stitution reaction of a tribromo derivative of isovaleraldehyde produced by a substitution reaction of bromine with α,β-dibromoisovaleraldehyde, the addition product first formed.

In the presence of mercuric sulfate[5] satisfactory analyses are possible by the procedure which follows. Into a 300 ml. g. s. conical flask, protected from the light by a black cloth or black coating, is pipetted 25.0 ml. (an excess) of 0.05 *N* bromate–bromide solution (0.00833 *M* in potassium bromate, *ca.* 0.1 *M* in potassium bromide). The flask is closed with a stopper carrying a stopcock and is evacuated. Then 10 ml. of 6 *N* sulfuric acid is run in and after waiting five minutes for the liberation of bromine, 15 ml. of 0.2 *N* mercuric sulfate, 2 *N* in sulfuric acid is added, followed by 25 ml. of the aqueous solution to be analyzed. The contents are well mixed by vigorous shaking and after standing for one and one-half minutes the reaction is stopped by the addition of 20 ml. of 2 *N* sodium chloride. Then 15 ml. of 20% potassium iodide is added and the liberated iodine is titrated with 0.025 *N* sodium thiosulfate. Variation in the time of bromination from one and one-half to five minutes caused no appreciable change in the analysis. The end-point did not drift with time. Known amounts of β,β-dimethylacrolein diethyl acetal gave 1.02 double bond per mole.

Summary

β,β-Dimethylacrolein hydrates in dilute aqueous nitric acid at a rate which is first order with respect to the aldehyde and to the acid catalyst. The reaction comes to equilibrium. In 1 *N* acid the hydration is 25% at 35°, 28% at 25°, and 32% at 20°. The position of equilibrium is not noticeably affected by changes in the acid concentration.

The heat of hydration of β,β-dimethylacrolein, ΔH, is -3.2 kcal., the heat of activation of the hydration, $\Delta H^{\ddagger}_{1}$ is 19.1 kcal. and the heat of activation of the dehydration of β-hydroxyisovaleraldehyde, $\Delta H^{\ddagger}_{-1}$, is 22.4 kcal. per mole.

PASADENA 4, CALIF.

RECEIVED JUNE 27, 1944

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[5] H. J. Lucas and D. Pressman, *Ind. Eng. Chem., Anal. Ed.*, **10**, 140 (1938).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS AND CO.]

ω-4-Morpholinehexyl Diphenylacetate[1]

BY W. R. COLEMAN AND W. G. BYWATER

During the course of an investigation of the pharmacological activity of a series of esters in this Laboratory[2] one, ω-4-morpholinehexyl diphenylacetate hydrochloride (S-29), was found to possess outstanding spasmolytic properties. Subsequent and more detailed study[3] confirmed the preliminary work and it became desirable to prepare larger quantities of this promising ester for complete toxicological studies and to initiate a clinical trial. We have, therefore, investigated its preparation in more detail in an effort to improve the yields originally obtained. Several new derivatives of *n*-hexyl diphenylacetate have been made during this investigation.

The reaction previously devised[2a] consisted of heating potassium diphenylacetate and hexamethylene bromide in dry xylene and, without isolating the intermediate bromoester, adding morpholine to the reaction mixture to obtain the desired ester. Employing a mole ratio of potassium diphenylacetate:hexamethylene bromide: morpholine of 1:1:2, the yields of ester varied between 10 and 36%. In the present study it has been found that the use of the potassium salt and the bromide in the molecular ratio of 1:2, isolation of the ω-bromohexyl diphenylacetate, and then causing the latter to react with morpholine, afforded yields of 56–61%. Moreover, one troublesome by-product, 1,6-di-4-morpholinehexane, is eliminated although hexamethylene bis-diphenylacetate is formed in small quantities. The over-all yield from hexamethylene glycol is 41–45%.

Synthesis of the morpholine hexyl ester via hexamethylene chlorohydrin proved to be the more satisfactory method. The alcohol, ω-4-morpholinehexanol, was prepared from hexamethylene chlorohydrin by the procedure of Anderson and Pollard.[4] Condensation of the alcohol with diphenylacetyl chloride gave a 91.6% yield of ω-4-morpholinehexyl diphenylacetate hydrochloride, or an over-all yield of 48–50% based upon hexamethylene glycol.

Incidental to the study of the reaction, the products from one run in which the mole ratio of salt:bromide:morpholine was 1:1:2, were isolated and identified. As was expected, the following compounds were found: α-ω-di-4-morpholinehexane dihydrochloride (21.4%), hexamethylene bis-diphenylacetate (7.6%), ω-4-morpholinehexyl diphenylacetate hydrochloride (10%) and diphenylacetic acid (42% recovery). Unreacted hexamethylene bromide was not recovered.

Experimental

Hexamethylene Chlorohydrin and Chloride.—One mole of hexamethylene glycol refluxed with 15 g. of cuprous chloride and 360 ml. of concentrated hydrochloric acid for two hours, and then continuously extracted with toluene during sixteen to eighteen hours while the reaction mixture was heated in a water-bath at 95–100°, gave 8–10% of hexamethylene chloride and 64–66% of the chlorohydrin, b. p. 114–117° (20 mm.),[5,6] n^{20}_{D} 1.4550. If the mixture

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[1] Original manuscript received May 17, 1943.

[2] (a) Cheney and Bywater, THIS JOURNAL, **64**, 970 (1942); (b) Rowe, *J. Am. Pharm. Assoc.*, **31**, 57 (1942).

[3] Chase, Lehman and Yonkman, *J. Pharmacol.*, **81**, 174 (1944).

[4] Anderson and Pollard, THIS JOURNAL, **61**, 3439, 3440 (1939).

[5] Boiling points were determined with 76 mm. immersion thermometers. No stem correction has been made.

[6] Bennett and Turner, *J. Chem. Soc.*, 814 (1938), give the b. p. as 116–117° (19 mm.).

is not continuously extracted but merely covered with toluene, the yield of chlorohydrin was 12% and no chloride was formed. Anderson and Pollard[4] report that in general 65% yields of chlorohydrin were secured by continuous extraction according to the method of Bennett and Moses.[7] We were unable to obtain a 65% yield without the aid of cuprous chloride.

The best yield of hexamethylene chloride (64%) was secured when one mole of hexamethylene glycol was refluxed for fourteen hours with 1000 ml. of concentrated hydrochloric acid. The chloride was separated from the acid and fractionated through a 15-inch Vigreaux column without further treatment, b. p. 95–98° (20 mm.).[8]

Hexamethylene Bromide.—A solution of 118 g. (1 mole) of hexamethylene glycol in 500 ml. of 48% hydrobromic acid was refluxed for twelve hours. The oil was then separated from the acid and distilled without further treatment. The yield was 74.5%; b. p. 108–109° (12 mm.)[9]; $n^{20}\text{D}$ 1.5051.

ω-Hydroxyhexyl Diphenylacetate.—A solution of 34.5 g. (0.15 mole) of diphenylacetyl chloride (prepared from diphenylacetic acid and thionyl chloride), 17.7 g. (0.15 mole) of hexamethylene glycol, 16.5 ml. of dry pyridine and 250 ml. of anhydrous acetone was allowed to stand in the refrigerator overnight. Pyridine hydrochloride separated from the straw-colored solution, which became blue during the reaction. The pyridine hydrochloride was removed by filtration and the filtrate concentrated *in vacuo* to a blue viscous oil which was transferred to a 125-ml. modified Claisen flask and distilled under reduced pressure. The forerun consisted of pyridine hydrochloride and 4 g. (22.6%) of hexamethylene glycol. The ω-hydroxyhexyl diphenylacetate was collected at 220–222° (3 mm.); 17.3 g. or 37% yield; $n^{20}\text{D}$ 1.5460.

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 76.88; H, 7.69; sapn. equiv., 312.4. Found[10]: C, 76.06; H, 7.36; sapn. equiv., 318, 319.

From the cold solid residue hexamethylene bis-diphenylacetate, described below, was obtained in 53% yield.

The yield of ω-hydroxyhexyl diphenylacetate was 21.5% when sodium hydroxide was substituted for pyridine in the above reaction. When two equivalents of hexamethylene glycol were employed in pyridine–acetone, the yield of twice distilled product was 29% (b. p. 223–225° (3 mm.); $n^{20}\text{D}$ 1.5478) and of hexamethylene bis-diphenylacetate was 27%.

ω-Chlorohexyl Diphenylacetate: A.—A solution of 20 g. (0.17 mole) of thionyl chloride in 25 ml. of carbon tetrachloride was added dropwise during one hour to a well-stirred solution of 26.3 g. (0.084 mole) of ω-hydroxyhexyl diphenylacetate in 100 ml. of carbon tetrachloride with no external cooling. The solution was then refluxed and stirred for two hours. The excess thionyl chloride was removed and the product distilled *in vacuo;* b. p. 215–222° (2.5 mm.); $n^{20}\text{D}$ 1.5420; yield, 20 g. or 72%.

B.—To 250 g. (1 mole) of potassium diphenylacetate suspended in 500 ml. of xylene in a 2-liter three-necked flask equipped with a reflux condenser and mechanical stirrer was added 232.5 g. (1.5 moles) of hexamethylene chloride. The well-stirred mixture was refluxed for twenty-four hours. It was then cooled and the precipitate collected by filtration. (Twenty per cent. of the original diphenylacetic acid was recovered from the latter.) The filtrate was then distilled *in vacuo* from a modified Claisen flask and the chloroester weighing 140 g. (42.3%), and boiling at 220–221° (3 mm.), collected. The residue remaining after the distillation weighed 56.5 g. and was identified by mixed m. p. as hexamethylene bis-diphenylacetate.

ω-Bromohexyl Diphenylacetate.—A suspension of 124 g. (0.496 mole) of finely ground potassium diphenylacetate in one liter of xylene and 231 g. (0.946 mole; 1.9 equivalents) of hexamethylene bromide was refluxed with stirring for twenty-five hours. The reaction products were isolated as described under (B) above. There was secured 107.3 g. (98% recovery of the excess) of hexamethylene bromide and 122 g. (65.6%) of ω-bromohexyl diphenylacetate; b. p. 223–226° (2.5 mm.); $n^{22}\text{D}$ 1.5572; and a residue 28 g. (18%) which was identified as hexamethylene bis-diphenylacetate. Upon redistillation the bromoester boiled at 228–230° (4 mm.), $n^{20}\text{D}$ 1.5555.

Anal. Calcd. for $C_{20}H_{23}O_2Br$: Br, 21.29. Found: Br, 21.67, 21.45.

ω-4-Morpholinehexyl Diphenylacetate Hydrochloride: A.—A solution of 28.9 g. (0.087 mole) of ω-chlorohexyl diphenylacetate and 80 ml. (0.92 mole) of morpholine was refluxed for four hours. The unreacted morpholine was removed *in vacuo*. The residue was taken up in diluted hydrochloric acid and extracted with ether to remove unchanged chlorohexyl ester. The acidic solution was then neutralized with dilute sodium hydroxide and the resulting oil extracted with ether. The combined extracts were washed with water, dried over calcium chloride, filtered, and finally saturated with hydrogen chloride. The ether was decanted from the oil which precipitated, and the latter was crystallized from isopropyl alcohol and petroleum ether. The morpholine ester, when recrystallized from amyl alcohol–petroleum ether, melted at 111.6–112.6° (cor.) (18%).

B.—A solution of 122 g. (0.325 mole) of ω-bromohexyl diphenylacetate, 112.8 g. (1.3 moles) of morpholine and 200 ml. of dry xylene was refluxed for seven hours. The resulting mixture was cooled and the precipitated morpholine hydrobromide removed by filtration. The xylene, and the remainder of the excess morpholine, were removed by distillation and the product obtained as described in A above. The crude hydrochloride was recrystallized from isopropyl alcohol to obtain 115.9 g. or 85.3% yield of the ester hydrochloride melting at 112.5–113.6° (cor.).

C.—To a mechanically stirred solution of 46.1 g. (0.2 mole) of diphenylacetyl chloride in 100 ml. of xylene, was added 37.4 g. (0.2 mole) of ω-4-morpholinehexanol.[4] The solution was allowed to stir for one-half hour, when crystallization started. It was refluxed gently for fifteen minutes. After standing overnight, the solid reaction product was collected and recrystallized. In this manner 76.5 g. (91.6%) of the desired ester was obtained.

D.—(a) A suspension of 110 g. (0.439 mole) of potassium diphenylacetate and 102 g. (0.418 mole) of hexamethylene bromide in 400 ml. of dry xylene was stirred rapidly at room temperature during one and one-half hours and then stirred and refluxed for three and one-half hours. An additional 400 ml. of xylene was added to the thick mixture and stirring and refluxing were continued for twenty-two and one-half hours. To complete the reaction, 80 g. (0.92 mole) of morpholine was added and the reaction was allowed to proceed as above for thirteen hours longer.

Filtration of the cooled suspension removed a solid which when precipitated from dilute alkali by hydrochloric acid was shown to be diphenylacetic acid (25.2 g. or 27.1%) by a mixed melting point with an authentic sample.

The filtered xylene mother liquor was extracted several times with 4% hydrochloric acid. These acid extracts were combined and worked up as in (b).

After the extraction with hydrochloric acid, the xylene was removed *in vacuo* and the residue was treated with dilute sodium hydroxide. The mixture was filtered to remove hexamethylene bis-diphenylacetate which, after two recrystallizations from dilute alcohol, melted at 77–78.5° (cor.).

Anal. Calcd. for $C_{34}H_{34}O_4$: C, 80.60; H, 6.75. Found[10]: C, 80.71, 80.48; H, 6.63, 6.81.

When the alkaline filtrate, obtained after removal of the above neutral ester, was acidified, 13.9 g. (15%) of diphenylacetic acid separated.

(b) The combined hydrochloric acid extracts separated into two phases on standing. This is not a common oc-

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[7] Bennett and Moses, *J. Chem. Soc.*, 1697 (1931).

[8] v. Braun, *Ber.*, **38**, 2345 (1905), reports the b. p. as 94° (22 mm.).

[9] v. Braun and Müller, *ibid.*, **39**, 2021 (1906), reported the b. p. as 115–116 (12 mm.).

[10] Microanalyses by Mr. A. W. Spang.

currence in these runs; consequently, each phase was worked up separately. Each was neutralized with solid sodium carbonate and extracted thrice with ether. The ether solutions were dried over anhydrous potassium carbonate, and that from the upper layer worked up according to (1), the one from the lower according to (2).

(1) Upon saturation of the extract with hydrogen chloride, di-4-morpholinehexane dihydrochloride precipitated; yield, 29.4 g (21.4%) after recrystallization from isopropyl alcohol; m. p. 261–261.5° (dec.). This material was found to be identical with that prepared from hexamethylene chloride and morpholine.

Anal. Calcd. for $C_{14}H_{30}O_2N_2Cl_2$: N, 8.50; Cl, 21.53. Found[10]: N, 8.62, 8.66; Cl, 21.37, 21.50.

The hydrochloride was converted to the free base with ammonium hydroxide. It melts at 40–42.5° (cor.).[11]

(2) The dried ether solution of the lower phase, when saturated with anhydrous hydrogen chloride, produced a dark viscous oil which, after three days in the refrigerator, finally solidified. After two recrystallizations, the product was dried *in vacuo* at 50° over phosphorus pentoxide; the ω-4-morpholinehexyl diphenylacetate hydrochloride weighed 17.8 g. (10.2%) and melted at 110.6–112.6° (cor.).

The ω-4-morpholinehexyl ester hydrochloride readily can be converted to the nitrate which is less soluble than the hydrochloride. A solution of 7.5 g. of the hydrochloride in 160 ml. of water was treated with 40 ml. of dilute nitric acid. The solution immediately became cloudy and crystals of the nitrate began to separate. These were collected after one-half hour and recrystallized from isopropyl alcohol, m. p. 119–120°, 7.1 g. or 90% yield.

Anal. Calcd. for $C_{24}H_{32}O_6N_2$: N, 6.30. Found[10]: N, 6.21, 6.28.

The nitrate will form a 4% aqueous solution when heated and allowed to cool; whereas, a 35% solution of the hydrochloride can easily be made.

Summary

A study has been made of the preparation of ω-4-morpholinehexyl diphenylacetate. The intermediates, ω-hydroxyhexyl, ω-chlorohexyl and ω-bromohexyl diphenylacetate, have been prepared and identified.

DETROIT, MICH. RECEIVED AUGUST 3, 1944

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[11] Anderson and Pollard[4] found 35.5–38.5°.

[CONTRIBUTION FROM THE COLLEGE OF CHEMISTRY AND PHYSICS, LOUISIANA STATE UNIVERSITY]

The Diacetone Alcohol–Hydroxide Ion Reaction from the Standpoint of Ion-Dipole Theory

BY EDWARD S. AMIS, GEORGE JAFFÉ AND RALPH THEODORE OVERMAN[1]

The kinetic equation for reaction between ions and dipolar molecules

$$\ln k = \ln k_{\kappa=0} + \frac{\epsilon z_B \cos \vartheta_0}{DkTr_0^2} (\mu_0^* - \mu^* e^{-\kappa r_0} (1 + \kappa r_0)) \quad (1)$$

derived by Amis and Jaffé[1a] was tested as to the dependence of the reaction rate (between ions and dipolar molecules) both on ionic strength and on dielectric constant of the solvent using a positive ion reactant, namely, hydrogen ion. Since $\mu_0^* > \mu^* e^{-\kappa r_0} (1 + \kappa r_0)$ and since the term $\mu^* e^{-\kappa r_0} (1 + \kappa r_0)$ decreases at a decreasing rate while μ_0^* remains constant with increasing ionic strength, then for positive ionic reactants (z_B positive) k should increase with decreasing rate as the ionic strength is increased. For negative ionic reactants, however, k should decrease with decreasing rate as ionic strength increases. Also k should increase, but progressively less, with decreasing dielectric constant of the medium for positive ion reactants since, although the term μ_0^*/D increases, the smaller term $\mu^* e^{-\kappa r_0} (1 + \kappa r_0)$ decreases faster proportionally with decreasing diectric constant. For negative ionic reactants k should decrease with decreasing rate as the dielectric constant is decreased.

For the hydrogen ion reacting with sucrose both in the presence and in the absence of salts, the predictions of Eq. (1) were fulfilled, as was the case also when hydrogen ion reacted with ethylene acetal in the absence of salts.[1a] The reaction between hydrogen ion and sucrose and that between hydrogen ion and glucose as a function of the dielectric constant of the media gave data in conformity with expectations.[1a]

It would be well, however, to test Eq. (1) using a *negative ion reactant* since there should not only be a change in the sign of the slope but also an inversion of the curvature of the empirical curves ($\ln k$ *vs.* ionic strength and $\ln k$ *vs.* $1/D^2$) if the equation correctly predicts the influences upon the rate constants of the ionic strength and dielectric constant of the medium.

Åkerlöf[2,3,4] has studied the rate of decomposition of diacetone alcohol by the hydroxide ion for various alkali metal hydroxides alone and in the presence of their uni-univalent and uni-bivalent salts. He has also studied the same reaction using sodium hydroxide in various mixed solvents. These data are ideal for testing Eq. (1).

In Fig. 1 we plot the data for the decomposition of diacetone alcohol in potassium hydroxide–uni-univalent potassium salt solutions of various ionic strengths. Also similar data for sodium hydroxide–uni-univalent sodium salt solutions are plotted in this figure. These data were plotted according to the suggestion of Amis and Jaffé[1a] who transformed Eq. (1) into the form

$$W = z^2/(1 + z + z^2/2 + (n^2/2D)(1 + z)) \quad (2)$$

by introducing the dimensionless variable

$$z = \kappa a = \kappa r_0 \quad (3)$$

and the dimensionless quantity

$$W = (\ln k - \ln k_{\kappa=0})(2DkTr_0^2)/\epsilon z_B \mu_0^* \cos \vartheta_0. \quad (4)$$

In Fig. 1 the solid line is the theoretical curve

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[1] Present address Louisiana College, Pineville, La.

[1a] Amis and Jaffé, *J. Chem. Phys.*, **10**, 598 (1942).

[2] Åkerlöf, THIS JOURNAL, **48**, 3046 (1926).

[3] Åkerlöf, *ibid.*, **49**, 2960 (1927).

[4] Åkerlöf, *ibid.*, **50**, 1272 (1928).