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A SYNTHETIC ROUTE TO MONO-ETHERS OF 2,4,6-TRIHYDROXYACETOPHENONE

H. CAIRNS

Fisons Limited—Pharmaceutical Division, Loughborough. England

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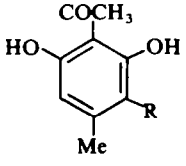
Abstract—The preparation of 4-alkoxy-2,6-dihydroxyacetophenones by the selective deacetylation of 2,4-diacetyl-5-alkoxyresorcinols is described.

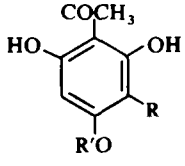
IT IS well established that the alkylation of 2,4,6-trihydroxyacetophenone results mainly in the formation of 2,4-dialkoxy-6-hydroxyacetophenones,[1,2] although aromatic ring C-alkylation has also been reported.[2] The preparation of mono-ethers of 2,4,6-trihydroxyacetophenone has proved difficult[6,7] and many different approaches to their preparation have been described.[3-8] Most of the reported routes involved several reaction stages.

This paper describes a new synthetic route by which 4-alkoxy-2,6-dihydroxy-acetophenones can be readily prepared without isomeric contamination.

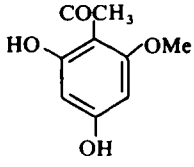
Desai and Mavani[9] reported that treatment of 2,4-diacetyl-5-methylresorcinol (I, R = $COCH_3$) with either N, NaOH or conc H_2SO_4 led to the selective removal of the 4-acetyl group to give 2,6-dihydroxy-4-methylacetophenone (I, R = H). This author has now shown that 2,4-diacetyl-5-alkoxyresorcinols (II, R = $COCH_3$; R′ = alkyl) can similarly be selectively deacetylated to give the corresponding 4-alkoxy-2,6-dihydroxyacetophenones (II, R = H; R′ = alkyl). However in this series of compounds only alkaline hydrolysis was successfully applied. The diacylbenzenes



I



II



III

remained unchanged on treatment with conc H_2SO_4. Dean and Robertson[10] have reported the deacetylation of 2,4-diacetyl-3,5-dimethoxyphenol with boron trifluoride etherate to give 6-hydroxy-2,4-dimethoxyacetopheone but the mono-ethers of diacetylphloroglucinol were quite stable to this reagent.

The 2,4-diacetyl-5-alkoxyresorcinols were synthesized by the mono-alkalytion of diacetylphloroglucinol (II, R = $COCH_3$; R′ = H). This was readily achieved since two of the phenolic OH groups are considerably less reactive than the third due to

H-bonding with the O atoms of the two adjacent acetyl groups. Thus treatment of diacetylphloroglucinol with allyl bromide and propylene oxide gave the novel 2,4-diacetyl-5-allyloxyresorcinol (II, R = $COCH_3$: R′ = $-CH_2CH{=}CH_2$) and 2,4-diacetyl-5-(2-hydroxypropoxy)resorcinol (II, R = $COCH_3$; R′ = $-CH_2CHOH-CH_3$) respectively.

The diacetylresorcinols were selectively deacetylated by refluxing in N NaOH for one hour to give the 4-alkoxy-2,6-dihydroxyacetophenones (II, R = H: R′ = alkyl) shown in Table I.

TABLE 1.

R′	m.p. °C	Calc. %	Found %	Chemical Shift in τ	
				aromatic H(2H)	OH(2H)
CH_3-	137–9 [a]			4·06	−2·26
CH_3CH_2-	164–5	C 61·2	61·1	4·12	−2·23
		H 6·17	6·09		
$PhCH_2-$	139–40	C 69·75	69·8	4·0	−2·35
		H 5·46	5·53		
$CH_2{=}CHCH_2-$	145–6	C 63·45	63·7	4·08	−2·21
		H 5·81	6·06		
$CH_3CHOHCH_2-$	177–8	C 58·4	58·4	4·08	−2·22
		H 6·24	6·34		

[a] Literature[6] m.p. 137°

The structure of the products was confirmed by NMR spectroscopy. The NMR spectra of these ethers clearly confirm the symmetrical structure of the products, the two equivalent aromatic protons occurring as a 2H singlet between 4 and 4·2 τ and the two phenolic protons as a second 2H singlet between −2·2 and −2·4 τ (Table I). In contrast, the NMR spectrum of 2,4-dihydroxy-6-methoxyacetophenone[11] (III), the unsymmetrical isomer of II (R = H: R′ = CH_3), gave an AB quartet for the non equivalent meta-coupled aromatic protons at 4·02 and 4·12 τ (J = 2·38 Hz) and two separate 1H singlets for the phenolic protons at −0·63 τ and −3·85 τ for the 4-OH and 2-OH groups respectively.

When this synthetic route was used no evidence was found for the presence of the isomeric 2,4-dihydroxy-6-alkoxyacetophenones as judged by either NMR spectroscopy or thin layer chromatography on silica gel plates.

EXPERIMENTAL

NMR spectra were recorded in deuterated dimethylsulphoxide, with TMS as an internal standard, on a Perkin–Elmer R 12 spectrometer. M.ps are uncorrected.

2,4-Diacetyl-5-allyloxyresorcinol (II, R = $COCH_3$: R′ = $-CH_2CH{=}CH_2$). A mixture of 2,4-diacetylphloroglucinol (10·5 g), allyl bromide (6·05 g) and anhyd K_2CO_3 (6·9 g) in dry acetone (200 ml) was refluxed for 48 hr. The acetone was evaporated to leave a solid which was washed thoroughly with water. This solid was crystallized from EtOH to give 2,4-diacetyl-5-allyloxyresorcinol (3·3 g) as colourless needles, m.p. 111–2°. (Found: C, 62·2; H, 5·64. Calc. for $C_{13}H_{14}O_5$: C, 62·39; H, 5·64%).

2,4-Diacetyl-5-(2-hydroxypropoxy)resorcinol (II, R = $COCH_3$; R' = $-CH_2CHOHCH_3$). A mixture of 2,4-diacetylphloroglucinol (10 g), propylene oxide (3·33 ml) and benzyl trimethylammonium hydroxide (0·25 ml) in dioxan (20 ml) was heated in a sealed vessel at 100° for 48 hr. The resulting orange soln was poured into water (200 ml) and the white solid which precipitated was crystallized from EtOH to give 2,4-diacetyl-5-(2-hydroxypropoxy)resorcinol (8·1 g) as colourless needles m.p. 152–4°. (Found: C, 58·0; H, 5·92. Calc. for $C_{13}H_{16}O_6$: C, 58·2; H, 6·10%).

2,6-Dihydroxy-4-methoxyresorcinol (II, R = H; R' = CH_3). A soln of 2,4-diacetyl-5-methoxyresorcinol (4·0 g) in N NaOH (84 ml) was refluxed for 1 hr. After cooling, the soln was acidified with conc HCl to give a buff coloured ppt. This solid was crystallized from aqueous EtOH to give 2,6-dihydroxy-4-methoxyresorcinol (2·28 g) as buff coloured needles, m.p. 137–9° (Lit.[6] m.p. 137°).

This deacetylation procedure was used for the preparation of all the compounds shown in Table I.

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