Synthesis of 4-Substituted Tetronic Acids: Multicolanic Acid

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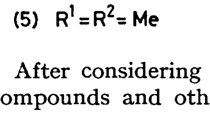
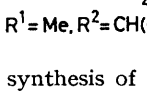
Summary Multicolanic acid (**3**), and other 4-substituted tetronic acids (**8**), (**9**), (**10**), and (**17**) are conveniently synthesised from the corresponding unsubstituted parent compounds by protection of the enolic hydroxy-groups with pyrrolidine, and reaction of the carbanions of the resultant derivatives with either alkyl halides or aldehydes, followed by acid catalysed removal of the protecting groups.

Multicolic and multicolosic acids, (**1**) and (**2**) respectively, are 4-ylidenetetronic acids isolated as metabolites of *Penicillium multicolor*.[1] These compounds, together with a minor metabolite multicolanic acid (**3**), isolated recently in this department[2] as its methyl *O*-methyl derivative (**4**), represent a biogenetically interesting group derived from aromatic precursors.[1] The stereochemistry of these compounds at the exocyclic double bonds has been established by syntheses of the methylated derivative (**4**) and its 2-methyl analogue (**5**),[3] as part of a wider investigation of the synthesis of derivatives of 4-ylidenetetronic acids.[4]

The generally applicable synthetic routes to derivatives of 4-ylidenetetronic acids involve either Wittig reactions between substituted methoxymaleic anhydrides and weakly nucleophilic phosphoranylides, or aldol type condensations between anions of 2-substituted-3-methoxybut-2-enolides and carbonyl components.[4] In both cases the products are *O*-methylated derivatives from which the parent compounds are not readily available.





(1) $R^1 = [CH_2]_4CH_2OH, R^2 = H$
(2) $R^1 = [CH_2]_4CO_2H, R^2 = H$
(3) $R^1 = [CH\ ]_4Me, R^2 = H$
(4) $R^1 = [CH_2]_4Me, R^2 = Me$
(5) $R^1 = R^2 = Me$

(6) $R^1 = Me, R^2 = H$
(7) $R^1 = [CH_2]_4Me, R^2 = H$
(8) $R^1 = R^2 = Me$
(9) $R^1 = Me, R^2 = CH_2CO_2H$
(10) $R^1 = Me, R^2 = CH(OH)CO_2H$

After considering a satisfactory synthesis of the parent compounds and other 4-substituted-tetronic acids we decided to investigate the generation of carbanions from suitably protected 2-substituted-3-hydroxybut-2-enolides. The protecting group for the enolic hydroxy function was chosen so that it might be readily removed under mild acid conditions at a late stage of the synthesis. We have found that the pyrrolidin-1-yl-group offers advantages and leads to a generally applicable synthetic route to a variety of 4-substituted tetronic acids.

2-Methyl- and 2-pentyl-tetronic acids (**6**) and (**7**), respectively, are converted into their 3-pyrrolidin-1-yl derivatives (**11**) and (**12**) respectively,† in *ca.* 85% yield by azeotroping solutions in pyrrolidine. The carbanions of

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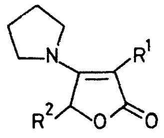
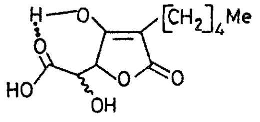
† All new compounds reported are crystalline solids for which satisfactory elemental analyses and the usual range of spectroscopic data have been obtained.

these compounds, generated with 1 mol equiv. of lithium di-isopropylamide in tetrahydrofuran (THF) at −78 °C, react satisfactorily with both alkyl halides and aldehydes to give the corresponding 4-substituted derivatives. Methyl iodide, ethyl bromoacetate, and anhydrous butyl glyoxylate are amongst those compounds which have been used and have led to the preparations of compounds (**13**), (**14**), (**15**), and (**16**) in moderate to excellent yields. These have been converted into the parent tetronic acids (**8**), (**9**), (**10**), and (**17**), respectively, by hydrolysis with dilute mineral acid.



(11) $R^1 = Me, R^2 = H$
(12) $R^1 = [CH_2]_4Me, R^2 = H$
(13) $R^1 = R^2 = Me$
(14) $R^1 = Me, R^2 = CH_2CO_2Et$
(15) $R^1 = Me, R^2 = CH(OH)CO_2Bu$
(16) $R^1 = [CH_2]_4Me, R^2 = CH(OH)CO_2Bu$



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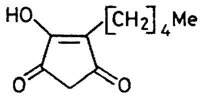

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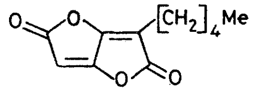

(19)

In the synthesis of multicolanic acid the anion of the protected 2-pentyltetronic acid derivative (**12**) was treated with freshly distilled anhydrous butyl glyoxylate to give the diastereoisomeric mixture (**16**) in 65% yield. Hydrolysis of this with refluxing 5 M-hydrochloric acid gave the corresponding tetronic acid mixture (**17**) in 80% yield. Alternatively, the diastereoisomers (**16**) were separated by preparative layer chromatography and converted into the corresponding acids, without epimerization, by similar hydrolysis. Dehydration of both epimers (**17**) was effected by sublimation *in vacuo* to give in each case a mixture of multicolanic acid (**3**) and the trione (**18**). These were separated by chromatography to give the former compound in 30% yield and the latter in 25% yield.

The formation of the trione (**18**) is analogous to the previously observed thermal isomerisation of pulvinones to the corresponding triones,[5] and other similar cases.[6] The more interesting aspect of the pyrolysis reaction is the stereospecificity, leading only to the *E*-isomer (**3**). The most probable reason for the absence of the corresponding *Z*-isomer appears to be that, in the cases of both diastereoisomers, elimination of water occurs from transition states in which the carboxy-group is held in the appropriate conformation by intramolecular hydrogen bonding, as shown in (**17**). An alternative explanation involving the intermediacy of the bislactone (**19**) can be discounted since the total sublimate from the epimeric alcohols shows no detectable amount of this compound, which is readily synthesised from multicolanic acid by dehydration with bicyclohexylcarbodi-imide. The ^1H n.m.r. spectrum shows the vinyl proton at δ 5·46, compared with that of multicolanic acid at δ 5·96.

Reaction of synthetic multicolanic acid with diazomethane in ether gave methyl *O*-methyl-multicolanate (**4**) as the sole product. This oil was identical to that obtained by similar methylation of the natural product.

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