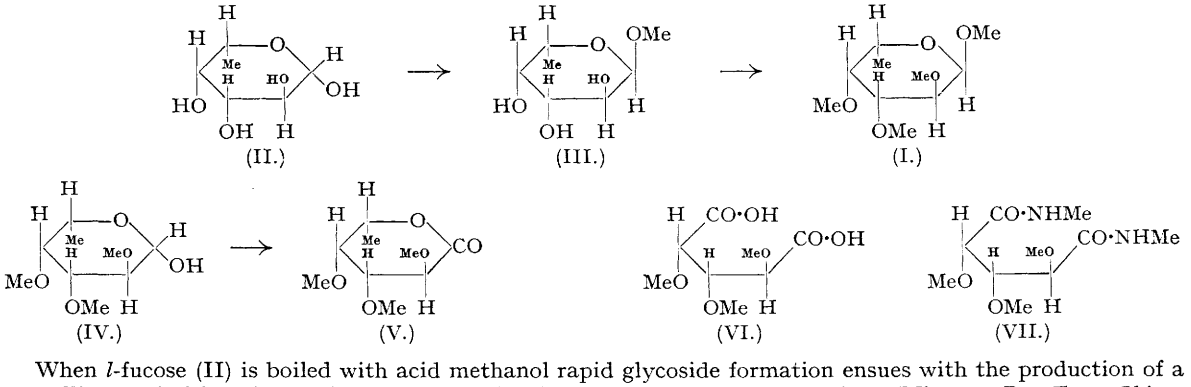
194. *The Chemistry of Gum Tragacanth. Part II. Derivatives of* d- *and* l-*Fucose.*

By Sybil P. James and F. Smith.

The fully methylated methyl pentose obtained from methylated tragacanthic acid (preceding paper) has been shown to be 2 : 3 : 4-trimethyl α-methyl-*l*-fucoside (I). Methylation of α-methyl-*l*-fucoside (III) gives (I) which upon hydrolysis affords 2 : 3 : 4-trimethyl *l*-fucose (IV) characterised as the crystalline *anilide*. Oxidation of (IV) with bromine leads to the formation of 2 : 3 : 4-*trimethyl*-δ-*fuconolactone* (V). Oxication of (I) with nitric acid gives trimethoxy *d*-araboglutaric acid (VI) identified in the form of its crystalline bismethylamide (VII). The synthesis of 2 : 3 : 4-trimethyl β-methyl-*d*-fucoside (XII) from galactose is described; the 2 : 3 : 4-trimethyl *d*-fucose (XIII) obtained from (XII) is shown to be the enantiomorph of (IV) by the preparation of the corresponding *anilide*.

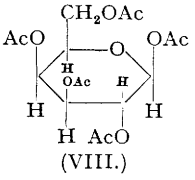
Hydrolysis of methylated tragacanthic acid (Part I) yielded a crystalline product the analysis of which showed it to be a fully methylated derivative of a methyl pentose. Since the occurrence of *l*-fucose in gum tragacanth had been reported (Kraut, *Ber.*, 1872, **4**, 650) this product was believed to be a derivative of *l*-fucose. This view has been proved by the following series of experiments which has shown that (I) is 2 : 3 : 4-*trimethyl* α-*methyl*-l-*fucopyranoside*.



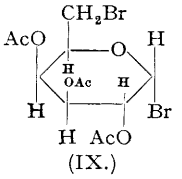
When *l*-fucose (II) is boiled with acid methanol rapid glycoside formation ensues with the production of a crystalline methyl fucoside (III) the rotation of which indicates that it is the α-form (Minsaas, *Rec. Trav. Chim.*, 1932, **51**, 475). Complete methylation of (III) with methyl iodide and silver oxide afforded the crystalline trimethyl α-methyl-*l*-fucoside (I) which was identical with the fully methylated methylpentoside isolated from methylated tragacanthic acid but which appeared to have a slightly different rotation ([α] −196°). The glycosidic methyl group of (I) is readily eliminated by heating with dilute sulphuric acid but in the methyl pentose series this cannot be regarded as an indication of a furanose type of structure because methyl methyl-

pentosides having a pyranose structure are known to undergo facile hydrolysis (Smith, *J.*, 1939, 744). The *trimethyl* l-*fucose* (IV) obtained on hydrolysis can be readily characterised in the form of its crystalline *anilide*. Oxidation of (IV) with bromine furnishes the corresponding *lactone* (V) an aqueous solution of which displays relatively rapid mutarotation thus suggesting the presence of a δ-lactone ring. Conclusive proof of the ring system and therefore the disposition of the methyl groups in (I) follows from the results of the oxidation of (I) with nitric acid. There is produced *d*-arabo-trimethoxyglutaric acid (VI), identified by its smooth transformation into the bis-methylamide (VII). The latter was identified by rotation, m. p. and by comparison with an authentic specimen (Goodyear and Haworth, *J.*, 1927, 3136). The formation of *d*-arabo-trimethoxyglutaric acid can only be explained if the three methyl groups are located in positions 2, 3, and 4, and accordingly the methylated fucoside (I) is designated 2 : 3 : 4-trimethyl α-methyl-*l*-fucopyranoside.

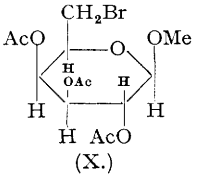
Confirmation of the formula (I) assigned to the trimethyl methylfucoside was afforded by the following preparation of 2 : 3 : 4-*trimethyl* β-*methyl*-d-*fucoside* by a synthetic method which leaves no doubt as to its structure.



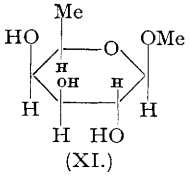
(VIII.)



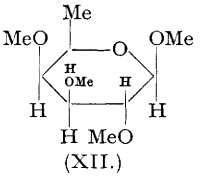
(IX.)



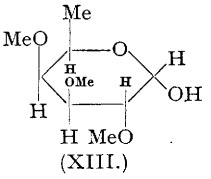
(X.)



(XI.)



(XII.)



(XIII.)

When penta-acetyl galactose (VIII) is allowed to react with liquid hydrogen bromide at room temperature for about eight hours (Armstrong and Fischer, *Ber.*, 1902, **35**, 837; Haworth, Jackson, and Smith, *J.*, 1940, 620) the α-acetobromogalactose 6-bromohydrin (IX) is produced. Treatment of the latter with methanol in the presence of silver carbonate yields the corresponding 2 : 3 : 4-triacetyl β-methylgalactopyranoside 6-bromohydrin (X). The halogen group in (X) can be smoothly replaced by hydrogen by shaking an alcoholic sodium hydroxide solution of (X) with a Raney nickel catalyst in an atmosphere of hydrogen according to the method of Levene and Compton (*J. Biol. Chem.*, 1935, **111**, 325); in the same process deacetylation also proceeds and there results β-methyl-*d*-fucopyranoside (XI) (cf. Schlubach and Wagenitz, *Ber.*, 1932, **65**, 304). Methylation of (XI) with methyl iodide and silver oxide yields the 2 : 3 : 4-trimethyl β-methyl-*d*-fucopyranoside (XII), treatment of which with dilute sulphuric acid caused the rapid removal of the glycosidic methyl group and the formation of 2 : 3 : 4-*trimethyl* d-*fucose* (XIII). The compound (XIII) proved to be the enantiomorph of the trimethyl *l*-fucose (IV) as shown by the fact that the crystalline *anilide* of this 2 : 3 : 4-trimethyl *d*-fucose (XIII) was found to be the enantiomorph of the trimethyl *l*-fucose anilide. Inasmuch as this synthetic 2 : 3 : 4-trimethyl β-methyl-*d*-fucopyranoside (XII) was not the enantiomorph of the 2 : 3 : 4-trimethyl methyl-*l*-fucoside (I) prepared from *l*-fucose, it follows that the glycoside (I) is the α-form

There can be no doubt therefore that the structure (I) assigned to the trimethyl methylfucoside is correct and that an " end " residue of *l*-fucose of the pyranose form is one of the constituents of tragacanthic acid.

Experimental.

Preparation of α-Methyl-l-fucoside (III).—*l*-Fucose (0·44 g.) was boiled for 3 hours with methanol (25 c.c.) containing 2% dry hydrogen chloride; the solution then no longer reduced Fehling's solution. The reaction mixture was neutralised with silver carbonate and filtered. Evaporation of the filtrate under reduced pressure gave a syrup (0·42 g.) which crystallised completely. After four recrystallisations from ethyl acetate the α-methyl-*l*-fucoside had m. p. 154—157°, $[\alpha]_D^{15°}$ −187° in water (c, 0·5) (Found : C, 47·1; H, 7·3; OMe, 17·4. Calc. for $C_7H_{14}O_5$: C, 47·2; H, 7·9; OMe, 17·4%).

2 : 3 : 4-*Trimethyl α-Methyl-l-fucoside* (I).—α-Methyl-*l*-fucoside (0·42 g.) was dissolved in the minimum amount of dry methanol and methyl iodide (10 c.c.) was added. The solution was refluxed for 6 hours in the presence of silver oxide (5 g.) which was added in small portions at hourly intervals; the methylation was facilitated by frequent agitation of the mixture. The methyl iodide was distilled off and the product was extracted with methanol. Concentration of the extract gave a syrup which was now soluble in methyl iodide. Two more methylations of the syrup with Purdie's reagents without the addition of methanol yielded a syrup (0·46 g.) which was distilled as a colourless liquid, b. p. (bath temp.) 100°/0·02 mm. The distillate crystallised spontaneously and after recrystallisation from ligroin the *trimethyl α-methyl-l-fucoside* had m. p. 85—92° alone or on admixture with a specimen derived from methylated tragacanthic acid, $[\alpha]_D^{15°}$ −196° in water (c, 0·5) (Found : C, 54·2; H, 9·1; OMe, 53·6. $C_{10}H_{20}O_5$ requires C, 54·5; H, 9·2; OMe, 56·3%).

2 : 3 : 4-*Trimethyl* l-*Fucose* (IV).—When a solution of crystalline trimethyl α-methyl-*l*-fucoside (1·8 g.) in 0·1N-sulphuric acid (100 c.c.) was heated on a boiling water bath it showed $[\alpha]_D$ −172° (initial value); −164° (after 0·5 hr.); −161° (1 hr.); −150° (2 hrs.); −144° (3 hrs.); −138° (4·5 hrs.); −130° (5·75 hrs.); −128° (7·25 hrs.); −123° (8·25 hrs.) (constant value). After 9 hours the concentration of sulphuric acid was increased to 1N and the heating continued but no further change in rotation was observed; hydrolysis was therefore complete. The solution was neutralised with barium carbonate, filtered, and evaporated to dryness under diminished pressure. Extraction with ether gave the 2 : 3 : 4-*trimethyl* l-*fucose* as a clear syrup (1·3 g.), $[\alpha]_D^{18°}$ −111° in water (c, 0·4) (Found : OMe, 45·4. $C_9H_{18}O_5$ requires OMe, 45·1%). When the hydrolysis of the crystalline trimethyl α-methyl-*l*-fucoside (0·29 g.) was effected

with normal sulphuric acid (20 c.c.) the following change in rotation was observed : $[\alpha]_D$ −163° (initial value); −140° (after 0·5 hrs.); −128° (1 hr.); −124° (1·25 hrs.); −121° (1·6 hrs.); −121° (2 hrs.). The free sugar (0·22 g.) was isolated as before.

2 : 3 : 4-*Trimethyl* l-*Lucose Anilide*.—The anhydrous, syrupy 2 : 3 : 4-trimethyl *l*-fucose was allowed to react for 2 hours with aniline (1 mol.) in boiling ethanol. On evaporation of the solvent a syrup was obtained which crystallised on keeping. The *trimethyl fucose anilide*, separated by trituration with ligroin followed by recrystallisation from ether, had m. p. 133—134°, $[\alpha]_D^{17°}$ −77° in ethyl alcohol (c, 1·0) (equilibrium value) (Found : N, 5·1. $C_{15}H_{23}O_4N$ requires N, 5·0%).

2 : 3 : 4-*Trimethyl*-l-*fuconolactone* (V).—Trimethyl fucose (0·29 g.) was dissolved in water (2 c.c.) and bromine (0·5 c.c.) was added. The solution was kept at room temperature for 24 hrs. after which time a portion of it had, when freed from bromine by aeration, no action on boiling Fehling's solution. The bromine was removed by aeration and the solution neutralised with silver carbonate and filtered. The filtrate was saturated with hydrogen sulphide, a little charcoal was added and the silver sulphide was filtered off. The residue was washed with hot water and the combined filtrate and washings evaporated to dryness under reduced pressure at 40°. Extraction of the residue with ether gave 2 : 3 : 4-*trimethyl*-δ-*fuconolactone* (0·17 g.), b. p. (bath temp.) 110°/0·025 mm., $n_D^{23°}$ 1·4505, $[\alpha]_D$ −138° (initial value); −91° (after 2·25 hrs.); −70° (3·75 hrs.); −56° (5 hrs.); −40° (9·75 hrs.); −38° (20·75 hrs.); −36° (24 hrs.); −36° (48 hrs.) (constant value) (Found : OMe, 44·7. $C_9H_{16}O_5$ requires OMe, 45·6%). Treatment of a small portion of this lactone with methyl alcoholic ammonia gave an amide, m. p. 102—103°, $[\alpha]_D^{18°}$ −35° in water (c, 0·4) (after crystallisation from alcohol–ether–ligroin).

Oxidation of 2 : 3 : 4-*Trimethyl* α-*Methyl*-l-*fucopyranoside with Nitric Acid*.—The crystalline material (0·20 g.) was heated with concentrated nitric acid (2·5 c.c.) for ½ hour at 50° and then, after the initial vigorous reaction had ceased, for 2 hrs. at 70—80°. The solution was diluted with water and distilled under diminished pressure, fresh addition of water and finally of methanol being made until all the nitric acid had been eliminated. The product, trimethoxy-*d*-araboglutaric acid was converted to the ester by boiling for 6 hours with 1% methanolic hydrogen chloride (20 c.c.). The solution was neutralised with silver carbonate, filtered, and evaporated to dryness under reduced pressure. Extraction of the syrupy residue with ether gave methyl trimethoxy-*d*-araboglutarate as a colourless mobile liquid, b. p. (bath temp.) 105°/0·06 mm., $n_D^{18°}$ 1·4330; $[\alpha]_D^{17°}$ −31° in water (c, 1·7), $[\alpha]_D^{18°}$ −40° in methyl alcohol (c, 1·0) (Found : equiv., 137. Calc. for $C_{10}H_{18}O_7$: equiv., 125).

d-*Arabo-trimethoxyglutaric Acid Bismethylamide*.—Treatment of methyl trimethoxy *d*-arabo-glutarate (0·045 g.) with a methanolic solution of methylamine for 48 hours at room temperature followed by evaporation of the solvent under reduced pressure in a desiccator gave the bismethylamide. Trimethoxy *d*-arabo-glutaric acid bismethylamide had m. p. 171—172° alone and in admixture with an authentic specimen (Goodyear and Haworth, *J.*, 1927, 3136), $[\alpha]_D^{15°}$ −56° in water (c, 1·3) (Found : C, 48·9; H, 8·1; N, 11·6; OMe, 38·0. Calc. for $C_{10}H_{20}O_5N_2$: C, 48·3; H, 8·1; N, 11·3; OMe, 37·5%).

Synthesis of 2 : 3 : 4-*Trimethyl* β-*Methyl*-d-*fucoside* (XII), 2 : 3 : 4-*Trimethyl* d-*Fucose* (XIII), *and the Corresponding Anilide*.—α-*Acetobromo galactose* 6-*bromohydrin* (IX). Penta-acetyl galactose (13 g.) was placed in a Carius tube which was gradually lowered into a bath of liquid air. Hydrogen bromide was then passed into the tube until about 30 c.c. of liquid had collected and solidified. The tube was sealed off and gradually raised from the liquid air bath and kept at room temperature for 8 hours. The tube was then cooled in liquid air and opened; after allowing the tube to attain room temperature the syrupy contents were washed out with ether. The ethereal solution was quickly freed from acid by shaking successively with water, sodium bicarbonate solution, and finally with water. After drying the ethereal solution over anhydrous magnesium sulphate, removal of the solvent yielded the 1 : 6-dibromo-2 : 3 : 4-triacetyl galactose as a syrup (13·4 g.).

2 : 3 : 4-*Triacetyl* β-*Methylgalactoside* 6-*Bromohydrin* (XI).—To a solution of the aceto dibromogalactose (17·5 g.) in dry methanol (200 c.c.) was added a slight excess of silver carbonate and the mixture shaken overnight. Filtration of the solution followed by removal of the solvent gave a syrup (14·4 g.) which was freed from a little silver by treatment of its ethereal solution with charcoal followed by filtration and evaporation. The syrup was dissolved in hot alcohol and water was added until the solution was turbid. On keeping at 0° crystalline 2 : 3 : 4-triacetyl-β-methyl-galactopyranoside 6-bromohydrin separated.

Simultaneous Deacetylation and Reduction of 2 : 3 : 4-*Triacetyl* β-*Methylgalactopyranoside* 6-*Bromohydrin*.—Many attempts to replace the bromine atom in position 6 by hydrogen by catalytic hydrogenation according to the method of Schlubach and Wagenitz (*loc. cit.*) were unsuccessful. The simultaneous reduction and deacetylation was, however, effected as follows. A solution of 2 : 3 : 4-triacetyl β-methylgalactose 6-bromohydrin (4 g.) in methanol containing a 10% ethanolic solution of sodium hydroxide (17 c.c.) was subjected to hydrogenation during 6 hours in the presence of about 1 g. of Raney nickel, under an excess pressure of 1 atmosphere of hydrogen. The solution, which then gave a strong test for bromide ion, was filtered and evaporated to dryness under reduced pressure. Extraction of the white solid (sodium acetate, sodium bromide, β-methylfucoside and unchanged material) with boiling ethyl acetate gave a syrup which partly crystallised on keeping overnight. Crystallisation of the product from ethanol–ligroin gave β-methyl-*d*-fucopyranoside (0·45 g.), m. p. 118—121°, $[\alpha]_D^{15°}$ −14·7° in water (c, 1·6).

Methylation of β-*Methyl*-d-*fucoside*.—The crystalline material (0·37 g.) which was insoluble in methyl iodide was dissolved in the minimum quantity of acetone containing a little methanol. The solution was then treated with methyl iodide and silver oxide according to the method previously described. The product, isolated by means of acetone, was given a second methylation with methyl iodide and silver oxide. Extraction of the product with acetone yielded 2 : 3 : 4-*trimethyl* β-*methyl*-d-*fucoside* (0·4 g.), m. p. 93—98°, $[\alpha]_D^{21°}$ +11·2° in water (c, 1·0) (after recrystallisation from ligroin) (Found : C, 54·6; H, 9·1; OMe, 56·3. $C_{10}H_{20}O_5$ requires C, 54·5; H, 9·2; OMe, 56·3%).

Hydrolysis of 2 : 3 : 4-*Trimethyl* β-*Methyl*-d-*glucopyranoside*.—When a solution of the crystals (0·20 g.) in N sulphuric acid (20 c.c.) was heated on a boiling water bath it showed $[\alpha]_D$ +16° (initial value); +105° (after 0·5 hr.); +107° (1 hr.) (constant value). After 1½ hours the solution was neutralised with barium carbonate and the trimethyl *d*-fucose (0·134 g.), isolated by the method previously described, had $[\alpha]_D^{15°}$ +106° in water (c, 1·0). The anhydrous trimethyl *d*-fucose was refluxed in ethanol with aniline (1 mol.) for 2 hours. On evaporation of the solvent a syrup was produced which slowly crystallised. The crystals of the anilide had m. p. 133—135°; $[\alpha]_D^{18°}$ +76° (equilibrium value) in ethanol (*c*, 0·8) (after recrystallisation from ether).*

A. E. Hills Laboratories,
The University, Edgbaston, Birmingham.

[*Received, July 2nd,* 1945.]

* *Note added, August 10th,* 1945.—This investigation was completed before 1940. Since the above paper was submitted for publication the authors' attention has been drawn to papers by Schmidt, Mayer, and Distelmarer (*Naturwiss.*, 1943, **31**, 247; *Annalen*, 1943, **555**, 26) in which some of the work has been anticipated.