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AROMATIZATION REACTION BY NUCLEOPHILIC ATTACK OF CYANIDE ION UPON A SULFONYLATED *myo*-INOSITOL

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ABSTRACT

The reaction of 2,3-di-*O*-acetyl-1,4,5,6-tetra-*O*-(methylsulfonyl)-*myo*-inositol with potassium cyanide in 2-methoxyethanol gave as the final product, through a series of rearrangements and eliminations, 4-cyano-1-*O*-(methylsulfonyl)-1,2-benzenediol, whose structure was ascertained by n.m.r. and mass spectrometry. The intermediate displacement of a mesyloxy group through intramolecular attack of an oxide anion, favored by an electrostatic-field effect of the cyano group, is postulated to explain this reaction.

INTRODUCTION

In a previous paper[1], the synthesis of 2,3-di-*O*-acetyl-1,4,5,6-tetra-*O*-(methylsulfonyl)-*myo*-inositol (**1**) was described, as well as its reaction at C-3 with the azido ion with concomitant replacement by a hydroxyl group (probably through an intermediate acetoxonium ion) of the mesyloxy group at C-4, with inversion of configuration.

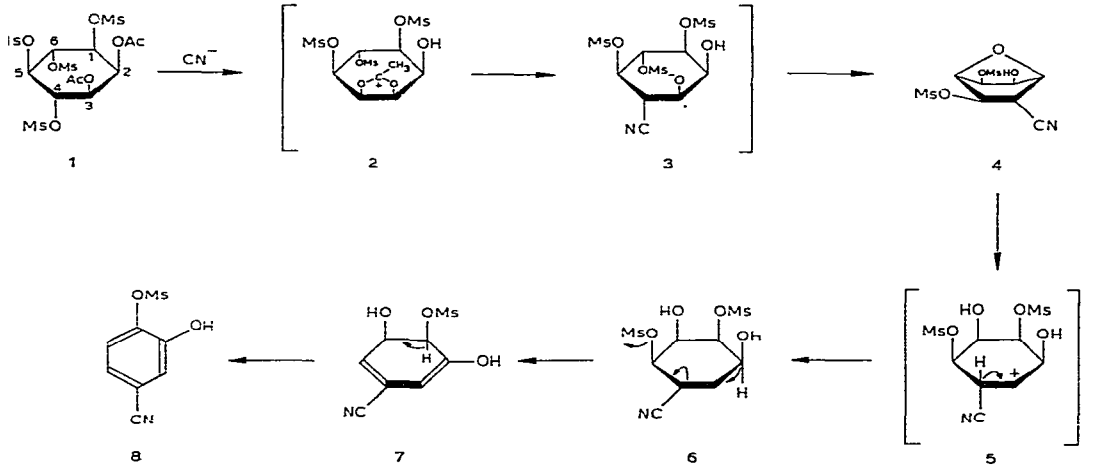
The behavior of cyanide ion as the nucleophile in an analogous reaction with **1** led, through a series of rearrangements and eliminations, to 4-cyano-1-*O*-(methylsulfonyl)-1,2-benzenediol (**8**), instead of the expected cyano derivative on C-3.

The reaction occurs in a few minutes at 100° with a 4:1 molar ratio of potassium cyanide to **1** in 2-methoxyethanol (methylCellosolve). Minor proportions of the nucleophile leave the starting sugar unaltered or only deacetylated.

RESULTS AND DISCUSSION

It has been shown that *myo*-inositol[2] and some of its derivatives[3–5] are aromatized on treatment with base, through eliminations that, in some cases[4,5], afford compounds having a ring pattern of substitution analogous to that of **8**. With the exception of a benzyl derivative[5], they all involve beta-eliminations from an intermediate, keto compound. The main difference in our example is the formation of a carbon–carbon single bond through the insertion of the nucleophilic reagent, to give the final, aromatic cyano derivative.

A possible pathway explaining this reaction is shown in Scheme 1.



Scheme 1

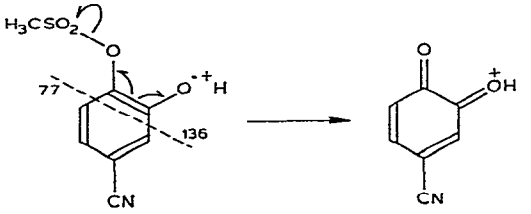
The formation of the cyclic acetoxonium ion **2** by displacement of the *trans*-mesyloxy group on C-4 is a generally accepted stage in anchimerically-assisted reactions of this type. As already mentioned, substitution by the incoming nucleophile usually takes place[1,6] at C-3, to afford the final, stable product of the reaction. The different behavior of the cyanide ion could be explained by an alternative insertion on C-4 to give **3**, which leaves the oxide anion on C-3 particularly susceptible to further reaction. Its nucleophilic character is probably enhanced by an electric-field effect of the cyano group, which would favor rearside attack on the mesyloxy group on C-6 through a transient, boat conformation leading to **4**. The noteworthy, electrostatic effect of the highly-polar cyano group was evidenced by n.m.r. studies on its long-range shielding-effects[7]. On the other hand, oxolane-ring formation through intramolecular, oxide-anion attack upon a sulfonated carbon atom is a known reaction of some sugar derivatives, in alkaline media[8,9], that can also occur by reaction with neutral reagents[10].

On the other hand, the direct, electron-attracting influence of the cyano group upon C-4 would promote the acidic character of H-4; and its elimination, concerted with the rupture of the oxolane ring, would lead to the unsaturated compound **6**. The opening of **4** in the direction depicted in **5** could also be favored by the field electron-releasing effect of the cyano group. The subsequent eliminations of the hydroxyl and mesyloxy substituents, favored by the easy splitting of allylic protons, would lead to the final compound, **8**.

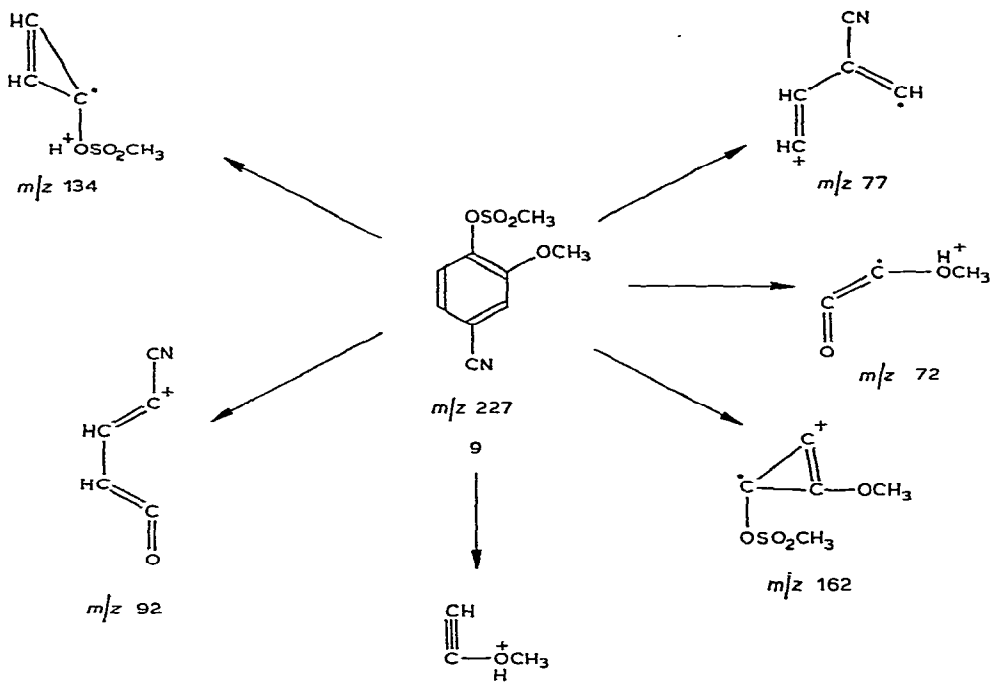
Alternative mechanisms, based on some published studies in the carbohydrate field, could be devised. For example, the formation of double bonds by reaction of certain nucleophiles with vicinal *trans*-disulfonates[9-11], or the formation of an intermediate, keto derivative followed by successive beta-eliminations[4], could be extended to this particular case. However, as more-speculative assumptions, principally of a stereochemical character, would be needed, these alternatives were not considered.

The structure of compound **8**, as yet undescribed in the literature, was ascertained by physical methods. Attempts to hydrolyze it, to obtain the known 3,4-dihydroxybenzoic acid, were not satisfactory. In acid media, the mesyl group was found resistant to hydrolysis, and, in alkaline media, as exceedingly long periods of heating are required, extensive destruction of the molecule occurs. The i.r. spectrum (potassium bromide) showed strong bands at 3270 (HO), 2180 (CN), 1606 (aromatic double bond), 1345 and 1140 cm^{-1} (SO_2 group). The n.m.r. spectrum of **8** at 100 MHz in acetone-d_6 showed a singlet at δ 3.32 (4 H) attributable to the superimposed protons of the methylsulfonyl and hydroxyl groups; the latter consequently appears at relatively high field, which would be explicable by a shielding effect by the vicinal sulfonyl group. The signals showed by the aromatic protons are characteristic for the substitution pattern present in **8**. At δ 7.17 appears a doublet ($J_{5,6}$ 9.0 Hz) corresponding to H-5. At δ 7.50, a pair of doublets corresponds to H-6, with $J_{5,6}$ 9 and $J_{2,6}$ 2.8 Hz, and, at δ 7.63, H-2 resonates, with $J_{2,6}$ 2.8 Hz. This distribution of signals and coupling constants is usual for a pattern of three protons in 1,2,4-relationship on the benzene ring[4,12].

This structure was confirmed by the mass spectrum of **8**, which showed the molecular ion at *m/z* 213 (52.5%), and evidenced an easy rupture of the methylsulfonyl group (*m/z* 79; 52.0%). The base peak at *m/z* 134 (100.0%) could be explained by the rearrangement depicted in **10** and **11**, in which is also shown the origin of peaks at *m/z* 136 (8.0%) and 77 (7.0%).



However, the mass spectrum of **8** did not describe the position of each oxygen substituent relative to the cyano group, but this was shown clearly by the mass spectrum of the methylated derivative (**9**) of **8**, obtained by reaction of **8** with diazomethane catalyzed by boron trifluoride. In this case, also, was observed the easy rupture of the methylsulfonyl group, affording the base peak at *m/z* 148, and the resistance of the methoxyl group to rupture. The *ortho* (relative) position of the methoxyl and mesyloxy groups was shown by the peaks at *m/z* 72 and 77, which, in turn, justified the structure assumed for the peak at *m/z* 162 (see Scheme 2). On the other hand, the position of both substituents relative to that of the cyano group was given by consideration of the peaks at *m/z* 134 and 92. Finally, the peaks at *m/z* 134, 72, and 57 unambiguously showed the *para* and *meta* positions of the mesyloxy and methoxyl groups, respectively, referred to that of the cyano group.



Scheme 2

EXPERIMENTAL

General procedures. — T.l.c. was performed on Silica Gel G (Merck) plates (0.25-mm layer thickness) with the following solvents: (*A*) 9 : 1 (v/v) benzene–absolute ethanol, and (*B*) 3 : 2 (v/v) benzene–2-butanone. The spots were detected with iodine vapor. Melting points were determined with a Kofler hot-stage apparatus, and are not corrected. I.r. spectra were recorded, for potassium bromide discs, with a Perkin–Elmer 421 spectrophotometer. N.m.r. spectra at 100 MHz were recorded at 20–25° with a Varian XL-100 spectrometer, with tetramethylsilane as the internal, reference standard. Mass spectra were recorded with a Varian-Mat CH-7 spectrometer commanded by a Varian-Mat Data System 166 computer, at an ionizing potential of 70 eV; the temperature of the direct-insertion probe was 130–140°.

*Synthesis of 1,2-di-*O*-acetyl-3,4,5,6-tetra-*O*-(methylsulfonyl)-*myo*-inositol* (**1**).— This compound was synthesized, as previously described[1], starting from 1,2-*O*-isopropylidene-*myo*-inositol. This substance was, in turn, prepared according to the procedure of Gigg and Warren[12], instead of that using zinc chloride[1], which, on a preparative scale, gave variable yields.

Reaction of compound **1** *with potassium cyanide.* — A mixture of **1** (4.5 g; 7.8 mmol) and potassium cyanide (2.02 g; 31.2 mmol) was suspended in dried 2-methoxyethanol (methylCellosolve), and heated at 100°, with magnetic stirring, until dissolution occurred. The mixture rapidly turned brown (within 3 to 5 min),

and a precipitate of potassium methanesulfonate (1.4 g) appeared; after cooling, it was filtered off and discarded. The solution was evaporated to dryness at 60°, the dried residual syrup was extracted with hot acetone (5 × 30 mL), and an inorganic residue (1.45 g) remained insoluble. The acetone solution was evaporated to dryness, and the brown residue (2.62 g) was chromatographed on a column (30 × 300 mm) of Silica Gel. Elution was conducted with increasing proportions of 2-butanone in benzene. The elution of the product began with a 2:3 ratio of these solvents, and 22 fractions (F 1–22, 200 mL each) were collected. Fractions 23–29 were eluted with mixtures of 2-butanone–benzene–absolute ethyl alcohol, with increasing concentrations of the last solvent, but these gave only colored products and inorganic material.

Fraction 2 afforded 390 mg of pure 4-cyano-1-*O*-(methylsulfonyl)-1,2-benzenediol (**8**). T.l.c. gave one spot, R_F 0.25 (solvent *A*) and 0.45 (solvent *B*). Fractions 3–22 contained a mixture of **8** and deacetylated starting-material (1.23 g) which was rechromatographed under the same conditions, giving a further 316 mg of pure **8**; total yield 706 mg (42.4%). This compound is soluble in the lower alcohols, and slightly soluble in chloroform or benzene. Recrystallized from water, it had m.p. 144–146°; n.m.r. data (acetone-d_6): δ 3.32 (4 H, Me and OH), 7.17 (d, H-5, $J_{5,6}$ 9.0 Hz), 7.50 (dd, H-6, $J_{2,6}$ 2.8 Hz), and 7.63 (d, H-2, $J_{2,6}$ 2.8 Hz); *m/z* (intensity, as percent of base peak, and assignments, are given in that sequence): 213 (52.5, M^+), 198 (2.6, M − CH_3), 184 (1.1, M − COH), 136 (8.0, HOC-$COSO_2CH_3$), 135 (68.0, M − $CH_2{=}SO_2$), 134 (100.0, M − CH_3SO_2), 106 (81.0, M − CH_3SO_2 − CO), 79 (52.0, CH_3SO_2), 78 (32.0, $CH_2{=}SO_2$), 77 [7.0, CN-C(CH)=CH-CH], 64 (5.0, NCC=CHCH), 54 (20.0, HC=CH-CO), 52 (54.0, NC-$C^+{=}CH_2$), and 51 (50.0, C^+N-C≡CH).

Anal. Calc. for $C_8H_7NO_4S$: C, 45.07; H, 3.28; N, 6.57; S, 15.02. Found: C, 45.01; H, 3.54; N, 6.32; S, 15.42.

Methylation of compound **8**. — An ethereal solution of diazomethane was prepared from nitrosomethylurea[14] (2 g). Compound **8** (12 mg) was dissolved in anhydrous ethyl ether, and the diazomethane solution was added stepwise (2 × 5 mL). The mixture was kept for 60 min at room temperature, filtered to eliminate polymethylene, and the filtrate evaporated, to give **9** as crystals, m.p. 128°. T.l.c. (solvent *A*) showed one spot, R_F 0.53; *m/z*: 227 (60.5, M^+), 162 [4.0, CH_3O-C=C(OSO_2CH_3)C^+], 156 (3.5, M − CH_3OC-CO), 149 (52.3, M − CH_2SO_2), 148 (100.0, M − CH_3SO_2), 134 [35.6, CH-CH-C(OSO_2CH_3) + H^+], 120 (42.4, M − CH_3SO_2 − CO), 107 (4.0, C-OSO_2CH_3), 92 (14.4, CN-C^+-CH-CH-CO), 79 (50.8, $CH_3SO_2^+$), 77 [10.6, CH-CH(CN)CH], 76 [4.5, HC≡C-C(CN)-CH], 57 (4.5, CH-C(OCH_3) + H^+], 54 (8.3, CH-CH-CO), and 51 (16.7, CN-C≡CH).

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