enol Acetate.—A solution of 156 g. (1 mole) of enol acetate and 200 ml. of carbon tetrachloride was cooled in an ice-bath and bromine, diluted with an equal volume of carbon tetrachloride, was added slowly with constant shaking, care being taken not to allow the temperature of the mixture to rise above 10°. The addition took about twenty minutes and the end-point was reached when the theoretical amount was absorbed and the bromine no longer decolorized.

Formation of Dimethyl Acetal.—To the above brominated mixture was added 500 ml. of methyl alcohol (99.5–100%), with shaking and cooling. The mixture was allowed to stand for two days with occasional shaking and was then diluted with 1.5 l. of water. The separated oil was dried and fractionated in the presence of a small amount of sodium carbonate. The fraction boiling at 117–119° (17 mm.) was collected as pure α-bromoheptaldehyde dimethyl acetal, $n^{25}\mathrm{D}$ 1.4520; d^{25}_4 1.195; yield, 186 g. (78%).

Anal. Calcd. for $C_9H_{19}O_2Br$: C, 45.19; H, 8.01; Br, 33.43. Found: C, 44.78; H, 7.90; Br, 33.21.

Hydrolysis of Acetal.—A mixture of 30 g. of dimethyl acetal and 25 ml. of concentrated hydrochloric acid was boiled gently and the methyl alcohol liberated allowed to distil off. When the vapor temperature reached 99°, heating was stopped and the residue and distillate diluted with water. The somewhat brownish oil obtained consisted of slightly impure α-bromoheptaldehyde which on distillation yielded pure α-bromoheptaldehyde, 23.5 g. (95%); b. p. 90° (17 mm.), $n^{25}\mathrm{D}$ 1.4600; d^{25}_4 1.230; 2,4-dinitrophenylhydrazone m. p. 106°. Kirrmann[2] reported the following constants for α-bromoheptaldehyde: b. p. 80° (11 mm.), d_{20} 1.256, n_D 1.4652.

Anal. of 2,4-dinitrophenylhydrazone $C_{13}H_{17}O_4BrN_4$: Calcd. N, 15.01. Found: N, 14.98.

Phenylacetaldehyde

Phenylacetaldehyde Enol Acetate.—Commercial phenylacetaldehyde which usually contains considerable polymerized material was distilled and the fraction boiling at

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(6) Bedoukian, This Journal, **66**, 651 (1944).

(7) The author is greatly indebted for the analyses to Mrs. D. Jewitt and Dr. G. A. Grant, of the Research Laboratories of Ayerst, McKenna and Harrison, Montreal, Canada.

(8) Zeisel and Daniek, *Monatsh.*, **30**, 727 (1909).

(9) Franke, *ibid.*, **21**, 211 (1900).

75–76° (10 mm.) was taken as the pure aldehyde. A mixture of 480 g. (4 moles) of freshly distilled phenylacetaldehyde, 720 g. (7 moles) of acetic anhydride, and 73.5 g. (0.75 mole) of crystalline potassium acetate was refluxed in an oil-bath kept at 160° for two hours. The reaction mixture was then allowed to cool and excess acid washed out several times with water and finally with 5% sodium carbonate solution. The resultant oil was dried over sodium sulfate and distilled. The fraction boiling at 113–117° (10 mm.) was taken as the enol acetate of phenylacetaldehyde; yield 390 g. (61%): redistilled enol acetate, b. p. 113–115° (10 mm.), n^{25}_D 1.550; d^{25}_4 1.061. Semmler[10] working with 10 g. of phenylacetaldehyde reported the following constants: b. p. 119–21 (10 mm.), d_{20} 1.065, n_D 1.5483, and yield of enol acetate, 80%.

Bromination of Enol Acetate.—A solution of 80.5 g. (0.5 mole) of enol acetate and 200 ml. of carbon tetrachloride was cooled in an ice-bath and bromine diluted with an equal volume of carbon tetrachloride was added slowly with constant shaking, care being taken not to allow the temperature to rise above 10°. The theoretical amount of bromine was absorbed in about thirty minutes.

Formation of Dimethyl Acetal.—To the above brominated mixture was added 200 ml. of methyl alcohol (99.5–100%) with shaking and cooling. The mixture was allowed to stand for two days with occasional shaking, and then diluted with 1 l. of water. The separated oil was dried and fractionated in the presence of a small amount of sodium carbonate. The fraction boiling at 130–135° (10 mm.) was taken as dimethyl acetal; yield, 202 g. (82%). Redistilled α-bromophenylacetaldehyde dimethyl acetal, b. p. 133–135° (10 mm.), n^{25}_D 1.5395; d^{25}_4 1.343.

Anal. Calcd. for $C_{10}H_{13}O_2Br$: C, 48.96; H, 5.34; Br, 32.64. Found: C, 48.76; H, 5.28; Br, 32.40.

Hydrolysis of Acetal.—Considerable difficulty was experienced in hydrolyzing the acetal, since the liberated aldehyde polymerized rapidly on heating. The yields varied with experimental conditions but in no case were they higher than 25%. On gently heating a mixture of 24.5 g. (0.1 mole) of the acetal with 25 ml. of 50% citric acid for fifteen minutes and allowing the liberated methyl alcohol to distil off, a partially hydrolyzed oil was obtained. This, upon distillation under vacuum with a small quantity of sodium carbonate, gave about 5 g. (25%) of α-bromophenylacetaldehyde, b. p. 108–9° (10 mm.), n^{25}_D 1.5900; d^{25}_4 1.521; 2,4-dinitrophenylhydrazone, m. p. 139°.

Anal. of α-bromophenylacetaldehyde, C_8H_7BrO: Calcd., C, 48.24; H, 3.54; Br, 40.15. Found: C, 48.76; H, 3.85; Br, 39.51.

Anal. of 2,4-dinitrophenylhydrazone, $C_{14}H_{11}BrO_4N_4$: Calcd., N, 14.78. Found: N, 14.72.

Summary

A general method for the synthesis of α-bromoaldehyde acetals has been developed, based upon the bromination of enol acetates with subsequent reaction of the brominated product with methyl alcohol. The method has the advantage of simplicity and higher yields as compared with previously reported syntheses.

Isobutyraldehyde, heptaldehyde and phenylacetaldehyde were considered representative of various types of aldehydes and were chosen to test the general applicability of this procedure The yield of enol acetates ranged from 40–60%, and the α-bromoaldehyde dimethyl acetals were obtained from these in 75–80% yields. Hydrolysis of acetals gave α-bromoaldehydes of varying yields (25–95%).

During the course of this investigation, the following new compounds were prepared in pure state and their constants determined: enol acetate of isobutyraldehyde, α-bromoheptaldehyde dimethyl acetal, α-bromophenylacetaldehyde dimethyl acetal, α-bromophenylacetaldehyde, and the 2,4-dinitrophenylhydrazones of α-bromoisobutyraldehyde, α-bromoheptaldehyde and α-bromophenylacetaldehyde.

MONTREAL, CANADA RECEIVED NOVEMBER 24, 1943

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[10] Semmler, *Ber.*, **42**, 584 (1909).

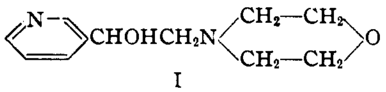
[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Amino Alcohol Studies. 3-Piperidyl Derivatives

BY ALFRED BURGER, ROBERT W. ALFRIEND[1] AND ADOLPH J. DEINET

In the course of investigations of amino alcohols in saturated cyclic systems, we planned to prepare a number of such 3-substituted derivatives of piperidine. This work had to be interrupted for external reasons, and we are reporting our method for the synthesis of such compounds.

3-Diazoacetylpyridine, prepared by a modification of the method of Dornow,[2] reacted with hydrobromic acid in ether to yield 3-bromoacetylpyridine hydrobromide which was converted to the corresponding morpholino ketone by treatment with morpholine. Reduction with aluminum isopropoxide furnished 1-(3-pyridyl)-2-(4-morpholino)-ethanol (I). The pyridine ring was then saturated by catalytic hydrogenation (II).



I

II

Experimental

The formation of tars in the reaction with diazomethane was minimized when free nicotinyl chloride instead of its hydrochloride[2] was used.

Nicotinyl chloride was prepared according to the directions of Douglass and Forman[3] but was purified by distillation over quinoline. The pure acid chloride was obtained in a yield of 90% as a colorless liquid, b. p. 75–77° (7 mm.), of an odor similar to that of benzoyl chloride.

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[1] Eli Lilly Research Fellow.

[2] Dornow *Ber.*, **73**, 156 (1940).

[3] Douglass and Forman, THIS JOURNAL, **56**, 1609 (1934).