

Hydrogen Bromide ω -Benzylcamphene.—A continuous stream of dry bromine-free hydrogen bromide, generated by the action of dry bromine on naphthalene, was passed into a solution of 7 g. (0.03 mole) of ω -benzylcamphene in 25 cc. of anhydrous ether for two hours at 15°. About 9 g. of a reddish-brown liquid was obtained after removal of the ether. This was dried over calcium chloride: d^{25} 1.194; n_D^{25} 1.55; decomposed on attempted distillation at 1 mm. into a hydrocarbon having the physical properties of ω -benzylcamphene and hydrogen bromide. *Anal.* Calcd. for $C_{17}H_{23}Br$: Br, 26.03. Found: Br, 25.83.

Inactivation Procedures: (a) ω -Amylcamphene.— ω -Amylcamphene (35.5 g., 0.17 mole, $[\alpha]^{20}_D +17.8$) was dissolved in anhydrous ether (100 cc.) and treated with dry hydrogen chloride. After two hours at 5–10°, and two additional hours at 10–15°, the saturate was stoppered securely and allowed to stand in a refrigerator for twelve hours; chlorine content, *ca.* 14% based upon the ether-free material. The ether was removed, 60 g. (0.64 mole) of aniline added, and the mixture refluxed for eighteen hours. Washing of the cool mass with ether left 22 g. of aniline hydrochloride as crystalline residue. The ether extract was dried, the ether removed and the liquid residue distilled (15 mm.) after addition of 5 g. of aniline hydrochloride. The two fractions (55 g. at 124°, and 12 g. at 124–126°) thus secured were dissolved separately in petroleum ether and extracted with 5% hydrochloric acid. The two portions were combined, washed, dried, and freed of petroleum ether. Final distillation yielded ω -amylcamphene (26 g.); b. p. 124–125° (15 mm.); d^{20} 0.8672; n_D^{25} 1.475; $[\alpha]^{20}_D +0.20^\circ$ (*c.* 86.72).

(b) ω -Benzylcamphene.— ω -Benzylcamphene ($[\alpha]^{25}_D +0.66^\circ$, 75.4 g., 0.33 mole), aniline (93 g., 1 mole) and aniline hydrobromide (58 g., 0.33 mole) were refluxed for twenty-two hours. The resulting hydrocarbon and excess aniline were distilled directly from the reaction mixture, and isolation of the hydrocarbon effected substantially as under (a) recovered ω -benzylcamphene, 58 g.: b. p. 138–140° (5 mm.); d^{25} 0.9668; n_D^{25} 1.538; $[\alpha]^{25}_D +0.10^\circ$ (*c.* 96.68).

Action of Trichloroacetic Acid on ω -Amylcamphene.— ω -Amylcamphene, 23 g. (0.11 mole), was heated with 90 g. (0.55 mole) of trichloroacetic acid at 40° for several days. The product was dissolved in ether (100 cc.), neutralized and distilled to remove ether, leaving 40 g. of ester (8 amylisobornyl trichloroacetate, III). The ester (34 g.) was hydrolyzed with a solution of 25 g. of potassium hydroxide in 180 cc. of 95% alcohol and 50 cc. of water by refluxing for four hours, yielding 9 g. of amylisoborneol, b. p. 105–120° (1 mm.). This product solidified in part on standing for two weeks. Dried on a porous plate, it melted at 63–64°.

Anal. Calcd. for $C_{15}H_{23}O$: C, 80.29; H, 12.58. Found: C, 80.17; H, 12.80.

This procedure is substantially that of Lipp and Lausberg¹⁴ for the transformation of ω -bromocamphene to an ester through trichloroacetic acid addition.

Summary

1. A method has been developed that has led to the synthesis of new optically active ω -substituted camphenes in good yield.
2. The character and structure of these ω -substituted camphenes has been shown by their synthesis from compounds of known structure, by their behavior with halogen and hydrogen halides, and by the action of trichloroacetic acid.
3. ω -Chloromethylcamphene has been prepared in improved yield by a method which involves a minimum of racemization.
4. Inactivation has been accomplished in this series without any apparent alteration of the carbon skeleton.

(14) Lipp and Lausberg, *Ann.*, **436**, 280 (1924).

WASHINGTON SQUARE

NEW YORK CITY, N. Y.

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Probable Structure of a Crystalline Substance Derived from Starches Oxidized with Periodate

BY J. H. MICHELL¹ AND C. B. PURVES

The oxidation of corn starch with periodic acid was first performed by Jackson and Hudson,^{2a} who afterward hydrolyzed the product with aqueous acid and isolated derivatives of glyoxal and *d*-erythrose in yields of 33 and 22%, respectively.^{2b}

(1) This article is based on a thesis submitted by J. H. Michell to the Faculty of the Massachusetts Institute of Technology in partial fulfillment of the requirements for the Degree of Doctor of Science, 1941.

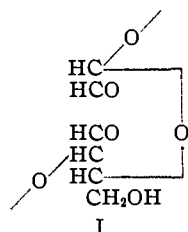
(2) Jackson and Hudson, *THIS JOURNAL*, (a) **59**, 2049 (1937); (b) **60**, 989 (1938).

These and similar results,³ together with the known behavior of 1,2 glycols toward oxidation with aqueous periodate,⁴ justified the conclusion that most or all of the oxidized starch had the structure I.

Jackson and Hudson observed that acid methanol changed the oxidized starch to a soluble, non-reducing, levorotatory sirup^{2a} from which an un-

(3) Caldwell and Hixon, *J. Biol. Chem.*, **123**, 595 (1938).

(4) Malaprada, *Bull. soc. chim.*, [5] **1**, 833 (1934).



known crystalline substance was later isolated.⁵ The substance was obtained from several root and cereal starches and also from a carefully purified soluble potato starch. The present article revises some of the earlier data and describes experiments which throw light on the nature of the crystalline material.

Isolation of the Crystals from Starch.—Commercial powdered potato starch (Mallinckrodt) gave an oxidized product which was granular and easy to manipulate. One-third mole (54 g., after correction for moisture, ash and protein) was oxidized with one-third mole of aqueous sodium periodate (100 g. of 98% $\text{Na}_2\text{H}_2\text{IO}_6$) buffered to pH 4.2 with acetic acid as previously described.⁵ The temperature was kept between 5 and 15° by external cooling, because one oxidation which warmed up above 20° resulted in an unfilterable gel. After the insoluble product was completely freed of iodate ion by repeated washing with water, it was dried by two washings with 400 ml. volumes of acetone followed by two with carefully purified light petroleum. Drying to constant weight *in vacuo* left the product as a white, light powder. Drying directly from water gave a tough, horny material which could scarcely be disintegrated in a mortar. The yield was 105–110% and combustion analyses showed that this was probably due to a tenacious retention of water. The dry, oxidized starch powder (41.4 g. based on periodate consumed), was heated with 410 ml. of dry, synthetic methanol containing 41 g. of dry hydrogen chloride. A flask with a ground joint reflux condenser equipped to exclude moisture was used. During the first twenty minutes of heating, the oxidized starch passed through a gummy, stringy state and dissolved to give a very dark brown solution. A specimen stored over anhydrous calcium chloride for three months took an hour to dissolve. After a total of three hours of heating, the solution was cooled, made neutral to moist congo red paper with a slight excess of lead carbonate, and filtered. The filtrate plus the methanol washings from the residue was diluted with 100 ml. of water and after treatment with 10 g. of decolorizing carbon the methanol was removed by distillation under diminished pressure. Chloroform extractions, repeated until the extracts became colorless, removed the product from the aqueous liquor. The combined extracts (1250 ml.) were dried over anhydrous sodium sulfate and distilled under diminished pressure to a sirup (31 g.). Distillation of this sirup (see following article) gave 9.1 g. of a viscid, amber fraction, b. p. 185–220° (3–4 mm.) which, on freezing in dry-ice and triturating with ether, deposited the crude crystalline product

(5) Grangaard, Michell and Purves, *THIS JOURNAL*, **61**, 1290 (1939).

as white flakes. Two recrystallizations from ether left the melting point constant at 148–148.5° (cor.)⁶ while the permanent specific levorotation in water was -4.3° (sodium light; c , 0.578% and 20°). The above modifications of the original method,⁵ raised the yield from about 1% to about 2% of the oxidized starch.

Anal. Calcd. for $\text{C}_{10}\text{H}_{13}\text{O}_6(\text{OCH}_3)_3$: C, 48.43; H, 6.86; OCH_3 , 28.9; mol. wt., 322. Found for two independent preparations: C, 48.21, 47.77, 47.75; H, 6.61, 6.59, 6.63; OCH_3 , 28.9, 29.2, 29.1%; mol. wt. (ebullioscopic⁷), 321, 323 for 87.0 and 76.7 mg. samples dissolved in 10 ml. of carbon tetrachloride.⁸

Examination of the Crystalline Material.—Micro and semi-micro technique was used throughout as the total amount of substance did not exceed 4.5 g. The crystals were neutral to litmus, stable to alkali and therefore contained no carboxylic acid or ester groups. Negative tests with Fehling solution, with bromine and with tetranitromethane⁹ revealed no aldehyde, α -hydroxy ketone or unsaturated groups. Methanol solutions of various concentrations were transparent to ultraviolet light and the complete absence of aromatic, unsaturated, carbonyl or carboxylic structural units was thereby confirmed.

Preparation of a Monoacetate.—The substance, 381.2 mg., was acetylated with 5 ml. of a 1:1 mixture of purified, dry pyridine and acetic anhydride. The glass-stoppered flask containing the reagents was warmed on the steam-bath until the crystals dissolved (three minutes) and was kept at room temperature for five days before its contents were poured onto crushed ice. The precipitate was filtered, washed with water, and recrystallized several times by adding water to a hot 50% alcoholic solution. After standing overnight at 10°, the solution deposited 310 mg. (72%) of long, fine needles which were dried *in vacuo* at 65°. They melted at 120–120.5° and at 107–113° when mixed with the original substance. They were freely soluble in most organic solvents but not in petroleum ether or water. A 0.89% solution in purified dioxane had a specific levorotation of -7.3° (sodium light and 21°) which was practically the same as that of the unacetylated material.

Anal. Calcd. for $\text{C}_{10}\text{H}_{12}\text{O}_6(\text{OCH}_3)_3(\text{O}-\text{COCH}_3)$: C, 49.5; H, 6.6; OCH_3 , 25.6; mol. wt., 364. Found: C, 49.1, 49.1; H, 6.7, 6.9; OCH_3 , 24.8, 25.0%; mol. wt. (ebullioscopic⁷), 365, 355, 351 for 84.0, 87.9 and 84.0 mg. samples in 10 ml. of carbon tetrachloride. In an acetyl estimation⁹ 13.8 and 21.5 mg. samples required 2.65 and 4.10 ml. of 0.01425 *N* potassium hydroxide, respectively. Calcd. for $\text{C}_{10}\text{H}_{12}\text{O}_6(\text{OCH}_3)_3(\text{OCOCH}_3)$: acetyl 11.8. Found: 11.8, 11.7. Five drops of *N*/10 barium methylate were just sufficient to render a solution of the acetate (70 mg.) in dry methanol permanently alkaline to phenol red. Next day, when deacetylation was complete, the solvent was evaporated and the residue recrystallized from ether. The melting point was 148–148.5° and was not depressed

(6) The structure $\text{C}_{13}\text{H}_{16}\text{O}_8(\text{OCH}_3)_4$ previously chosen⁵ also agreed with the analytical results and by chance with molecular weights determined by the Rast method. Recalibration of the latter corrected the earlier molecular weights from 419–432 to 339–350. The melting point was previously given as 150–150.5°.

(7) Swietoslawski, *Bull. soc. chim.*, **49**, 1563 (1931).

(8) Werner, *Ber.*, **42**, 4324 (1909).

(9) Kunz and Hudson, *THIS JOURNAL*, **48**, 1978 (1926).

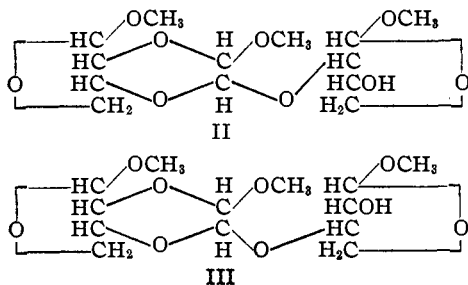
by admixture with the original, unacetylated substance. Acetylation of the latter therefore involved no unexpected structural alterations but gave a monoacetate.

Preparation of the *p*-Toluenesulfonyl Monoester.—A solution of the crystals (296 mg.) in 4.1 g. of purified dry pyridine was mixed at 0° with a solution of carefully purified *p*-toluenesulfonyl chloride (2.15 g.) in 3.1 g. of dry pyridine. These molar amounts (1:12:92) were known to give a fairly rapid and complete esterification.¹⁰ The mixture was stoppered and set aside for one week¹¹ in a dark place before being poured into 40 ml. of aqueous 5% acetone cooled to 0°. The precipitate was washed with water at 0°, dried and recrystallized twice from warm petroleum ether, in which it was sparingly soluble; yield, 179 mg. or 41%. The well-formed, long needles melted at 87–88° and were freely soluble in common organic solvents.

Anal. Calcd. for C₁₀H₁₂O₆(OCH₃)₃(SO₂·C₇H₇): C, 50.4; H, 5.9; OCH₃, 19.5; S, 6.7. Found: C, 49.6, 49.6, 49.7; H, 5.9, 5.9, 6.4; OCH₃, 19.6, 19.5; S, 6.8, 6.8.

The formation of this monoester supported the presence in the original substance of only one hydroxyl group. A test with ferric chloride showed that the latter was not of a phenolic or enolic nature.

The above work showed that the substance was C₁₀H₁₂O₆(OH)(OCH₃)₃ and that the five oxygen atoms in the saturated, aliphatic nucleus were involved in ether or acetal linkages. Application of the mathematical relationship called the "condensation number"¹² to the formula indicated three cyclic systems. Although several types of structure compatible with the requirements were possible, the substance was derived from periodate oxidized starch (I) which consists of alternating erythrose (C₄) and glyoxal (C₂) units. Two erythrose residues with their two furanose¹³ rings, plus one glyoxal unit forming part of a third ring, in acid methanol might form structures II or III,¹⁴ either of which would satisfy all the evidence so far gathered from the study of the crystals. Further experimental work supported this hypothesis.



(10) Cramer and Purves, *THIS JOURNAL*, **61**, 3458 (1939).

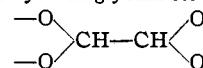
(11) A week was probably too short a time for an optimum yield of ester in this case.

(12) Frèrejacque, *Bull. soc. chim.*, **6**, 1008 (1939).

(13) Hockett and Maynard, *THIS JOURNAL*, **61**, 2111 (1939). Professor R. C. Hockett suggested the possibility of structures II and III to the authors.

(14) The chemistry of highly substituted 1,4-dioxanes was reviewed in *J. Chem. Soc. Ann. Reports*, **35**, 307 (1938).

Presence of a Glyoxal Unit.—A 168.4-mg. sample of the crystals was boiled for twenty-four hours with 15 ml. of dry methanol containing 10% of hydrogen chloride. Steam distillation of the neutralized solution gave a distillate containing 64.7 mg. or 82.5% of the calculated amount of glyoxal tetramethylacetal, (CH₂O)₂CH—CH(OCH₃)₂, estimated after acid hydrolysis as glyoxal-bis-2,4-dinitrophenylhydrazone.¹⁵ The



unit was therefore present in the crystals.

Proof of Absence of Primary Alcohol Group.—The *p*-toluenesulfonyl ester of the substance (105 mg., 1 mole), pure sodium iodide (51.2 mg., 1.5 moles) and 3.2 ml. of pure, dry acetone were sealed in a dry 10 mm. × 10 cm. Pyrex tube. Enclosed in wire gauze for safety, the tube and contents were kept at 100° for two hours. On cooling, less than 3 mg. of crystalline material separated and was removed. The solid recovered by evaporation of the mother liquor was extracted with 2 ml. of water to remove sodium iodide and the dried residue was repeatedly extracted under reflux with low boiling petroleum ether. After cooling, the combined petroleum ether extracts deposited 88.7 mg. or 84.5% of the original *p*-toluenesulfonate in a pure crystalline condition. The melting point was correct at 87–88° and a mixed melting point was not depressed.

The recovery of 84.5% of the original ester in this semi-micro scale experiment showed that it was not derived from a primary alcohol, since a *p*-toluenesulfonate group attached to the latter is known to be replaced quantitatively by iodine in the conditions used.¹⁶

Titration of the Hydrolyzed Substance with Periodic Acid.—One ml. of an aqueous solution containing 0.368 mg. (0.114 × 10⁻⁵ mole) of the substance, was heated on the steam bath with 5 ml. of 0.08% aqueous potassium metaperiodate (KIO₄ = 1.74 × 10⁻⁵ mole) and 3.3 ml. of 5% sulfuric acid (1.7 × 10⁻³ mole). Two blanks were also run. Forty minutes of heating completed the hydrolysis of the substance and the concurrent oxidation of the hydrolyzate by the periodic acid. After cooling, an addition of 6.6 ml. of 12% dipotassium phosphate reduced the acidity to pH 6.8. A single crystal of potassium iodide was added and the liberated iodine was titrated with *N*/200 aqueous sodium thiosulfate, using freshly prepared starch as indicator.¹⁷ The blanks each required 6.66 ml. while the other solutions took 3.98, 3.94 and 3.93 ml. of thiosulfate. These data corresponded to the consumption of 5.97, 6.05 and 6.08 moles of periodic acid, respectively, by 322 g. (1 mole) of the substance.

The above result assumed that the glyoxal also liberated in the hydrolysis used up a negligible amount of periodic acid. Trials in which 0.26 to 1.3 × 10⁻⁵ mole of glyoxal tetramethylacetal were substituted for the substance showed that this was often the case. On other occasions, undetermined causes probably connected with the technique of titration led to apparent consumptions of up to

(15) Grangaard and Purves, *THIS JOURNAL*, **61**, 428 (1939). The principle of the method for isolating the tetramethyl acetal was based on unpublished work by these authors. More recent unpublished work shows that the estimation was almost certainly too high by a substantial amount.

(16) Oldham and Rutherford, *ibid.*, **54**, 366 (1932).

(17) Rappoport and Reifer, *Mikrochemica Acta*, **2**, 273 (1937).

0.55 mole of oxidant per mole of glyoxal acetal¹⁸ (two hours of heating) and of 6.6 moles per mole of the crystalline substance from starch (one hour of heating). Control experiments with mixtures of glyoxal tetramethylacetal and glucose showed that the latter always accounted for the proper amount of 4.8 to 5.0 moles of oxidant when correction was made for the rather capricious behavior of the former. Aldose titrations with alkaline hypiodite¹⁹ were unreliable.

Rotation Change in Aqueous Acid.—A suspension of 368.5 mg. of the crystals in 10.0 ml. of 0.1 *N* hydrochloric acid was warmed for twenty minutes on the steam-bath until solution was complete and no crystals separated on cooling. The rotations observed in a 2-dm. tube with sodium light were 4.50, 4.74 and 4.50° after total heating times of 30, 60 and 135 minutes, respectively. Later readings were uncertain because the strongly reducing solution turned yellow and slowly deposited a brown precipitate. The corresponding specific dextro rotations were +81, 85 and 81° when calculated on the assumption that two moles of erythrose resulted from the hydrolysis of one mole of substance ($[\alpha]^{20}_D -4.3^\circ$ in water). These rotations were in sharp contrast to the final value of -14.5° which was found for *d*-erythrose dissolved in water or dilute acid.²⁰

The above experiments supported the assignment of either formula II or III to the crystals by demonstrating the presence of a glyoxal unit and the absence of a primary alcoholic group. Simultaneous hydrolysis and oxidation with periodic acid reduced about six moles of the oxidant per mole of substance, as theory for the production of two moles of an aldotetrose demanded.⁴ On the other hand, attempts to prove that the aldotetrose was erythrose failed. When the crystals were hydrolyzed with aqueous acid, the specific rotation remained far removed from the value usually accepted for this sugar. Erythrose was not recovered from the hydrolyzate either as crystalline brucine *d*-erythronate^{2b} or as potassium acid tartrate.^{21,22} An attempt to distinguish between the possible structures II and III by the selective hydrolysis of the *p*-toluenesulfonyl ester of the crystals to either 3- or 2-erythrose *p*-toluenesulfonate also gave a negative result. Although these failures were perhaps partly due to

(18) Clutterbuck and Reuter, *J. Chem. Soc.*, 1467 (1935), showed that methyl glyoxal, biacetyl and other substituted glyoxals could be quantitatively cleaved by one mole of periodic acid.

(19) Willstätter and Schudel, *Ber.*, 51, 780 (1918).

(20) Ruff, *ibid.*, 32, 3672 (1899). This rotation is uncertain because erythrose has not yet been crystallized and specific rotations ranging up to +30.5° have been observed for the *d*-sugar. See Felton and Freudenberg, *THIS JOURNAL*, 57, 1637 (1935).

(21) Hirst and Smith, *J. Chem. Soc.*, 3147 (1928).

(22) Nelson, *J. Assoc. Off. Agr. Chem.*, 9, 375 (1926).

the marked instability of erythrose in aqueous acid²⁰ and to the semi-micro scale of the work, their consistency pointed to some kind of chemical interaction between erythrose and glyoxal during acid treatments. The following article supports the C₄-C₂-C₄ skeleton assigned to the crystals by describing the degradation of an isomer to a C₄-C₂ derivative. As such isomers and derivatives together accounted for almost 50% by weight of the original oxy-starch, their structures of necessity were based upon erythrose.

Summary

1. Minor revisions of the method of isolating a crystalline material, m. p. 148–148.5° (cor.), from starch first oxidized by periodate and then heated with 10% hydrogen chloride in methanol raised the yield from about 1% to about 2%. The earlier formula was corrected to C₁₀H₁₆O₅·(OH)(OCH₃)₃ and the specific levorotation in water found to be -4.1° . Structural investigations showed that all the oxygen atoms in the saturated, tricyclic nucleus were of an ether or hemiacetal type. The substance probably consisted of a methylerythrofuranside unit combined in a 1,4-dioxane ring with a glyoxal residue, to which a second methylerythrofuranside residue and a methyl group were separately attached through glyoxal hemiacetal linkages. Such a structure represented one of the isomeric hexahydro-3,5-dimethoxy-2-(1-methyl-3 or 2-erythrofuransyloxy)furo[3,4]-*p*-dioxins.

2. The above structural assignment was supported by the recovery of glyoxal tetramethylacetal when the substance was heated in acid methanol with drastic conditions. Several attempts to recover erythrose derivatives, however, failed.

3. The long white needles of the monoacetate of the substance melted at 120–120.5° and had a levorotation of -7.3° in dioxane.

4. The corresponding mono-*p*-toluenesulfonate consisted of well-formed long needles, m. p. 87–88°, which were stable when heated at 100° with sodium iodide in acetone. This stability showed that the ester was not derived from a primary alcohol and thereby supported the structure proposed above.

CAMBRIDGE, MASSACHUSETTS

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