Synthesis of 2,4-Dihydroxy-1,5-Diphenyl-Pentane-1,5-Dione and its Reactions with Ureas.

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Summary: 2,4-Dihydroxy-1, 5-diphenyl pentane-1, 5-dione (3b) has been synthesised by the hydrolysis of 2,4-dibromo-1, 5-diphenyl pentane-1, 5-dione in 75% aqueous acetone containing silver oxide acting as catalyst. During hydrolysis compound (5) is obtained alongwith (3b). The reaction mechanism pertaining to formation of compound (3b) is also proposed. The structural elucidation of compounds (3b,5) has been done by spectroscopic techniques. Unfortunately our target compound (3b) does not react with urea and its alkyl derivatives. It is also possible that steric factors play a part in making (3b) unreactive.

Butane-2,3-dione [1] (diacetyl) and 1-phenylpropane-1,2-dione [2] react with 1,3-dimethylurea in acid conditions to give (1a) and (1c) respectively. These unexpected products were identified by inter alia nmr spectroscopy and, in the case of (1a), by X-ray crystallography [3]. One reason for our interest in these reactions is that both diacetyl [4] and 1-phenylpropane-1,2-dione [5] are used for the colorimetric assay of urea, an important tool in clinical diagnosis of kidney dysfunction. We proposed [1,6] that, by analogy with the reaction of 1,3-dimethylurea, urea

reacts with diacetyl to give (1b) and that further spontaneous oxidative reaction results in generation of a highly coloured carbonium ion. A comparable reaction is possible for (1d). One major fault in these assays for urea is that fairly vigorous conditions of temperature and acidity are required. An improved procedure would be one that works at room temperature and low acidity. Acyloins react with ureas under rather mild conditions to give 4-imidazolin-2-ones (2), [1] and (2) may be looked upon as half of molecule (1). Thus, if we begin with a 'diacyloin' (3) we should be able to generate (1) under mild conditions to give an improved colorimetric assay for urea. In this paper we report our efforts to prepare (3a) and (3b).

Results and Discussion

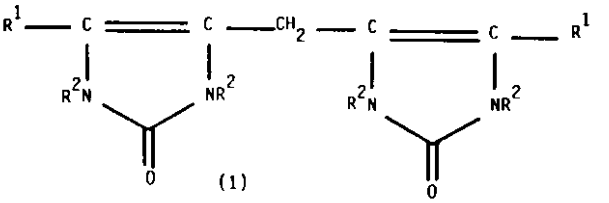
Attempted synthesis of 3,5-dihydroxyheptane-2,6-dione (3a):

Heptan-2,6-dione was prepared by the reaction of formalin with diketene [7]. Reaction of this with lithium dimethylamide and chlorotrimethylsilane at -78°C in tetrahydrofuran [8] gave a low yield of the O-silylated enol (4) as a mixture of isomers. Oxidation of this with chromyl chloride in dichloromethane [9], which should have given (3a), gave largely unreacted starting material and a number of unidentified, highly coloured, products.

Synthesis of 1,5-diphenyl-2,4-dihydroxypentane-1,5-dione (3b):

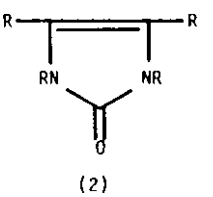
1,3-Dibenzoylpropane was prepared by a Friedel-Crafts reaction of glutaryl chloride with benzene. Reaction of this with an excess of bromine gave 2,4-dibromo-1,5-diphenylpentane-1,5-dione. Further reaction with silver oxide in aqueous acetone gave two products, one of which was the target compound (3b), and the other a greenish yellow solid of formula $C_{17}H_{12}O_3$. The i.r. spectrum of the latter indicated the presence of a carbonyl group and the proton nmr spectrum that of a hydroxyl group and an olefinic proton, as well as 10 aromatic protons. The carbonyl group was confirmed from the ^{13}C n.m.r. spectrum but all the other resonances were in the region 115 to 147 ppm and not readily characterised. However, the DEPT ^{13}C nmr spectrum showed six quaternary carbons and no methyl or methylene groups. From this evidence we propose structure (5).

Our proposed mechanism for the formation of (5) is based upon the ready synthesis of furans from 1,4-diols [10] (Scheme). The partially brominated compound (6) is a probable intermediate in the conversion of 2,4-dibromo-1,5-diphenylpentane-1,5-dione into (3b). This should undergo enolisation to give (7) and ionisation of the 1-hydroxy group gives a nucleophile right for cyclisation by displacement of bromide. Oxidation of (8) by air/Ag_2O results in aromatisation to give the furan (5).

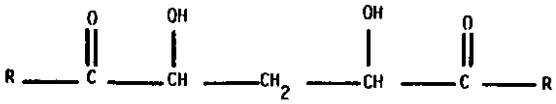


(1)

a; R^1 = Me, R^2 = Me
b; R^1 = Me, R^2 = H
c; R^1 = Ph, R^2 = Me
d; R^1 = Ph, R^2 = H

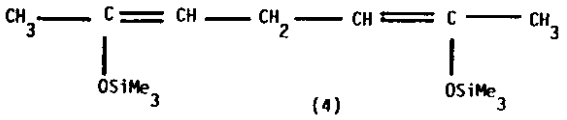


(2)

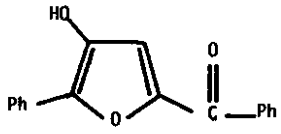


(3)

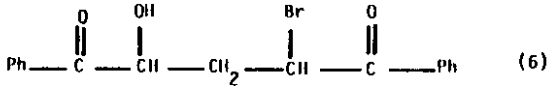
a; R = Me
b; R = Ph



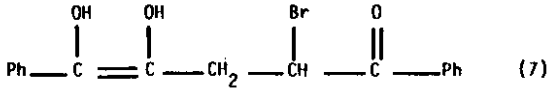
(4)



(5)

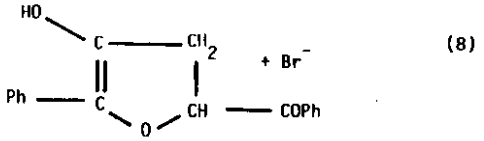


(6)



(7)

base



(8)

[O]

(5)

SCHEME

Reaction of (3b) with urea:

Although urea reacts readily with α-hydroxybenzyl methyl ketone in acid solution [1] we could detect no reaction between urea and (3b) under similar conditions. In the scheme we suggested for the reaction of acyloins with urea [1] the reactive species is the hydroxyl-protonated acyloin. In (3b) it is the carbonyl group which is adjacent to the phenyl, the opposite arrangement to that in α-hydroxybenzyl methyl ketone. Thus, the site favoured for protonation is the carbonyl group because of charge delocalisation over the phenyl ring. Protonation here does not generate a good leaving group and there cannot be enough protonation on the hydroxyl group for reaction to occur. We chose (3b) as the target compound because carbonyl groups adjacent to the central methylene would have allowed enolisation. It is also possible that steric factors play a part in making (3b) unreactive; 1,3-dimethylurea does not react with α-hydroxybenzyl methyl ketone. We conclude that (3b) is not a colorimetric reagent for the assay of urea. The reasons for its failure do not apply to (3a) but here the synthetic difficulties were not overcome.

Experimental

Trimethylsilylation of heptane-2,6-dione [3]:

The dione (4.8 g) in dry THF (10 ml) was added, under nitrogen, to a solution of n-butyl lithium (64 ml) and diethylamine (12 ml) in dry THF (25 ml) at -78°C during 10 mins. After stirring for 15 mins, still at -78°C, a solution of triethylamine (10 ml) and chlorotrimethylsilane (30 ml) in THF (30 ml) was added. After stirring for a further 30 mins the mixture was allowed to warm to room temperature. After washing with $NaHCO_3$ solution (3 x 100 ml) the material was extracted with hexane (100 ml), washed with water (2 x 50 ml) and dried (Na_2SO_4). After removal of the solvent the residue was

distilled in vacuo (52°C/1 mmHg) to give (4) as a colourless liquid (yield 12%), m/z 272 (M^+).

Oxidation of (4) [9]:

Chromyl chloride (2.1 g) in dry dichloromethane (20 ml) was added to a solution of the O-silylated enolate (4) (1 g) in dry dichloromethane at -78°C under nitrogen and stirred for 30 mins. The dark red solution was added to cold sodium bisulphite (1 M; 20 ml) solution and stirrerd for 30 mins. The dark green solution was shaken with $NaHCO_3$ solution (10%; 10 ml), water (2 x 10 ml) and dried (Na_2SO_4). After removal of the solvent a green tar remained. Examination by TLC indicated at least five products and from the mass spectrum it was clear that substantial amount of unreacted (4) was present. No further separation was attempted.

Preparation of 1,3-dibenzoylpropane:

Glutaryl chloride (16.9 g) was added to dry benzene (150 ml) and anhydrous $AlCl_3$ (30 g) with careful temperature control at 0°C. After stirring for 2 h. at room temperature the mixture was poured onto a mixture of crushed ice (50 g) and conc. HCl (15 ml) and allowed to stand overnight. The benzene layer was separated, washed with 10% $NaHCO_3$ solution (2 x 50 ml) and water (2 x 50 ml). Benzene was removed by evaporation and the product recrystallised from ethanol (yield, 75%), m.p. 64° (lit. [11] 67°); Mass: m/z 252 (M^+), ^{1}H-NMR ($CDCl_3$,100MHz): δ 2.15 (2H, t, J 7Hz), 3.05 (4H, t, J 7Hz), 7.37 - 8.05 (10H), ^{13}C-NMR ($CDCl_3$): δ 18.7, 37.5, 127.9, 128.5, 132.9, 136.9, and 192.7 ppm.

Bromination of 1,3-dibenzoylpropane:

Bromine (2 ml) was added dropwise to a solution of dibenzoylpropane (5 g) in ether (50 ml) containing anhydrous aluminium chloride (0.1 g) at 0° with stirring. After stirring for further 30 mins. the ether was removed and the residue washed with $Na_2S_2O_3$ solution, water, and dried (Na_2SO_4). The solvent was removed by evaporation and the residue recrystallised from ether to give 2,4-dibromo-1,5-diphenylpentane-1,5-dione (yield 68%), m.p. 119° (lit. [12] 115°), Mass: m/z 250 (M^+ - 2Br), IR (mull): 1680 (C=O), 705 cm^{-1} (C-Br), ^{1}H-NMR ($CDCl_3$,100MHz): δ 2.98 (2H, m), 5.54 (2H, m), 7.43 - 8.04 (10H); ^{13}C-NMR ($CDCl_3$): δ 36.5, 45.8, 128.8, 133.9, and 191.9 ppm. (Found: C, 49.89; H, 3.42. $C_{17}H_{14}Br_2O_2$ requires C, 49.30; H, 3.41%). Further crystals of a different diastereoisomer were obtained from the mother liquor, m.p. 89° (lit. [12] 89°).

Reaction of 2,4-dibromo-1,5-diphenylpentane-1,5-dione with silver oxide:

The dione (12.3 g; 0.03 mol) and freshly prepared silver oxide (7.5 g) were stirred in 75% aqueous acetone for 1 h. at room temperature and then refluxed for 2 h. The silver oxide was filtered off and the acetone removed by evaporation to leave a solid in suspension. After filtration the solid was crystallised from acetone to give white crystals of (3b) (yield 42%), m.p. 144°, Mass: m/z 267 (M^+ - OH), IR (mull): 1684 (C=O), 3510 cm^{-1} (OH), ^{1}H-NMR ($CDCl_3$,100MHz): δ 1.88 (2H, m), 3.92 (2H, s), 5.62 (2H, m), 7.40 - 7.98 (10H) (the peak at

39.2 disappeared on addition of D_2O), ^{13}C-NMR (d_6-DMSO): δ 39.2, 69.6, 128.5, 128.7, 133.3, 134.7, and 201.0 ppm. (Found: C, 71.53; H, 5.55. $C_{17}H_{16}O_4$ requires C, 71.8; H, 5.67 %). The mother liquor on evaporation yielded a greenish yellow solid (5) (yield 35%), m.p. 244°C, Mass: m/z 264 (M^+), IR (mull): 1635 cm^{-1} (C=O), ^1H-NMR (d_6-DMSO): δ 7.15 (1H, s), 7.37 - 8.07 (10H), 10.27 (1H, s), ^{13}C-NMR (d_6-DMSO): δ 115.2, 123.8, 127.3, 128.6, 128.9, 129.7, 132.4, 137.2, 139.8, 143.7, 147.2, and 180.8 ppm. (Found: C, 77.21; H, 4.60. $C_{17}H_{12}O_3$ requires C, 77.26; H, 4.57%).

* The compound (3b) is a mixture of diastereoisomers.

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