Under these similar conditions, including the arbitrary reaction time, only II among the possible dicarbonyl structures could be expected to take up less deuterium than I, and the relative figures for deuterium content can be taken therefore as qualitatively significant.

Reduction of 13-ketoprotopine with lithium aluminum hydride.[16] To a slurry of 150 mg. (4 mmoles) of lithium aluminum hydride in 30 ml. of dry ether was added rapidly 230 mg. (0.63 mmole) of 13-ketoprotopine in 30 ml. of dry benzene. After stirring for 11 hours at 25° the mixture was decomposed with 10 ml. of 6*N* hydrochloric acid. The aqueous phase was basified with saturated potassium carbonate solution and extracted with methylene chloride. The dried extracts were evaporated to a gray powder, from which 122 mg. (52%) of colorless prisms (III) were obtained on crystallization from acetone, m.p. 257–259° (dec.). Gadamer[4] reported a melting point of 255–256° for "tetrahydroöxyprotopine."

Anal. Calc'd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.67; H, 5.85; N, 3.66.

The infrared spectrum in Nujol showed strong OH absorption at 3260 cm.$^{-1}$ and no carbonyl absorption.

Oxidation of tetrahydroketoprotopine with periodic acid.[17] A solution of 81 mg. (0.22 mmole) of the diol in 0.4 ml. of 1*N* H_2SO_4 was treated with a solution of 50 mg. of periodic acid in 0.8 ml. of water. The resulting solution was allowed to stand at 25° for 27 hr. Basification with saturated potassium carbonate solution was followed by ether extraction. The dried extracts were evaporated to give 64 mg. of a gray powder. The infrared spectrum in Nujol showed carbonyl absorption at 1678 cm.$^{-1}$, characteristic of an aromatic aldehyde (IV).

The powder was treated with 0.5 ml. of methanol followed by 0.5 ml. of 1*N* sodium hydroxide solution and 30 mg. of hydroxylamine hydrochloride. About 50 mg. of dioxime was obtained after 3 hr. at 25°. The dioxime (V) was washed with hot 90% ethanol and dried in vacuum at room temperature (to avoid decomposition), m.p. 209°.

Anal. Calc'd for $C_{20}H_{21}N_3O_6 \cdot H_2O$: C, 57.55; H, 5.55; N, 10.07. Found: C, 57.45; H, 5.15; N, 9.50.

The ultraviolet spectrum in 95% ethanol showed maxima at 272 mμ (log ε 4.26) and 306 mμ (log ε 4.09). The values reported by Russell[17] for the dimethoxy analog (Vb) are: 270 mμ (log ε 4.32) and inflexion at 290–310 mμ (log ε 4.00).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF OREGON]

Ester Derivatives of Mucic Acid[1]

MARK D. BAELOR[2] AND GEORGE GORIN[3]

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The reaction of "mucic acid lactone" with ethanol and methanol produced monoesters of mucic acid, which were purified and characterized as the tetraacetyl derivatives. Monoethyl mucate was also prepared, in impure form, by partial hydrolysis of the diethyl ester. Tetraacetylmucic acid and one mole of diazomethane gave mainly the dimethyl ester. Mucic acid or tetraacetylmucic acid and one mole of silver nitrate gave the respective disilver salts.

A derivative of mucic acid in which the hydroxyl groups and one carboxyl group are esterified, such as monoethyl tetraacetylmucate, was desired as the starting point for a projected synthesis of inositol.[1] The monoesters of dicarboxylic acids are usually prepared by treatment of the appropriate cyclic anhydride with one mole of alcohol, but this type of compound is not available in the case of mucic acid. Therefore, the preparation of monoethyl mucate was first attempted by partial hydrolysis of the diethyl ester.

A mixture of one mole of diethyl mucate with one mole of potassium hydroxide became neutral in a very short time. Rapid evaporation of the solution to dryness and treatment of the residue with the calculated amount of 1 *M* hydrochloric acid gave a white solid, m.p. 177–179°, with a neutralization equivalent of 200 and a saponification equivalent of 117. Saponification produced mucic acid quantitatively. It appears, accordingly, that the solid was a mixture of 84% monoethyl mucate and 16% mucic acid. Unfortunately, this product could not easily be purified by recrystallization; water would cause some hydrolysis, and all other liquids tried were not sufficiently good solvents.

Monoethyl mucate could be prepared, in somewhat purer form, from Fischer's[4] "mucic acid lactone." This viscous liquid, obtained from an aqueous solution of mucic acid by rapid evaporation to dryness, is, likely, a mixture of lactones and intermolecular esters. From a solution of this substance in anhydrous ethanol there separated, in the course of several days, crystals of monethyl mucate mixed with a little mucic acid, of neutralization equivalent 211. Further purification was effected by first converting this product to the tetraacetyl derivative, which could be purified by crystallization from ethanol, m.p. 181–183°.

Monomethyl mucate was obtained similarly from a solution of mucic acid in anhydrous methanol. Acetylation of the crude ester and crystalliza-

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[1] Abstracted from a thesis submitted by M. D. Bealor in partial fulfillment of the requirements for the Ph.D. degree, University of Oregon, June 1956.

[2] Present address, Niagara Chemical Division, Research Department, Middleport, N. Y.

[3] Present address, Department of Chemistry, Oklahoma Agricultural and Mechanical College, Stillwater, Okla.

[4] Fischer, *Ber.*, **24**, 2141 (1891).

tion from toluene gave monomethyl tetraacetylmucate, m.p. 169–172°. Treatment of this compound with diazomethane gave a good yield of dimethyl tetraacetylmucate, identical with the product prepared by the acetylation of dimethyl mucate.

Treatment of the mucic acid lactone with ethanolic hydrogen chloride, gave, even at 10°, a good yield of diethyl mucate.

The preparation of monoesters of mucic acid was also attempted in ways which were not successful. It had been expected that, in dimethyl or diethyl tetrabenzoylmucate, one alkyl ester group would be preferentially hydrolyzed. Accordingly, both dimethyl and diethyl tetrabenzoylmucate were prepared and treated with one mole of dilute ethanolic potassium hydroxide; it was found, however, that at least half of the base was converted to potassium benzoate, while part of the tetrabenzoyl diester was recovered unchanged.

Disodium mucate and disodium tetraacetylmucate were treated with one mole of silver nitrate in the hope of obtaining the mixed silver sodium salt, which might be converted to the half-ester by reaction with methyl iodide. However, this method of preparation gave the disilver salts. In these circumstances solubility determines the nature of the products, and the disilver salt, apparently the less soluble, separates first.

Finally, partial esterification of tetraacetylmucic acid was attempted, using one mole of diazomethane in ethanol. A good yield of dimethyl tetraacetylmucate was obtained (91% based on diazomethane); it would seem that the half-esterified product reacts faster than tetraacetylmucic acid, although why this should happen is not clear. The product was identical with that prepared by acetylation of dimethyl mucate.

EXPERIMENTAL[5,6]

Partial hydrolysis of diethyl mucate. Diethyl mucate (1.33 g., 0.005 mole) in 18 ml. of water was mixed with 19.4 ml. of 0.258 *M* potassium hydroxide (0.005 mole). After mixing, the *p*H of the solution was 6.4. The solution was evaporated to dryness under reduced pressure and the residue triturated with 5.00 ml. of 1.012 *M* hydrochloric acid (0.005 mole). The solid was collected, washed with 3 ml. of water to remove potassium chloride, and dried; m.p. 177–179°; yield 0.70 g. (59%).

Anal. Calc'd: Neut. Equiv. 238.2; Sapon. Equiv. 119.1. Found: Neut equiv. 200; Sapon. Equiv. 117.

Attempts to characterize this compound as the benzylthiouronium salt and the *p*-bromophenacyl ester were unsuccessful.[7]

Monoethyl mucate. Fischer's[4] "mucic acid lactone" (5.2 g.) in 25 ml. of anhydrous ethanol was kept at room temperature for 6 days; a white solid separated slowly, m.p. 174–176°. Yield 1.15 g.

Anal. Calc'd: Neut. Equiv. 238.2. Found: 211 (the neutralization equivalent indicates a mixture of 90% monoethyl mucate and 10% mucic acid).

Monoethyl tetraacetylmucate. Monoethyl mucate (2.3 g.), acetic anhydride (25 g.) and 5 drops of concentrated sulfuric acid were placed in a 50 ml. flask equipped with a reflux condenser. The mixture was gently refluxed for 30 min., and the resulting clear solution evaporated under reduced pressure to 15 ml. The solid which precipitated was collected, washed with acetic anhydride, dried, and crystallized twice from 95% ethanol; white needles, m.p. 181–183°. Yield 0.5 g. (12%).

Anal. Calc'd for $C_{16}H_{22}O_{12}$: C, 47.29; H, 5.46. Found: C, 46.78, H. 5.43.

Monomethyl mucate. Mucic acid lactone (8.64 g.) in 45 ml. of anhydrous methanol was kept at room temperaure for 6 days; a white solid separated, m.p. 188–190° (dec.). Yield 1.5 g.

Anal. Calc'd: Neut. Equiv. 224.2. Found: 191 (the neutralization equivalent indicates a mixture of 85% monomethyl mucate and 15% mucic acid).

Monomethyl tetraacetylmucate. Monomethyl mucate (1.5 g.), acetic anhydride (10.2 g.) and 2 drops of concentrated sulfuric acid were placed in a 25-ml. flask equipped with a reflux condenser. The mixture was refluxed gently for 30 min. and the clear solution was then evaporated to dryness at reduced pressure. The residue was crystallized twice from toluene; white needles, m.p. 169–172°. Yield 0.8 g. (32%).

Anal. Calc'd for $C_{15}H_{20}O_{12}$: C, 45.92; H, 5.14. Found: C, 46.03; H, 5.23.

Reaction of "mucic acid lactone" with ethanolic hydrogen chloride. Mucic acid lactone (7.0 g.) in 100 ml. of absolute ethanol was chilled in an ice-salt bath and saturated with hydrogen chloride. After standing for one day at 10° C. a precipitate of white needles had formed; m.p. 161–163°. Yield 6.1 g. (63%). The m.p. was not depressed on admixture with an authentic sample of diethyl mucate.[8]

Diethyl tetrabenzoylmucate. Diethyl mucate[8] (2.66 g.) and 25 ml. of anhydrous pyridine were warmed until a clear solution resulted. After cooling to room temperature, 7.00 g. of benzoyl chloride was added slowly; the mixture became warm and light red in color, and some solid precipitated. The reaction mixture was poured into 50 ml. ice water and the solution neutralized with 8.5 g. of sodium bicarbonate; the precipitate was collected, washed, first with 5% sodium bicarbonate solution and then with water, dried, and crystallized twice from 95% ethanol; feathery white needles, m.p 151–152.5°. Yield 4.85 g. (70%).

Anal. Calc'd for $C_{38}H_{34}O_{12}$: C, 66.83; H, 5.00. Found: C, 66.98; H, 5.13.

Dimethyl mucate. This compound was prepared according to the procedure of Fischer and Speier[8] from mucic acid, anhydrous methanol, and hydrogen chloride, m.p. 193–195° (dec.). Reported[9] m.p. 165–167° (dec.).

Anal. Calc'd: Sapon. Equiv. 119.1. Found: 120.0.

Dimethyl tetrabenzoylmucate. Dimethyl mucate (11.9 g.), 275 ml. of anhydrous pyridine and 42.0 g. of benzoyl chloride, by the same procedure used for diethyl tetrabenzoylmucate, gave a solid which was crystallized from 95% ethanol acetone; white powder, m.p. 169.8–170.8°. Yield 8.8 g. (27%).

Anal. Calc'd for $C_{36}H_{30}O_{12}$: C, 66.05; H, 4.62. Found: C, 66.20; H, 4.71.

Hydrolysis of diethyl tetrabenzoylmucate. Diethyl tetrabenzoylmucate (3.41 g., 0.005 mole), 200 ml. of absolute ethanol and 20 ml. of 0.25 *M* alcoholic potassium hydroxide (0.005 mole) were placed in a 500 ml. flask equipped with a reflux condenser and the mixture was refluxed 16 hr. Five ml. of 1.00 *M* hydrochloric acid (0.005 mole) was added;

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(5) All melting points are corrected capillary tube melting points.

(6) Carbon and hydrogen analyses were done by Micro-Tech Laboratories, 8000 Lincoln Ave., Skokie, Ill.

(7) Shriner and Fuson, *Identification of Organic Compounds*, 3rd ed., John Wiley and Sons, Inc., New York, 1948, pp. 157, 159.

(8) Fischer and Speier, *Ber.*, **28**, 3252 (1895).

(9) Curtius, *J. prakt. Chem.*, [2] **95**, 244 (1917).

the solution was evaporated under reduced pressure to 25 ml., diluted with 100 ml. of water, and chilled. The precipitate was collected on a filter, washed with water, and dried; m.p. 120–122°. The m.p. was not depressed on admixture with an authentic sample of benzoic acid. Yield 0.3 g. (50% based on potassium hydroxide).

Anal. Calc'd: Neut. Equiv. 122.1. Found: 122.2.

Further chilling of the mother liquor caused a second precipitate to form. Yield 2.05 g. (60%), m.p. and mixed m.p. with an authentic sample of diethyl tetrabenzoylmucate, 150–152°.

Hydrolysis of dimethyl tetrabenzoylmucate. In a 500-ml. flask equipped with a reflux condenser were placed dimethyl tetrabenzoylmucate (3.27 g., 0.005 mole), 200 ml. of anhydrous methanol, and 20 ml. of 0.25 M methanolic potassium hydroxide (0.005 mole). The mixture was heated under reflux for 12 hr. and the pH was then 6.8. Five ml. of 1.00 M hydrochloric acid (0.005 mole) was added, the solution was evaporated under reduced pressure to 50 ml., and chilled. The precipitate was collected and dried. Yield 1.63 g. (50%). Melting point and mixed melting point with an authentic sample of dimethyl tetrabenzoylmucate was 168–170°.

The mother liquor was diluted with 100 ml. of water and chilled. The precipitate was collected and washed with water. Yield 0.24 g. (40% based on potassium hydroxide); m.p. and mixed m.p. with an authentic sample of benzoic acid, 119–122°.

Anal. Calc'd: Neut. Equiv. 122.1. Found: 123.0.

Reaction of disodium mucate with one mole of silver nitrate. To 100 ml. of 0.103 M sodium hydroxide (0.01 mole) was added 1.05 g. of mucic acid (0.005 mole), and the mixture was warmed. To the resulting clear solution was added a solution of 0.842 g. of silver nitrate (0.005 mole) in 25 ml. of water. The fine white solid which precipitated was separated by centrifugation, washed with water and acetone, and dried. Yield 2.1 g. (90% based on silver nitrate).

Anal. Calc'd for $C_6H_8O_8Ag_2$: Ag, 50.90. Found: Ag, 49.63.

Reaction of disodium tetraacetylmucate with one mole of silver nitrate. To 50 ml. of 0.103 M sodium hydroxide (0.0052 mole) was added 0.98 g. of tetraacetylmucic acid[10] (0.0026 mole), and the mixture was warmed. To the resulting clear solution was added a solution of 0.438 g. of silver nitrate (0.0026 mole) in 15 ml. of water. The fine white solid which precipitated was separated by centrifugation, washed with water and acetone, and dried. Yield 0.5 g. (65% based on silver nitrate).

Anal. Calc'd for $C_{14}H_{16}O_{12}Ag_2$: Ag, 36.44. Found: Ag, 36.20.

Dimethyl tetraacetylmucate. Dimethyl mucate (2.38 g.), 20 g. of acetic anhydride and 5 drops of concentrated sulfuric acid were placed in a 50-ml. flask equipped with a reflux condenser and the mixture was heated to just under reflux for 30 min. The solid which precipitated on cooling was collected, washed with ethyl acetate, dried, and crystallized from absolute ethanol; white needles, m.p. 195.8–196.6°. Yield 10 g. (25%).

Anal. Calc'd for $C_{16}H_{22}O_{12}$: C, 47.29; H, 5.46. Found: C, 47.31; H, 5.65.

Reaction of monomethyl tetraacetylmucate with diazomethane. To monomethyl tetraacetylmucate (0.50 g.) in 25 ml. of absolute ethanol was added, with swirling, a solution of diazomethane[11] (0.73 g.) in 15 ml. of benzene. The solid which precipitated on cooling was collected, dried, and crystallized from absolute ethanol; white needles, m.p. 195–196°. Yield 0.36 g. (65%). The melting point was not depressed on admixture with a sample of dimethyl tetraacetylmucate prepared as described above.

Reaction of tetraacetylmucic acid with one mole of diazomethane. In a 200-ml. flask equipped with a stirrer, reflux condenser, and dropping funnel were placed 3.78 g. of tetraacetylmucic acid[10] (0.01 mole) and 75 ml. of absolute ethanol. To the clear solution was added dropwise over a period of 30 min. a solution of 0.42 g. of diazomethane (0.01 mole) in 30 ml. of ether, prepared and standardized according to Arndt.[11] The solid which precipitated after chilling was collected, washed with ethanol, and dried; m.p. 190–193°. Yield 1.85 g. (91% based on diazomethane). The melting point was not depressed on admixture with an authentic sample of dimethyl tetraacetylmucate. Concentration of the mother liquor to one half its volume and chilling yielded 1 g. (26.5%) of starting material.

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[11] Arndt, *Org. Syntheses*, Coll. Vol. II, 165–166, 461 (1943).