A Descent of the Sugar Series based on Ketose Mercaptols.

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The diethyl and dibenzyl mercaptols of penta-*O*-acetyl-*keto*-D-fructose have been prepared and converted into the corresponding disulphones with monoperphthalic acid. With methanolic ammonia, the disulphones yield the D-erythrose bisacetamide derivative and a tetra-alkylsulphonylpropane. The mechanism of this reaction is discussed, and a comment is made on the structures of the supposed unsaturated disulphones derived from aldose mercaptals by oxidation.

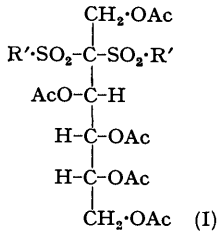
Macdonald and Fischer (*J. Amer. Chem. Soc.*, 1952, **74**, 2087; *Biochim. Biophys. Acta*, 1953, **12**, 203) and Hough and Taylor (*Chem. and Ind.*, 1954, 575) have shown that the unsaturated disulphones produced by oxidation of unsubstituted aldose diethyl mercaptals are hydrolysed by aqueous ammonia to diethylsulphonylmethane and the next lower aldose. The reaction is analogous to that described by Rothstein (*J.*, 1934, 684; 1940, 1560) for simpler compounds, thus :

$$R\cdot CH{:}C(SO_2\cdot Et)_2 + HX \longrightarrow R\cdot CHX\cdot CH(SO_2\cdot Et)_2 \xrightarrow{(X = OH)} R\cdot CHO + CH_2(SO_2\cdot Et)_2$$

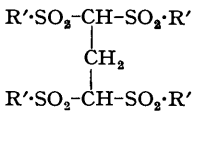
We now report a similar cleavage with ammonia of disulphones derived from penta-*O*-acetylfructose dialkyl mercaptols, but in these cases two carbon atoms are removed from the sugar chain. This degradation should be useful in the characterisation of new ketoses.

Penta-*O*-acetyl-*keto*-D-fructose (Hudson and Brauns, *J. Amer. Chem. Soc.*, 1915, **37**, 2736) was converted into the diethyl mercaptol, from which D-*fructo*-1 : 3 : 4 : 5 : 6-penta-acetoxy-2 : 2-diethylsulphonylhexane (I; R′ = Et) was produced by oxidation with monoperphthalic acid in ether (cf. MacDonald and Fischer, *loc. cit.*, 1952). The presence of sulphone groups was confirmed by the infra-red absorption spectrum, which showed peaks at 1333, 1319, 1305, and 1150 cm.$^{-1}$, in good agreement with the values 1336—1312 and 1164—1130 cm.$^{-1}$ assigned to these groups by Barnard, Fabian, and Koch (*J.*, 1949, 2442). In dry pyridine the disulphone gave a colourless solution, in contrast to the cherry-red solutions reported for unsaturated disulphones of the supposed type $R\cdot CH{:}C(SO_2\cdot R')_2$ (MacDonald and Fischer, *loc. cit.*, 1952). Moreover, the ultra-violet absorption spectrum

of an ethanolic solution of the disulphone corresponded to the " saturated type " illustrated by these authors.



(I)



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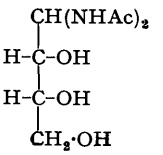
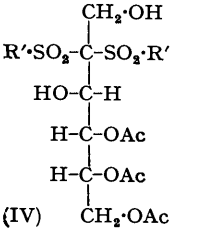


(III)

Treatment of the disulphone (I; R′ = Et) with ammonia in methanol at room temperature for 2 days effected partial deacetylation and cleavage of the main carbon chain. Two crystalline fragments were isolated, namely, 1 : 1 : 3 : 3-tetraethylsulphonylpropane (II; R′ = Et) and the D-erythrose bisacetamide derivative (III). The latter was characterised by its consumption of 2·1 mols. of lead tetra-acetate, by conversion into its triacetate, and by comparison of its infra-red absorption spectrum with that of the L-erythrose analogue, prepared by Wohl's method (*Ber.*, 1899, **32**, 3666) from L-arabinose.

In analogous reactions, penta-*O*-acetyl-*keto*-D-fructose was converted, *via* the dibenzyl mercaptol and the disulphone (I; R′ = C_6H_5·CH_2), into the bisacetamide (III); in this case, however, the disulphone was not purified. An attempt to isolate the other fragment (II; R′ = C_6H_5·CH_2) produced by ammonolysis gave only a syrup, which slowly decomposed to a deep red tar.

The profound changes occurring during ammonolysis of the disulphones (I) can be explained readily in terms of well-established reactions. Electron-attracting centres are known to increase the rate of the usual bimolecular basic hydrolysis (with acyl–oxygen fission) of neighbouring ester groups (cf. Ingold, " Structure and Mechanism in Organic Chemistry," G. Bell and Sons, Ltd., London 1953, pp. 754—760; see also Henne and Pelley, *J. Amer. Chem. Soc.*, 1952, **74**, 1426), and so it is reasonable to suppose that the 1- and 3-acetoxy-groups would be more labile in ammonia than the others, and that a D-*fructo*-4 : 5 : 6-triacetoxy-1 : 3-dihydroxy-2 : 2-dialkylsulphonylhexane (IV) would be produced during the early stages of the reaction.



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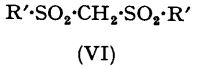

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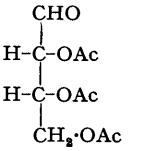


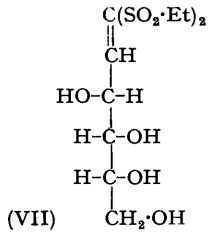
(V)

From Rothstein's observations (*loc. cit.*), (IV) would be expected to yield, in two stages, 2 : 3 : 4-tri-*O*-acetyl-*aldehydo*-D-erythrose (V), formaldehyde, and a dialkylsulphonylmethane (VI). In this part of the reaction, the role of (VI) can be likened to that of HCN in the reversal of cyanohydrin formation. Further action of the ammonia on (V) would entail acetyl migration and partial deacetylation to the D-erythrose bisacetamide derivative. There would of course be a certain amount of overlapping of the above steps in the reaction, giving rise to other intermediates; the main outline of the mechanism advanced is in keeping with current theories that bisacetamido-sugars arise, not from acetamide, but by an intramolecular acyl migration from oxygen to nitrogen (Isbell and Frush, *J. Amer. Chem. Soc.*, 1949, **71**, 1579; Deulofeu and Deferrari, *J. Org. Chem.*, 1952, **17**, 1087).

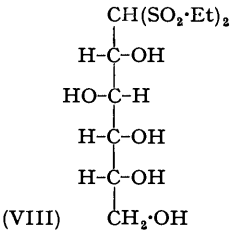
It is known that formaldehyde and diethylsulphonylmethane in the presence of a basic catalyst give 1 : 1 : 3 : 3-tetraethylsulphonylpropane (Kötz, *Ber.*, 1900, **33**, 1120); indeed, we employed this reaction to prepare a reference sample of the latter compound. Since these two precursors were expected to arise during ammonolysis (see above), the origin of

the tetrasulphone (II) is clear. Of several aldehydes examined by Kötz, formaldehyde was the only one which condensed with disulphones in this way, and so it is unlikely that 2 : 3 : 4-tri-*O*-acetyl-*aldehydo*-D-erythrose would undergo a similar reaction.

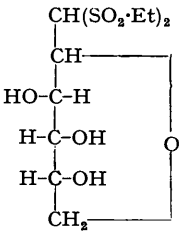
Interesting comparisons can be made between the acetylated fructose-derived disulphones and those produced from aldoses, which in every case except one (that of the mannose-derived material which appears to be an uncharacterised mixture) have been assigned



(VII)



(VIII)



(IX)

a structure of type (VII), rather than (VIII); the products from acetylated aldose mercaptals have been represented as the corresponding unsaturated acetates (MacDonald and Fischer, *locc. cit.*; Hough and Taylor, *loc. cit.*). Presumably, the saturated disulphone (VIII) is formed first and then loses the elements of water (or of acetic acid in the case of an acetate). A fructose-derived disulphone cannot become unsaturated in this way, because it does not carry an acidic hydrogen on the same carbon atom as the two sulphone groups.

The action of ammonia on disulphones derived from aldoses is interesting. The disulphones from xylose, arabinose, and 3-deoxyglucose diethyl mercaptals [designated as of type (VII)] yield diethylsulphonylmethane and the next lower aldose, whereas the glucose-derived tetra-acetate of (VII) adds ammonia across the double bond to give a 2-acetamido-2-deoxy-derivative (MacDonald and Fischer, *locc. cit.*; Hough and Taylor, *loc. cit.*). It may well be that in all these cases the 2-amino-2-deoxy-compound and the 2-hydroxy-compound are the first products, and that these then disproportionate in the manner shown by Rothstein (*loc. cit.*) for simpler compounds, unless acyl migration can occur to stabilise the amino-group as its *N*-acetyl derivative. There is another possibility, which has a bearing on our observation (to be reported in detail later) that treatment of D-*arabo*-3 : 4 : 5 : 6-tetra-acetoxy-1 : 1-diethylsulphonylhex-1-ene with sodium methoxide in methanol gives a methoxy-compound; this is that unsubstituted compounds of type (VII), but not their acetates, may exist, under suitable conditions, in equilibrium with the cyclic form (IX).

Note Added in Proof.—Other evidence that the diethylsulphonyl derivatives of D-galactose, D-glucose, and D-mannose are cyclic has now been provided by Hough and Taylor (*Chem. and Ind.*, 1954, 1018).

Experimental

1 : 3 : 4 : 5 : 6-*Penta*-O-*acetyl*-keto-D-*fructose*.—Tetra-*O*-acetyl-D-fructose {39%; m. p. 127—129°; $[\alpha]_D^{15}$ −80·5° (*c*, 5·3 in $CHCl_3$)} was prepared by partial acetylation of D-fructose, as described by Hudson and Brauns (*loc. cit.*) (Found: C, 48·6; H, 6·0; Ac, 50·3. Calc. for $C_{14}H_{20}O_{10}$: C, 48·3; H, 5·8; Ac, 49·4%); Tollens ("Kurzes Handbuch der Kohlenhydrate," Barth, Leipzig, 1934, p. 373) gave m. p. 130—132° and $[\alpha]_D$ −92° (in $CHCl_3$). Further acetylation of this compound by Hudson and Brauns's method yielded 1 : 3 : 4 : 5 : 6-penta-*O*-acetyl-*keto*-D-fructose (25% based on fructose), m. p. 65—68°, $[\alpha]_D^{16}$ +13·0° (*c*, 6·1 in $CHCl_3$) (Found: C, 49·5; H, 5·8; Ac, 56·7. Calc. for $C_{16}H_{22}O_{11}$: C, 49·2; H, 5·7; Ac, 55·1%); Hudson and Brauns (*loc. cit.*) reported m. p. 70° and $[\alpha]_D^{20}$ +34·4° (in $CHCl_3$). The ultra-violet absorption spectrum of an ethanolic solution showed a peak at 280 mμ ($\log_{10}\varepsilon$ 1·5), in agreement with the results of Bredereck, Höschele, and Huber (*Ber.*, 1953, **86**, 1271).

1 : 3 : 4 : 5 : 6-*Penta*-O-*acetyl*-keto-D-*fructose Diethyl Mercaptol*.—The above penta-acetate was treated with ethanethiol according to Wolfrom and Thompson's method (*J. Amer. Chem. Soc.*, 1934, **56**, 880), and the product was crystallised from ether–light petroleum (b. p. 60—80°) and then from absolute ethanol, to give the mercaptol (25%), m. p. 80—81°, $[\alpha]_D^{16}$ +20·0° (*c*, 1·5 in $CHCl_3$) (Found: C, 48·0; H, 6·3; S, 13·2; Ac, 43·0. Calc. for $C_{20}H_{32}O_{10}S_2$: C, 48·4;

H, 6·5; S, 12·9; Ac, 43·3%). Wolfrom and Thompson (*loc. cit.*) gave m. p. 83°, $[\alpha]_D^{27}$ +20·0° (in $CHCl_3$).

1 : 3 : 4 : 5 : 6-*Penta*-O-*acetyl*-keto-D-*fructose Dibenzyl Mercaptol.*—1 : 3 : 4 : 5 : 6-Penta-*O*-acetyl-*keto*-D-fructose (16·0 g.) was condensed with toluene-ω-thiol (20 c.c.), by Wolfrom and Thompson's method (*loc. cit.*) except that, after the initial mixing at −10°, the temperature was maintained at *ca.* 25° for 24 hr. Repeated crystallisation of the product from absolute ethanol afforded the *dibenzyl mercaptol* (4·40 g.), m. p. 110—111°, $[\alpha]_D^{12}$ +40·1° (*c*, 5·0 in $CHCl_3$) (Found: C, 58·3; H, 5·7; S, 10·7; Ac, 37·4. $C_{30}H_{36}O_{10}S_2$ requires C, 58·1; H, 5·8; S, 10·3; Ac, 34·7%).

D-fructo-1 : 3 : 4 : 5 : 6-*Penta-acetoxy*-2 : 2-*diethylsulphonylhexane.*—To an ice-cold solution of the above diethyl mercaptol (0·75 g.) in dry ether (20 c.c.) was added an ethereal solution (30 c.c.) of monoperphthalic acid (4·8 mols.; Böhme, *Org. Synth.*, 1940, **20**, 70); the mixture was cooled in ice for 1 hr. and then kept at room temperature for 40 hr. The solvent was removed at 12 mm. and the residue was extracted with chloroform. The extract was washed with aqueous sodium hydrogen carbonate, and then with water, dried (Na_2SO_4), and evaporated at 12 mm. The residue, crystallised several times from ethanol, gave rectangular plates of the *disulphone* (0·62 g.), m. p. 144—145°, $[\alpha]_D^{17}$ +7·2° (*c*, 2·2 in $CHCl_3$) (Found: C, 43·0; H, 5·7; S, 11·3. $C_{20}H_{32}O_{14}S_2$ requires C, 42·9; H, 5·75; S, 11·4%). A solution of the compound in dry pyridine remained colourless.

Treatment of D-fructo-1 : 3 : 4 : 5 : 6-*Penta-acetoxy*-2 : 2-*diethylsulphonylhexane with Ammonia in Methanol.*—A methanolic solution (200 c.c.) of the hexane derivative (2·09 g.) was saturated with ammonia gas at 0°, kept at room temperature for 48 hr., and evaporated at 12 mm. to a crystalline mass, from which acetamide was removed by sublimation at 60°/0·01 mm. Recrystallisation of the residue from absolute methanol gave the D-erythrose bisacetamide derivative (1 : 1-bisacetamido-1-deoxy-D-erythrose) (0·40 g.), m. p. 210—211° (decomp.), $[\alpha]_D^{19}$ +9·0° (*c*, 1·3 in H_2O) (Found: C, 43·5; H, 7·2; N, 12·3. Calc. for $C_8H_{16}O_5N_2$: C, 43·6; H, 7·3; N, 12·7%). The infra-red absorption spectrum, over the frequency range 1800—650 $cm.^{-1}$, was identical with that of the L-erythrose analogue, m. p. 212° (decomp.), prepared by Wohl's method (*loc. cit.*). Wohl recorded m. p. 210° (decomp.), $[\alpha]_D$ −7·9°.

The mother-liquors subsequently deposited large rectangular plates of 1 : 1 : 3 : 3-tetraethylsuphonylpropane (0·13 g.), m. p. 158—159°, unchanged by recrystallisation from absolute ethanol (Found: C, 32·2; H, 5·9; S, 31·3. Calc. for $C_{11}H_{24}O_8S_4$: C, 32·0; H, 5·9; S, 31·1%). The infra-red absorption spectrum, measured from 1800 to 650 $cm.^{-1}$, was identical with that of an authentic specimen of 1 : 1 : 3 : 3-tetraethylsulphonylpropane (m. p. and mixed m. p. 158—160°), prepared from diethylsulphonylmethane and 40% aqueous formaldehyde in the presence of piperidine (cf. Kötz, *loc. cit.*); the spectra differed from that of diethylsulphonylmethane (m. p. 103°).

Oxidation of the D-*Erythrose Bisacetamide Derivative with Lead Tetra-acetate.*—The bisacetamide derivative (0·0232 g.) was treated with lead tetra-acetate in glacial acetic acid and the extent of the oxidation was determined iodometrically, as described by Hockett and McClenahan (*J. Amer. Chem. Soc.*, 1939, **61**, 1667). The amount of tetra-acetate consumed was 2·0 mols. after 15 hr. and 2·1 mols. after 40 hr.

2 : 3 : 4-*Tri*-O-*acetyl*-D-*erythrose Bisacetamide Derivative.*—The D-erythrose bisacetamide derivative (0·40 g.), treated with acetic anhydride (1·40 c.c.) in pyridine (2·00 c.c.) by Deulofeu's method (*J.*, 1932, 2973), gave a water-soluble acetate, which crystallised from ethanol–ether in needles (0·45 g.), m. p. 148—150°, $[\alpha]_D^{20}$ +23·2° (*c*, 4·5 in $CHCl_3$). The infra-red absorption spectrum, measured between 1800 and 650 $cm.^{-1}$, was identical with that of an authentic specimen of the 2 : 3 : 4-tri-*O*-acetyl-L-erythrose bisacetamide derivative, m. p. 149—150°, $[\alpha]_D^{22}$ −25·0° (*c*, 3·3 in $CHCl_3$).

The D-*Erythrose Bisacetamide Derivative from* 1 : 3 : 4 : 5 : 6-*Penta*-O-*acetyl*-keto-D-*fructose Dibenzyl Mercaptol.*—The dibenzyl mercaptol (4·40 g.) was oxidised with monoperphthalic acid (4·8 mols.) in ether (80 c.c.), as described above. A methanolic solution (200 c.c.) of the product (4·26 g.) was saturated with ammonia gas at 0°; a pale orange colour soon developed. After 48 hr. at room temperature, the crystalline precipitate of the D-erythrose bisacetamide derivative (0·98 g.) was collected; it had m. p. 206—209° (decomp.), not depressed on admixture with the specimen mentioned above. The infra-red absorption spectra (1800—650 $cm.^{-1}$) of the two samples were identical. An attempt to isolate 1 : 1 : 3 : 3-tetrabenzylsulphonylpropane by evaporation of the mother-liquors gave a syrup, which slowly decomposed to a deep red tar.

Infra-red Absorption Spectra.—Infra-red absorption spectra were determined on mulls in "Nujol," with a Grubb–Parsons Single Beam Spectrometer with sodium chloride optics.

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