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Octabenzoylsucrose and Some of its Transformation Products

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A crystalline form of octabenzoylsucrose is described. Cleavage of this compound with hydrogen bromide in glacial acetic acid affords a mixture of halides which with water gives 2,3,4,6-tetrabenzoyl-D-glucose and 1,3,4,6-tetrabenzoyl-D-fructose. With methanol in the absence of an acid acceptor the mixture of halides produced methyl tetrabenzoyl-β-D-glucopyranoside as the only crystalline product.

While several fully benzoylated disaccharides as well as partially benzoylated derivatives of sucrose are known in the crystalline state[1] there appears to be no record of crystalline octabenzoylsucrose.[2] This fact, somewhat surprising in view of the practical importance of octaacetylsucrose, leads us to describe here a crystalline form of octabenzoylsucrose; the preparation of certain benzoylated derivatives of D-glucose and D-fructose from octabenzoylsucrose will also be described.

Benzoylation of sucrose with benzoyl chloride in pyridine solution readily gives an amorphous friable powder which is essentially pure octabenzoylsucrose. Further purification by chromatography on alumina affords analytically pure material. Extensive attempts to crystallize this in solvent-free form have failed; however, from solutions in carbon tetrachloride alone, carbon tetrachloride–methanol or carbon tetrachloride–pentane the octabenzoylsucrose crystallizes with carbon tetrachloride of crystallization.[3] This solvent of crystallization is readily lost on exposure to the air and there is obtained a pure amorphous octabenzoylsucrose.[4]

Like the benzoylated glycosides reported in earlier papers[5–10] octabenzoylsucrose proved to be relatively resistant to the action of dilute acid. However, hydrogen bromide in glacial acetic acid readily cleaved it to give a mixture of tetrabenzoyl-α-D-glucopyranosyl bromide and tetrabenzoyl-D-fructofuranosyl bromide. Although the former of these halides crystallizes with ease, the latter appears to be markedly unstable and no attempt was made to isolate crystalline material at this stage. The nature of the mixture was elucidated in several different ways. Hydrolysis of a sample with aqueous acetone in the presence of silver carbonate gave the known 2,3,4,6-tetrabenzoyl-D-glucose[11] in 48% yield and 1,3,4,6-tetrabenzoyl-D-fructose[12–14] in 42% yield. On standing in methanol solution the mixture of bromides afforded methyl tetrabenzoyl-β-D-glucopyranoside in 76% yield as the only crystalline product. With 1:9 dioxane–methanol its over-all rate of reaction was characteristic of a rapid reaction superimposed on a slow one; the rate of the slow reaction was almost identical with that of tetrabenzoyl-α-D-glucopyranosyl bromide with 1:9 dioxane–methanol. While in the latter case the end rotation corresponded quite closely with that of methyl tetrabenzoyl-β-D-glucopyranoside in 1:9 dioxane–methanol, the end rotation attained by the mixed halides was less positive than would be expected on the basis of the methyl tetrabenzoyl-β-D-glucopyranoside alone, indicating the presence of a second, weakly levorotatory product. Since benzoylation of the known crystalline methyl α-D-fructofuranoside[15–17] gave an amorphous product which was dextrorotatory and stable in 1:9 dioxane–methanol containing hydrogen bromide, it appears likely that the fructose moiety of the sucrose has here been converted to methyl tetrabenzoyl-β-D-fructofuranoside.[18]

Experimental[19]

Octabenzoylsucrose.—Ordinary granulated sucrose was powdered and 25.0 g. of this suspended in 250 ml. of dry pyridine. The suspension was cooled and treated over the course of two minutes with 85 ml. (10 mole equivalents) of benzoyl chloride. After one hour at room temperature the reaction mixture was heated at 60° for four hours. Excess of benzoyl chloride was destroyed by the addition of 3 ml. of water, the solution diluted with methylene chloride and washed successively with cold water, cold 3 N sulfuric acid and cold, saturated sodium bicarbonate solution. After desiccation with sodium sulfate, the solution was filtered through decolorizing carbon and concentrated *in vacuo* to a friable powder (80.8 g., 94%). This crude material (71.3 g.) was dissolved in a mixture of 265 ml. of carbon tetrachloride and 260 ml. of methanol, the solution cooled to

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(1) *Cf.* H. Vogel and A. Georg, "Tabellen der Zucker und Ihrer Derivate," Julius Springer, Berlin, 1931, pp. 260–262.

(2) E. Fischer and K. Freudenberg [*Ber.*, **45**, 2709 (1912)] mentioned the preparation of an amorphous octabenzoylsucrose but gave no experimental details.

(3) It is interesting to note that both 3,5,6-tribenzoyl-D-glucose [E. Fischer and C. Rund, *ibid.*, **49**, 88 (1916)] and tetrabenzoyl-α-D-glucopyranosyl bromide [L. W. Mazzeno, THIS JOURNAL, **72**, 1039 (1950)] have also been found to crystallize with carbon tetrachloride.

(4) In contrast to its acetyl analog, octabenzoylsucrose is not detectably bitter.

(5) H. G. Fletcher, Jr., R. K. Ness and C. S. Hudson, THIS JOURNAL, **73**, 3698 (1951).

(6) R. K. Ness, H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **73**, 959 (1951).

(7) R. K. Ness, H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **73**, 296 (1951).

(8) H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **72**, 4173 (1950).

(9) R. K. Ness, H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **72**, 2200 (1950).

(10) R. Jeanloz, H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **70**, 4055 (1948).

(11) E. Fischer and H. Noth, *Ber.*, **51**, 321 (1918).

(12) P. Brigl and R. Schinle, *ibid.*, **66**, 325 (1933).

(13) P. Brigl and R. Schinle, *ibid.*, **67**, 127 (1934).

(14) P. Brigl and R. Schinle, *ibid.*, **67**, 754 (1934).

(15) C. B. Purves and C. S. Hudson, THIS JOURNAL, **56**, 708 (1934).

(16) C. B. Purves and C. S. Hudson, *ibid.*, **56**, 1973 (1934).

(17) C. B. Purves and C. S. Hudson, *ibid.*, **59**, 49 (1937).

(18) Various amorphous methyl tetrabenzoyl-D-fructofuranosides have been reported in the literature. Brigl and Schinle (ref. 14) methylated 1,3,4,6-tetrabenzoyl-D-fructose and obtained a sirupy product rotating +5.0° in chloroform. F. Klages and R. Niemann [*Ann.*, **529**, 185 (1937)] converted 1,3,4,6-tetrabenzoyl-D-fructose to an amorphous tetrabenzoyl-D-fructofuranosyl bromide showing $[\alpha]_D$ +12°. Reaction of this latter with methanol in the presence of silver carbonate afforded a sirupy methyl tetrabenzoyl-D-fructofuranoside, $[\alpha]_D$ −10°.

(19) Melting points cited are corrected. Rotations are specific rotations for the D-line of sodium at 20°; concentration is expressed in g. of substance per 100 ml. of solution.

−5° and seeded.[20] After 4 days at −5° the crystalline product (76.2 g.) was removed and washed at −5° successively with carbon tetrachloride–methanol, carbon tetrachloride–pentane and pentane. Recrystallization from carbon tetrachloride–methanol gave material containing 18.8% carbon tetrachloride, melting at 60–63° (with loss of carbon tetrachloride) and showing +32.6° in chloroform (*c* 2.1).

Anal. Calcd. for $C_{68}H_{54}O_{19}\cdot 2CCl_4$: CCl_4, 20.75. Found: CCl_4, 22.56,[21] 18.83.[22]

The addition compound rapidly lost carbon tetrachloride at room temperature. On heating *in vacuo* at 57° for several hours an amorphous, solvent-free product showing +40.6° in chloroform (*c* 1.55) was obtained. Further recrystallization from carbon tetrachloride–methanol failed to change the rotation of the solvent-free material.

Anal. Calcd. for $C_{68}H_{54}O_{19}$: C, 69.50; H, 4.63. Found: C, 69.57; H, 4.90.

2,3,4,6-Tetrabenzoyl-D-glucose and 1,3,4,6-Tetrabenzoyl-D-fructose from Octabenzoylsucrose.—A solution (100 ml.) of 7.05 g. of amorphous octabenzoylsucrose in 30% hydrogen bromide–glacial acetic acid was held at room temperature until mutarotation had ceased (295 min.). After dilution with methylene chloride the solution was washed successively with ice-water and cold aqueous sodium bicarbonate. Moisture was removed with sodium sulfate and the solution concentrated *in vacuo* to a volume of *ca.* 200 ml. Acetone (240 ml.), 10 ml. of water and 3.1 g. of silver carbonate were then added and the suspension shaken for 8 hours at room temperature. The solids were then filtered off and the solution concentrated *in vacuo* to a sirup which was dissolved in 25 ml. of absolute alcohol and reconcentrated. The residue was dissolved in a mixture of 150 ml. of methanol and 24 ml. of water, filtered through decolorizing carbon and seeded with 1,3,4,6-tetrabenzoyl-D-glucose which had been recrystallized from methanol.[23] The product, dried *in vacuo* to remove solvent of crystallization, weighed 1.71 g. (48%) and melted at 104–108°. Recrystallization at 70–80° from 250 parts of Skellysolve E[24] gave material melting at 123–126° and rotating in chloroform +76.1° (*c* 1.09). When mixed with authentic 2,3,4,6-tetrabenzoyl-D-glucose, melting at 125–129°,[25] there was no depression of the melting point.

From the filtrate, on seeding with 1,3,4,6-tetrabenzoyl-D-fructose,[13] 1.50 g. (42%) of crude product, melting at 119–121°, was obtained. Recrystallization from 20 parts of 1:2 absolute alcohol–pentane and then from 3.5 parts of absolute alcohol gave material melting at 122–126° and showing in chloroform −4.8° (28 min.) → −11.0° (22.7 hr.) (*c* 2.17). Mixture with authentic 1,3,4,6-tetrabenzoyl-D-fructose [m.p. 124–127°, $[\alpha]^{20}D$ −5.7° (30 min.) → −12.2° (22 hr.) in chloroform] resulted in no depression of the melting point. Brigl and Schinle[12,13] recorded a melting point of 123–124° and a rotation in chloroform of −6.1° (30 min.) → −13.7° (20 hr., final) for 1,3,4,6-tetrabenzoyl-D-fructose.

Methyl Tetrabenzoyl-β-D-glucopyranoside from Octabenzoyl-D-sucrose.—Pure, amorphous octabenzoylsucrose (7.01 g.) was dissolved in sufficient 30% hydrogen bromide–glacial acetic acid to make 100 ml. of solution which was then held at 20°. When mutarotation had ceased (3.5 hr.), the solution was diluted with methylene chloride and washed thrice with ice-water and once with cold, saturated sodium bicarbonate. After desiccation with sodium sulfate and filtration through decolorizing carbon, the solution was concentrated *in vacuo* (40° bath) to a very stiff sirup. A portion (513.3 mg.) of this sirup was dissolved in 1:9 (v./v.) dioxane–methanol (50.0 ml. total volume) and the mutarotation of the resulting solution observed at 20°.

DATA OBTAINED, AND FIRST-ORDER CONSTANTS CALCULATED THEREFROM

Time, min.	Obsd. rotation, αD (2 dm., circular degrees)	*k*, min. decadic logs
0	+1.22° (extrapd.)	.....
3.7	1.21	0.00110
42	1.16	.00062
78	1.13	.00052
98	1.12	.00046
147	1.09	.00041
224	1.05	.00036
370	0.98	.00032
458	.94	.00032
1902	.47	.00031
2882	.33	.00032
3604	.29	.00031
5717	.21	.....
7582	.21	.....

On the basis of complete conversion to methyl tetrabenzoylhexoside, the final rotation corresponds to a specific rotation of + 11.1°; the specific rotation of methyl tetrabenzoyl-β-D-glucopyranoside in 1:9 dioxane–methanol is + 28.8° (*c* 0.27).

The remainder of the sirup (6.40 g.) was dissolved in 750 ml. of absolute methanol and left at 20°. After four days, seeding with methyl tetrabenzoyl-β-D-glucopyranoside led to the isolation of 2.26 g. (76% based on the mixture of tetrabenzoylglycosyl bromides) of this compound melting at 161–162°. The product did not depress the melting point of authentic material. Concentration of the mother liquor afforded 0.32 g. (11%) more crude methyl tetrabenzoyl-β-D-glucopyranoside; no other product could be obtained in crystalline form.

The Rate of Reaction of Tetrabenzoyl-α-D-glucopyranosyl Bromide with 1:9 Dioxane–Methanol at 20°.—Pure tetrabenzoyl-α-D-glucopyranosyl bromide (513.3 mg.), prepared as described in an earlier publication,[9] was dissolved in 1:9 (v./v.) dioxane–methanol (50.0 ml., total volume) and the mutarotation of the resulting solution observed at 20°.

DATA OBTAINED AND FIRST-ORDER REACTION CONSTANTS

Time, min.	Obsd. rotation, αD (2 dm., circular degrees)	*k*, min. decadic logs
0	+2.67° (extrapd.)	.....
6.6	2.66	0.00030
50.5	2.60	.00030
93.5	2.54	.00030
135	2.48	.00030
150	2.45	.00032
211	2.41	.00028
540	2.02	.00030
1163	1.52	.00030
1581	1.27	.00031
2602	0.86	.00034
2780	0.83	.00034
4845	0.59	.....

The initial, extrapolated rotation corresponds to a specific rotation of +130°; the specific rotation of tetrabenzoyl-α-D-glucopyranosyl bromide in chloroform is +123.6°.[9] The final rotation corresponds to a specific rotation of +31° assuming complete conversion to methyl tetrabenzoylhexo-

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[20] Seed crystals were initially obtained from a carbon tetrachloride–pentane solution stored 5 weeks at +5°.

[21] Loss of weight *in vacuo* at 57° for a sample which had been superficially dried on paper at −5° for 15 minutes.

[22] Loss of weight *in vacuo* at 57° for a sample which had been exposed to the air at −5° overnight.

[23] E. Fischer and H. Noth (ref. 11) showed that 2,3,4,6-tetrabenzoyl-D-glucose crystallizes from methanol with solvent of crystallization.

[24] A petroleum fraction (b.p. 100–140°) manufactured by Skelly Oil Co., Kansas City, Mo.

[25] Authentic 2,3,4,6-tetrabenzoyl-D-glucose was prepared in a manner similar to that described by Fischer and Noth (ref. 11). As indicated by these authors the substance is difficult to obtain in definite form. Recrystallization of material melting at 125–127° from 1:1 benzene–pentane gave material much less soluble in 95% alcohol and showing m.p. 103–110° and $[\alpha]^{22}D$ +40.2° (*c* 1.05, $CHCl_3$). A further recrystallization from 250 parts of Skellysolve E[24] at 80° yielded a form melting at 125–129° and rotating in chloroform +75.8° (*c* 0.77) and in alcohol +76.5° (*c* 1.00). In 1:9 (v./v.) dioxane–methanol, a slow mutarotation was observed: +75.5° (4 min.) → +70.1° (1 month). Fischer and Noth recorded a m.p. of 119–120° and a rotation in alcohol of $[\alpha]^{21}D$ +70.6°.

side; methyl tetrabenzoyl-β-D-glucopyranoside shows +28.8° in 1:9 dioxane–methanol (*c* 0.27).

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Preparation and Reactions of *o*-Hydroxycinnamic Acids and Esters

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The superiority of aniline–pyridine as a solvent and catalyst combination for the condensation of malonic acid with *o*- and *p*-hydroxybenzaldehydes has been demonstrated. The use of aqueous sodium bisulfite for the decarboxylation of 3-carboxycoumarins has been shown to be of general application. Although methyl *o*-hydroxycinnamate condenses with isoprene to form a pyrone in low yield, *o*-hydroxy- and 2,6-dihydroxycinnamic acids and the methyl ester of the latter do not react with isoprene under conditions similar to those which are effective with the analogous compounds having methoxy in place of hydroxy groups. When the hydroxy groups are protected with acetal linkages, either prepared from ethyl vinyl ether or dihydropyran, the addition of isoprene does not occur.

The low reactivity of *o*-hydroxycinnamic acid or ester with isoprene in the Diels–Alder reaction has been observed by previous investigators[2] in the field of natural products. An attempt has now been made to determine, if possible, conditions which might bring about the desired addition more satisfactorily and to observe the reactivity when the phenolic group or groups are blocked with acetal formation. A detailed study of the use of aniline[3] as a catalyst in obtaining *o*- and *p*-hydroxycinnamic acids has been made.

o-Hydroxycinnamic acid and 2,6-dihydroxycinnamic acid were selected as type compounds. Abnormally low yields were reported when *o*- and *p*-hydroxybenzaldehydes were condensed with malonic acid in the presence of pyridine–piperidine, whereas other aromatic aldehydes condensed very satisfactorily. Aniline[3] was found to be superior to piperidine in the condensation of 2,6-dihydroxy-4-methylbenzaldehyde with malonic acid to produce 3-carboxy-5-hydroxy-7-methylcoumarin (75% yield). The use of aniline was therefore applied to a similar condensation with various hydroxybenzaldehydes. The results which are listed in Table I indicate the high yields of products. *m*-Hydroxybenzaldehyde was included to demonstrate that aniline is not limited in its catalytic effect merely to the *o*- and *p*-hydroxy compounds.

The reactions proceeded without significant side reactions when the temperature was below approximately 55°. In the case of vanillin increasing the temperature 10° reduced the yield from 86 to 71%. In those compounds without an *o*-hydroxy group where cyclization could not occur, very little difficulty was encountered in obtaining the corresponding cinnamic acids under various conditions.

In the condensation of molecules with *o*-hydroxy groups, 3-carboxycoumarins formed. The temperature was critical and had to be maintained at that of the room in order to avoid substantial amounts of polymeric styrenes which appeared at higher temperatures. The other by-products, Schiff bases, were less when a minimum quantity of aniline was used. In a series of reactions using salicylaldehyde, no yield of 3-carboxycoumarin resulted when the ratio of pyridine to aniline varied from 20 to 50:1 and the reaction mixture was allowed to stand for 5–25 hours, either at 27 or 55°. However, a mixture of 0.05 ml. of aniline, 1 ml. of pyridine, 1.5 g. (1 mole equivalent) of salicylaldehyde and 2.4 g. (2 mole equivalents) of malonic acid gave a yield of 77–83% after 1–2 hours. With double the quantities of 2-resorcylaldehyde, the pyridine was increased proportionately but not the aniline.

TABLE I

THE REACTION OF ALDEHYDES WITH MALONIC ACID

A, 3-carboxycoumarin, m.p. 187–189° (cor.); B, 3-hydroxycinnamic acid, m.p. 191° (cor.); C, 4-hydroxycinnamic acid, m.p. 210–211° (cor.) (dec.); D, 4-hydroxy-3-methoxycinnamic acid, m.p. 168.5–169.5° (cor.); E, 3-carboxy-7-hydroxycoumarin, m.p. 262° (cor.) (dec.); F, 3,4-dihydroxycinnamic acid, m.p. 194° (cor.) (dec.); G, 3-carboxy-5-hydroxycoumarin, m.p. 277° (cor.) (dec.).

Benzaldehyde	Product,[a]	Aniline, ml.	Pyridine, ml.	Moles ald.	Time in hr.	Temp., °C.	Yield, %
o-OH	A	0.05	1	0.0164	2	27	83
m-OH	B	.1	2	.0164	5	55	90
p-OH	C	.025	1	.0041	7.5	65	84
4-OH,3-OMe	D	.05	2	.0165	14	55	86
2,4-Di-OH	E	.075	2	.0167	12	27	71
3,4-Di-OH	F	.05	3	.0167	13	55	77
2,6-Di-OH	G	.075	5	.0347	20	27	83

[a] Previously prepared: A, U. S. Patent 2,338,569, Dow Chemical Company; B, K. C. Pandya and T. A. Vahidy, *Proc. Indian Acad. Sci.*, **4A**, 144 (1936); C, P. N. Kurian, K. C. Pandya and V. R. Surange, *J. Indian Chem. Soc.*, 11, 823 (1934); D, K. C. Pandya, T. S. Sodhi and D. S. Mittal, *Proc. Indian Acad. Sci.*, **9A**, 511 (1939); E, S. Rangaswami, T. R. Seshadri and V. Venkateswarlu, *ibid.*, **13A**, 316 (1941); F, see D; G, reference 10.

2-Resorcylaldehyde was prepared by a method similar to that used for 2,6-dihydroxy-4-methylbenzaldehyde; resorcinol dimethyl ether, after treatment with *n*-butyllithium, followed by N-methylformanilide, gave 2-resorcylaldehyde dimethyl ether. This was demethylated with alumi-

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[1] An abstract of a thesis submitted by Mr. Theodore E. Bockstahler to the Graduate College of the University of Illinois, 1949, in partial fulfillment of the requirements for the Degree of Doctor of Philosophy.

[2] R. Adams, W. D. McPhee, R. B. Carlin and Z. W. Wicks, THIS JOURNAL, **65**, 356 (1943).

[3] R. Adams and J. Mathieu, *ibid.*, **70**, 2120 (1948); F. Vorsatz, *J. prakt. Chem.*, **145**, 265 (1936); U. S. Patent 2,338,569 [*C. A.*, **38**, 3671 (1944)].