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SELECTIVE REACTIVITY OF THE HYDROXYLS OF METHYL QUINATE TOWARDS ACYLATING AGENTS[1].

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Quinic 1, 5-dehydroquinic 2 and shikimic 3 acids have long been recognized as intermediates in the biosynthesis of aromatic acids[2]. Despite the importance of these acids, little is known about the reactivity and modification of their hydroxyl groups. As an "entry" into a series of analogues of methyl quinate, we decided to investigate the selective esterification of methyl quinate 4.

We report in this communication the preparation of partially substituted derivatives of methyl quinate and the order of reactivity of their hydroxyl groups towards the acylating agents, benzoyl chloride and toluene-p-sulphonyl chloride.

Selective benzoylation of hydroxyl groups of the carbohydrates has been the subject of several recent papers[3-5], but benzoate esters of quinic acid have not been previously reported.

Reaction of methyl quinate 4 with 2.2 molar equivalents of benzoyl chloride in pyridine at - 20° to - 30° for 16 hours gave a mixture of products. From this mixture a sirupy tribenzoate (5%), two crystalline dibenzoates (3.6 % and 10%), and two crystalline monobenzoates (20% and 10%) were isolated by silica gel column chromatography. The structure of the tri-O-benzoate $[\alpha]_D$ -81° 5 was supported by its mass spectrum and N.M.R. data (Table 1). The presence of the molecular ion peak at m/e 518 and another peak at m/e 500 (M-18) corresponding to dehydration at C-1 in the mass spectrum of the tri-O-benzoate 5 establishes, that 3-OH, 4-OH and 5-OH are benzoylated. In the N.M.R. spectrum of 5 the three protons at carbons 3, 4 and 5 adsorb in the region δ = 5.45 - 6.10. The quartet of equal intensities centered at δ = 5.60 could be attributed to H_4, for which $J_{3,4}$ is 10.0 (axial-axial coupling) and $J_{4,5}$ is 4.0 c/s (axial-equatorial coupling). The complex signals undoubtedly belong to H_3 ($\delta \simeq 6.1$) and H_5 (δ = 5.95). The same tribenzoate 5 was prepared in 85% yield from methyl quinate using an excess of benzoyl chloride.

A second crystalline compound, m.p. 98-100°, $[\alpha]_D$ -66.5°, isolated in 3.6% yield had a molecular weight (determined by mass spectroscopy) of 414, and elemental analyses corresponding to a di-O-benzoate of methyl quinate. In its N.M.R. spectrum (Table 1) the H_4 proton appears, as quartet of equal intensities centered at δ = 4.10. That the proton at H_4

(δ = 4.10) does not exhibit a paramagnetic (downfield) shift suggest structure 6 for the di-O-benzoate.

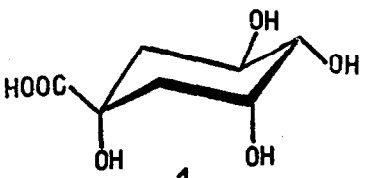
Another crystalline benzoate ester, m.p. 118-120°, $[\alpha]_D$ -67.5°, isolated in 10% yield, turned out to be methyl 4, 5-di-O-benzoyl-quinate 7 on the basis of its mass and N.M.R. spectra (Table 1 and Figure 1). The next crystalline substance isolated by chromatography on silica gel, in 20% yield, m.p.120-122°, $[\alpha]_D$ -59.2°, was identified as methyl 4-O-benzoyl-quinate 8 by the following evidence. It had a molecular weight 310 and its N.M.R. spectrum (Table 1) had the expected quartet of H_4 centered at δ = 4.9, which was clearly isolated from the rest of the protons. The low field signal of the ring proton at C_4 is entirely consistent with the 4-O-benzoate 8. The last crystalline substance, m.p., 130-132°, $[\alpha]_D$ - 47°, isolated in 10% yield, was identified as methyl 5-O-benzoyl-quinate 9, on the basis of its elemental analyses, N.M.R.spectrum (Table 1) and mass spectrum.

Unimolar benzoylation of methyl quinate gave a mixture, which was shown by TLC to contain at least 6 minor components. Five of them were identified as 5-9, respectively. The monobenzoylation appeared to be completely non-selective, therefore it was abandoned.

The isolation of the 4 5-di-O-benzoate 7 (10% yield) and 3, 5-di-O-benzoate 6 (3.6% yield) in the dimolar benzoylation of methyl quinate clearly shows that the 3-OH is the least reactive. The preponderance of the 4-O-benzoate 8 (20% yield) over 5-O-benzoate 9 (10% yield) suggest that the 4-OH group is the most reactive ; thus the decreasing order of reactivity of the hydroxyl groups to benzoylation in methyl quinate is 4 > 5 > 3.

Few systematic studies have been reported on selective sulphonylation of carbohydrates and cyclic polyols[6-8]. Chemical modification of methyl quinate would be facilitated by the availability of partially substituted sulphonyl derivatives. Accordingly we have investigated the toluene-p-sulphonylation of 4.

Reaction of methyl quinate with 8 molar equivalents of toluene-p-sulphonyl chloride in pyridine at 0° over 18 hours gave a mixture of products. From this crude mixture a crystalline tri-O-toluene-p-sulphonate A (56%) and two di-O-toluene-p-sulphonate B and C (4.5 % and 18% yields) were separated by chromatography on silica gel. Product A, m.p.70-72°, $[\alpha]_D$ +29°, was identified as methyl 3, 4, 5-tri-O-toluene-p-sulphonyl-quinate 10, on the basis of its mass and N.M.R. spectra (Table 1) and its 1-O-p-nitrobenzoyl derivative 11. The presence of the molecular ion peak at m/e 668 and another important peak at m/e 609 (M-59) in the mass spectrum of 10 establishes that the toluene-p-sulphonates are located at C_3-C_4-C_5. The remaining tertiary hydroxyl group was very smoothly converted to its 1-O-p-nitrobenzoate 11, m.p. 155-157°, $[\alpha]_D$ -9°. The product B (45% yield), m.p.100-102°, $[\alpha]_D$ -3°, was 3, 5-di-O-toluene-p-sulphonate 12 (Table 1).



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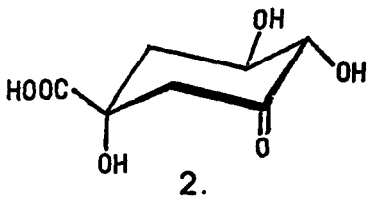

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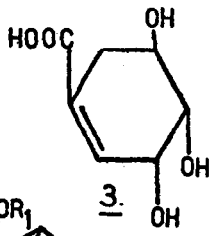

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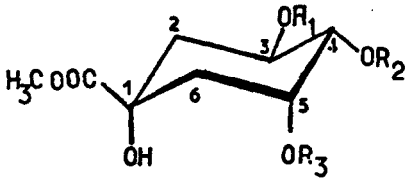

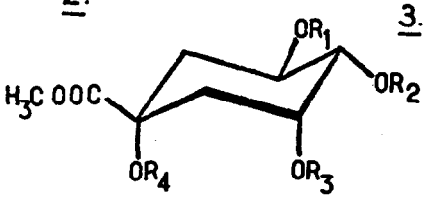

4. $R_1=R_2=R_3=H$

5. $R_1=R_2=R_3=COPh$

6. $R_1=R_3=COPh$; $R_2=H$

7. $R_1=H$; $R_2=R_3=COPh$

8. $R_1=R_3=H$; $R_2=COPh$

9. $R_1=R_2=H$; $R_3=COPh$

10. $R_1=R_2=R_3=Ts$; $R_4=H$

11. $R_1=R_2=R_3=Ts$; $R_4=CO-C_6H_4-NO_2$

12. $R_1=R_3=Ts$; $R_2=R_4=H$

13. $R_1=R_4=H$; $R_2=R_3=Ts$

14. $R_1=COPh$; $R_2=R_3=Ts$; $R_4=H$

15. $R_1=R_4=COPh$; $R_2=R_3=Ts$

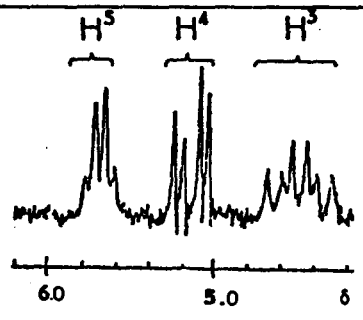

Fig.1 - Signals of H-3, 4 and 5 of methyl-4, 5-di-O-benzoyl quinate 7 in deuteriochloroform-deuterium oxide at 60 MHz.

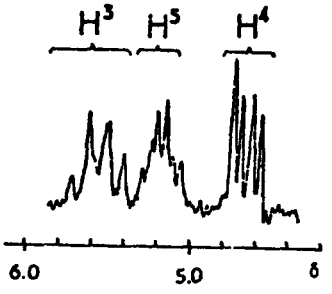

Fig.2 - Signals of H-3, 4 and 5 of methyl-3-O-benzoyl-4, 5-di-O-toluene-p-sulfonyl quinate 14 in deuteriochloroform at 60 MHz.

Table 1

N.M.R. data for derivatives of methyl quinates
Chemical shifts (δ values)

Compounds	H_3	H_4	H_5	Compounds	H_3	H_4	H_5
5	5.95	5.55	5.90	10	4.90	4.35	5.0
6	5.65	4.05	5.60	11	4.90	4.40	5.0
7	4.6	5.25	5.80	12	4.80	4.20	5.0
8	4.30	4.9	4.45	13	5.0	4.40	4.30
9	4.30	4.3	5.5	14	5.52	5.15	4.62

The third product C (18% yield), m.p. 85-87°, $[\alpha]_D$ - 21°, had a molecular weight 514 and elemental analyses corresponding to a di-O-toluene-p-sulphonate of methyl quinate. Although its N.M.R. spectrum did not provide clearcut evidence of the location of the sulphonate esters, after treatment with benzoyl chloride, it was readily converted to its crystalline monobenzoate 14, m.p. 173-175°, $[\alpha]_d$ -30°, and dibenzoate 15, m.p. 90-92°, $[\alpha]_D$ -10.7° The N.M.R. spectrum of the monobenzoate 14 (Table 1, Figure 1) is entirely consistent with structure 14 ; consequently, compound C must be methyl 4, 5-di-O-toluene-p-sulphonyl quinate 13.

In contrast with the toluene-p-sulphonylation of 4 using a great excess of reagent, unimolar and dimolar toluene-p-sulphonylation is a very poor procedure from a preparative viewpoint. The preponderance of the 4, 5-di-O-toluene-p-sulphonate 14 (18%) on 3, 5-di-O-toluene-p-sulphonate 12 (4.5%) clearly suggests again that the 3-OH is the least reactive. Unfortunately we were unable to isolate a mono-O-sulphonate derivative of methyl quinate. From these results we can only deduce, that the 4- and 5-OH groups have greater reactivity than the 3-OH towards toluene-p-sulphonylation.

The above results are in discordance with the generally accepted generalization that the acylation of axial hydroxyl groups in a chair conformation proceeds less rapidly than that of the equatorial hydroxyl groups. N.M.R. data of the examined esters unequivocally show that these derivatives have a conformation as shown in 4 ; the carboxyl group occupies an equatorial and the hydroxyl groups at C_1 and C_5 an axial orientation. The ready acylation of the 1, 3-diaxial hydroxyls in 4 can be explained by strong hydrogen bonding between the 1-hydroxyl and 5-hydroxyl groups which renders these functions more reactive.

The intermediates described above should provide the basis for the preparation of quinic acid analogues of biological interest.

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