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AROMATIZATION OF ALIPHATIC COMPOUNDS[1]. o- and m-tolylacetic acids.

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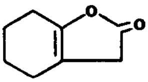
Summary: The title compounds were obtained when the reaction products of formaldehyde with tetrahydrobenzofuranones were treated with PyHCl.

In the course of our studies on the synthesis of arylacetic acids through aromatization of 2-oxo-cyclohexeneacetic acids or their chemical equivalents[2] we investigated the action of formaldehyde on the β-γ-butenolide (I)[3]. The behaviour of β-γ-butenolides towards aromatic aldehydes in slight alkaline medium is well known to give α-benziliden derivatives[4], while very little is known about the action of formaldehyde[5].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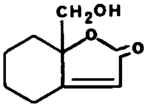

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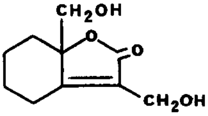

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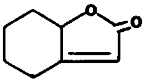
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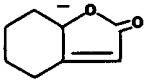
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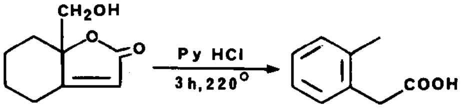
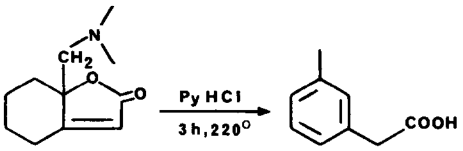
When a solution of (I) (5 g, 0.036 mol) in DMSO (10 ml) was dropped at room temperature into a solution of trioxymethylene (2.07 g, 0.072 mol) in DMSO (25 ml) to which a 0.5 M solution of EtONa in ethanol (7 ml) had been added and the reaction mixture was fractionated on a preparative SiO$_2$ HPLC column, the hydroxymethyl-butenolide (II)[6] (1.8 g, 29.6% yield), m.p. 122-24°C (isopropanol), and the diol (III)[7] (1.7 g, 23.7% yield) were obtained. (III), glassy oil, IR (CHCl$_3$), ν_{max} 3400 (broad), 1738 cm^{-1}. Diacetyl derivative, m.p. 91-3°C (hexane-ethyl acetate).

(II) and (III) were also obtained, although in lower yields, starting from the α-β-butenolide (IV)[3]. The behaviour of (I) and (IV) towards formaldehyde in the presence of a strong base resembles the Michael addition of butenolide anions to vinyl ketones which was recently shown in our laboratory[8] and, independently, by A. Kraus and B. Roth[9], to give γ-substitution through the carbanion (V)[10]. The butenolide (II) was shown to have, towards pyridine hydrochloride (PyHCl), the behaviour of a 2-oxo-cycloheneacetic acid equivalent. In fact, when it was heated with five weights of molten PyHCl at 220°C for three hours and the resulting mixture was poured into water, o-tolylacetic acid (VI)[11] was obtained, m.p. 86-7°C (45.6% yield).

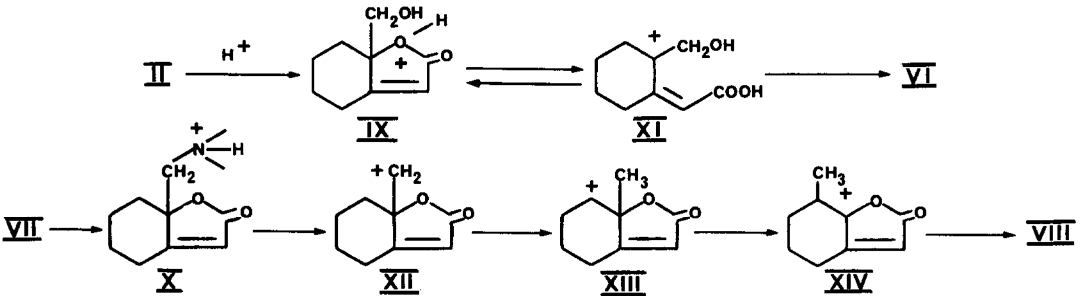


II VI



VII VIII

On the other hand, when in a suggestive modification of the Mannich reaction[12] methaniminium-N-methyl-N-methylene chloride[13] (1.9 g, 0.02 mol) was reacted with (I) (2.8 g, 0.02 mol) in acetonitrile (10 ml) for 30 min at reflux, a gummy residue was obtained after removal of the solvent. This residue was eluted on a SiO_2 column with benzene:triethylamine (9:1) to give (VII) (26.5 % yield), m.p. 44-5°C (hexane); IR (CCl_4) ν_{max} 1760 cm^{-1}; NMR ($CDCl_3$), δ 1.15-2.80 (8H, very broad multiplet, cyclohexane $C\underline{H}_2$) superimposed 2.30 (6H, s, N-$C\underline{H}_3$), and AB system centered at 2.67 (2H, J=12 cps, $\Delta\nu$=24 cps, N-$C\underline{H}_2$-, prochiral center), 5.79 (1H, s, $C\underline{H}$=)[14]. Hydrochloride m.p. 215-16.5°C (ethanol). Also (VII) was shown to have the behaviour of a 2-oxo-cyclohexeneacetic acid equivalent towards aromatization, but, rather surprisingly, when (VII) hydrochloride was treated with PyHCl under the same conditions described for (II), m-tolylacetic acid (VIII)[11] was obtained as the sole aromatization product (m.p. 63-4°C, 51.8 % yield).



A reasonable explanation of this difference seems to be the following one. Both (II) and (VI) are at first protonated to give (IX) and (X) respectively. Afterwards, while (IX), via cation (XI), gives (VI) through dehydration and several allylic like transpositions, (X) gives the cation (XII) which undergoes a 1,3-hydride shift to (XIII) followed by a 1,2-methyl shift to give (XIV), which is the conjugated acid of a dihydrobenzofuranone able to aromatize when heated with PyHCl[2].

References and Notes

1. Note VI; Note V - M. Giannangeli and L. Baiocchi, Tetrahedron in Press
2. L. Baiocchi, M. Bonanomi, M. Giannangeli and G. Picconi, Synthesis 6, 434 (1979).
3. M.S. Newmann and C.A. Verderwerf, J. Am. Chem. Soc. 67, 233 (1945).
4. Y. Shyamsunder Rao, Chem. Rev. 64, 353 (1964).
5. S. Olsen and M.Russwurm (Ann.639,1961) described the reaction of formaldehyde in a large excess and in drastic acidic conditions on α and β angelica lactone, to give several derivatives of 3,5,5-tris (hydroxy-methyl-dihydro-deoxypatulinic acid).
6. (II) was obtained by J.V.Frosh et al., J.Chem.Soc.Perkin I 2005 (1974) in six steps starting from 2-acetoxy-methyl-cyclohexenone.
7. Both (II) and (III) were also obtained, together with some unreacted (I), when an equimolecular ratio of trioxymethylene was used in the above described reaction.
8. L. Baiocchi, M. Giannangeli and M. Bonanomi, Tetrahedron 34, 955 (1978).
9. A. Kraus and B. Roth, Tetrahedron Lett. 3129 (1977).
10. α,β and β,γ-butenolides showed the same behaviour due to the common carbanion (V).
11. Atkinson and Thorpe, J. Chem. Soc., 91, 1699 (1907).
12. In the classic Mannich conditions (trioxymethylene, dimethylamine hydrochloride, some drops of conc.HCl and iso-amyl alcohol) the same (VII) is obtained in 13.6% yield together with 3-dimethylaminomethyl-2-oxo-cyclohexan acetic acid hydrochloride. m.p. 170-71°C, 10.1% yield.
13. G. Kinast and L.F. Tietze, Angew. Chem. Int. Ed. 15, 239 (1976).
14. The lacking of any signal due to $\underline{H}C$-O proton excludes any isomeric structure for(VII).