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# A NOVEL AND DIRECT PRODUCTION OF HYDROXYPYRONES FROM FUROIC ACID DERIVATIVES.

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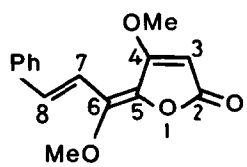
SUMMARY. Alkaline bromine-methanol oxidation of 5-(α-hydroxybenzyl)furoic acids gives 6-aryl-5-hydroxy-2H-pyran-2-ones by a unique multistep oxidative decarboxylation-ring expansion sequence. Some studies into the reaction sequence are given.

In the course of studies[1] into activity-structure relationships of butenolides relating to the natural products piperolide, 1[2] and fadyenolide, 2[3], it was necessary to produce butenolides 3, which retain the exocyclic 6-methoxy group but lack the ring 4-methoxy group

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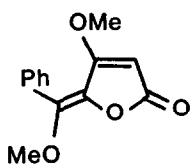


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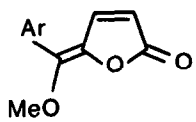
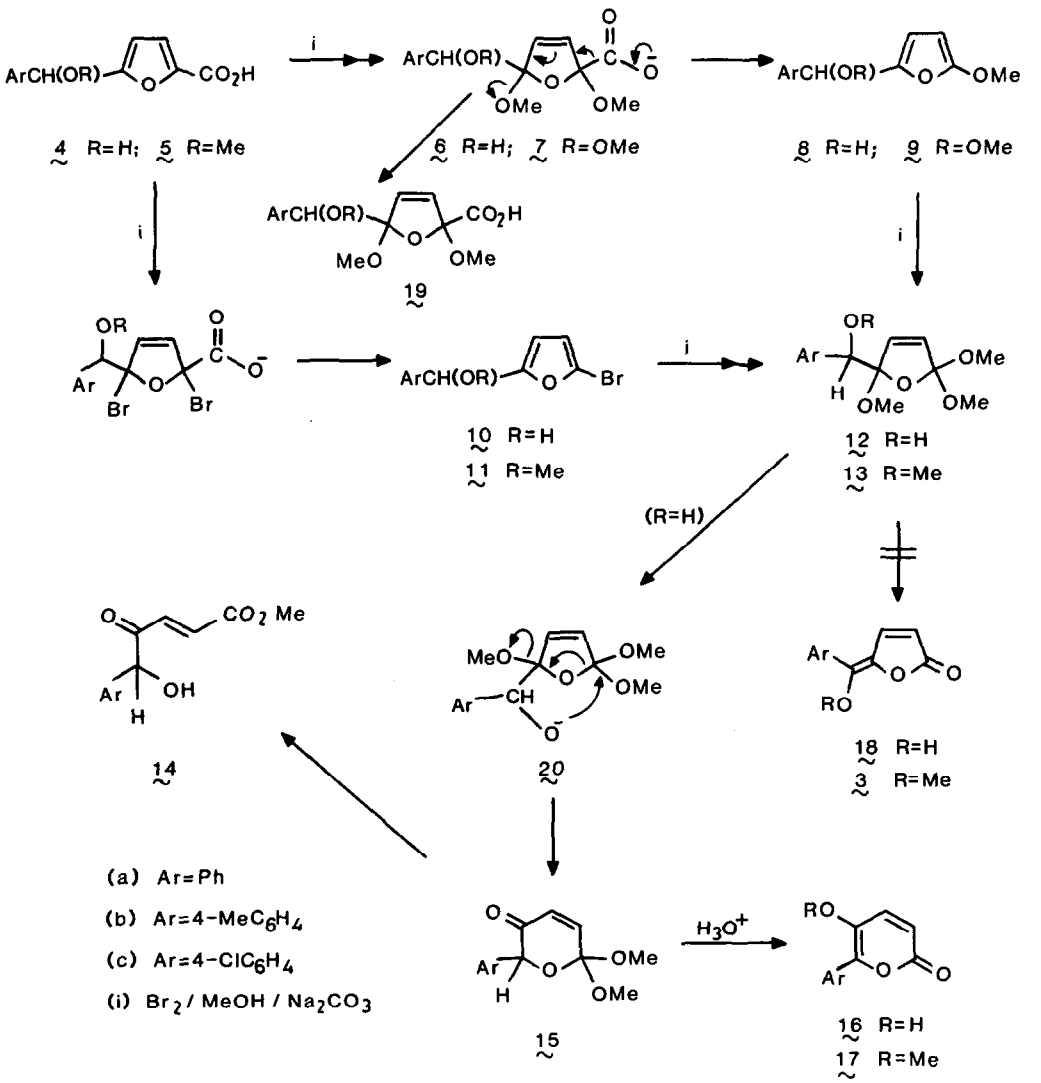



3

It seemed possible that 3 could be obtained in a direct fashion from the readily available precursors 4 and 5[4] in a one-pot reaction sequence as outlined in the Scheme overleaf.

The oxidative addition of two methoxy groups across a furan is well known[5]. An appositely placed, ionised carboxyl group could act as an electron source to aid the departure of a methoxy or bromine group with simultaneous loss of carbon dioxide.

Furans such as 8 or 10 would result which should then undergo further reaction to yield for example 12 from which 18 could be produced. The overall process would be a novel, useful and direct conversion of furans to ylidene-butenolides. A photochemical analogy has been described[6].




Scheme

In the event it was found that the alcohols 4(a-c) do indeed undergo a double oxidation accompanied by decarboxylation when subjected to the action of bromine in methanol containing sodium carbonate. However, an unanticipated rearrangement occurs at a late stage of the multistep sequence, so that the products are not butenolides but the isomeric 6-aryl-5-hydroxypyran-2-ones, 16 (a-c) m.p. 244-248°C, 246-248°C and 250-253°C respectively. All three compounds were obtained in yields of ca 40% after recrystallisation. Methylation with diazomethane gave the corresponding O-methyl ethers, 17(a-c).

The products gave the correct analyses and mass spectra for either the butenolide or pyrone formulations. However, the i.r.spectra had no bands in the carbonyl stretching region at above 1740cm$^{-1}$ , and in the $^{13}$C n.m.r. had the lowest field signal at ca 160 p.p.m., in strong contrast to butenolides[8] but very similar to the carbonyl carbon of known hydroxypyrones and of 2-pyrone itself[9]. In the $^{1}$H n.m.r. the coupling constant of the H-3 and H-4 protons is ca.10 Hz, characteristic of 2-pyrones[10] but unlike the 3-4Hz found for butenolides. Thus the structures 16(a-c) are firmly based.

Examination of the mother liquors from the isolation of 16c showed the presence of the open chain hydroxyketone 14c (14%) and some 4-chlorobenzoic acid (10%).

We decided to examine the sequence further, though it is by no means certain that, in a multistep pathway of this sort, any one unique route is taken. In particular, we have examined the reactions of 4a and 5a in greater detail.

If the reaction mixture obtained from 4a is extracted directly rather than by adjusting the pH to 4-6 as normally done, a neutral substance identified as 15a, the final intermediate of the Scheme, is isolated in 68% yield. Acidification of 15a gives 16a in 80% yield. When the residual aqueous layer is acidified then the acid, 19a is isolated in 15% yield. This corresponds to 6a, the first intermediate of the Scheme.

Treatment of 4a with one equivalent rather than the usual two equivalents of bromine, followed by extraction without acidification gave some 15a and 19a as before. Somewhat to our surprise we also isolated the bromofuran 10a, which we also synthesised independently by reacting 5-bromofurfural with phenyl magnesium bromide. This gave 16a, in 28% yield on treatment with bromine in methanol. It is not clear, however, whether

10a is an intermediate under our normal reaction conditions.

Treatment of the methoxy acid, 5a with two equivalents of bromine in methanol-sodium carbonate allowed the isolation of the bromofuran 11a, but more importantly we could also isolate the labile adduct, 13a in 73-100% yield. The isolation of this compound highlights an important difference between the reactions of the hydroxy and methoxy acids since in the case of the hydroxy acid the analogous adduct 12a was not observed, presumably due to its facile rearrangement to 15a via the oxyanion 20a.

These results lead to the sequence 12a — 20a — 15a (isolated directly from 5a) — 16a. The origin of 12a is not unambiguous, and indeed it may arise by two pathways. The isolation of 19a shows the involvement of 6a, but the isolation of 10a and 11a indicates what may be an alternative pathway, also yielding 12.

Regardless of these details, the direct conversion of 4 to 16 is a novel and convenient, one-pot reaction to yield 5-hydroxypyrones from 2-furoic acids. The yields, though not high, are very acceptable in view of the directness of the procedure.

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