Quinones of Interest in Tetracycline Chemistry

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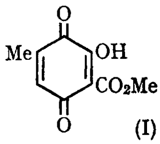
THE characterisation of 4-hydroxy-6-methylpretetramid as a precursor in tetracycline biosynthesis[1] was of considerable interest to us since the Imperial College route to synthetic tetracyclines involves related compounds. In the course of our work we have studied methods for the synthesis of 1,2,4-trihydroxybenzenes and the hydroxyquinones derived therefrom.

Methyl *p*-orsellinate[2,3] was oxidised with Frémy's salt at pH 6·5 to the quinone (I) (93%), m.p. 115—116°, ν_{max} 3400, 1670, and 1590 cm.$^{-1}$ (in Nujol), λ_{max} 209 (ϵ 14,200), 263 (ϵ 14,900), 327 (ϵ 1490) mμ (all ultraviolet spectra in EtOH except where otherwise stated). The n.m.r. spectrum (all measurements in $CDCl_3$) demonstrated that an equilibrium mixture of approximately equal amounts of *o*- and *p*-quinones was present. The methyl signals appeared at τ 7·93(3) and 7·77(3); the methoxyl signals at 6·03(3) and 5·97(3), ring protons at 3·72(2), and a broad signal centred at 0·45(2) that was exchanged by D_2O.

Methyl 2-formyl-*p*-orsellinate was hydrogenolysed over 10% Pd/C in glacial acetic acid to give methyl 2,6-dihydroxy-3,4-dimethylbenzoate[4] (96%). Oxidation of this compound was conducted under the same conditions as for (I)-

The crystalline quinone (II) was obtained after low-temperature work-up (94%), m.p. 68°, ν_{max} 1678, 1660, 1643 cm.$^{-1}$ (in Nujol), λ_{max} 208 (ϵ 9440), 272 (ϵ 17,800), 397 (ϵ 920) mμ. The simple n.m.r. spectrum, τ 7·91(6), 6·00(3), $-$1·38 to $-$2·73(1) exchanged by D_2O, suggested that (II) exists predominantly as the *p*-form.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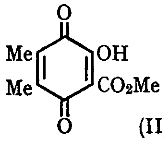
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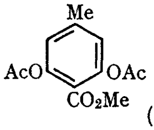
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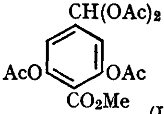
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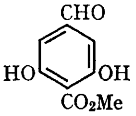
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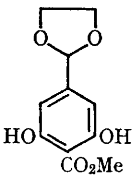
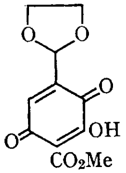

(VI)

Low-temperature Thiele oxidation of methyl *p*-orsellinate diacetate[5] (III) under controlled conditions produced (IV), (48%), m.p. 112°, ν_{max} 1780, 1730 cm.$^{-1}$ (in $CHCl_3$), λ_{max} 204 (ϵ 20,000), 224 (ϵ 5740) mμ, τ 7·81(6), 7·74(6), 6·18(3), 2·76(2), 2·38(1). Mild acid hydrolysis of the tetra-acetate (IV) gave (V) (82%), m.p. 140°, ν_{max} 3460, 1695, 1660 cm.$^{-1}$ (in $CHCl_3$), λ_{max} 217 (ϵ 18,000), 268 (ϵ 9460), 274 (ϵ 8950), 399 (ϵ 3020), 363 (ϵ 2880) mμ, and τ 5·88(3), 3·06(2), 0·30(2, exchanged by D_2O), 0·11(1). The ethylene acetal (VI), m.p. 108°, ν_{max} 3420, 1686 cm.$^{-1}$ (in Nujol), λ_{max} 220 (ϵ 13,850), 256 (ϵ 7930), 324 (ϵ 2170) mμ, τ 6·00(3), 5·96(4), 4·13(1), 3·43(2), 0·40(2, exchanged by D_2O) was prepared from (V) (85%) in the usual way.

Oxidation of (VI) with Frémy's salt proceeded cleanly at pH 6·5 to give the quinone (VII) (92%), m.p. 164°, ν_{max} 3600 weak, 1682, 1656 cm.$^{-1}$ (in Nujol), λ_{max} 210 (ϵ 9350), 256 (ϵ 11,620), 369 (ϵ 1830) mμ. N.m.r. data illustrated, again [τ 5·95(3), 5·89(4), 4·07(1), 3·12(1), very broad OH exchanged by D_2O] that the *p*-quinone dominated.

Hydrogenation of (I) over 5% Pd/$BaSo_4$ furnished (VIII) quantitatively. It had m.p. 82° sub., ν_{max} 3560, 3450, 1670 cm.$^{-1}$ (in $CHCl_3$), λ_{max} 221 (ϵ 19,500), 255 (ϵ 13,100), 323 (ϵ 3440) mμ, τ 7·70(3), 5·88(3), 3·62(1), [1·25(1), 0·34(1), 0·08(1), all exchanged by D_2O]. A modified Gatterman reaction on (VIII) gave (IX) (98%), m.p. 202°, ν_{max} 3570, 1660, 1640 cm.$^{-1}$ (in $CHCl_3$), λ_{max} 256 (ϵ 27500), 305 (ϵ 1840) mμ, τ 7·50(3), 5·98(3), $-$10·12(1), [$-$1·50(1), $-$2·60(1), $-$3·00(1), all exchanged by D_2O]. The mass spectrum of (IX) exhibited a molecular ion at *m/e* 226, corresponding to $C_{10}H_{10}O_6$.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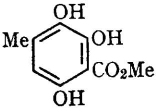
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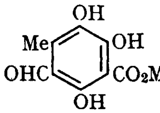
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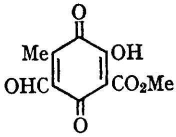
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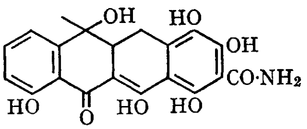
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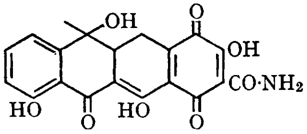
(XII)

Dehydrogenation of (IX) with DDQ (2,3-dichloro-5,6-dicyanobenzoquinone) gave the quinone (X) (97%), m.p. 145°, ν_{max} 3500, 1706, 1684, 1664 cm.$^{-1}$ (in Nujol), λ_{max} 206 (ϵ 11,400), 272 (ϵ 13,500), 376 (ϵ 470) mμ, τ 7·54(3), 5·85(3), $-$0·50(1), very broad OH exchanged by D_2O.

4a,12a-Anhydro-4-hydroxy-4-dedimethylaminotetracycline[6,7] (XI) was treated with DDQ in dry dioxan to give the dark red quinone (XII) (74%), m.p.: decomposes over a very wide range of temperature, ν_{max} 3500, 3400, 3280, 1667, 1625 cm.$^{-1}$ (in Nujol) λ_{max} 257 (ϵ 18,000), 340 (ϵ 9190), 382 (ϵ 5890) mμ in dioxan. This quinone has synthetic interest and may also be of biosynthetic importance.

Hassall and Winters[8] have recently carried out some analogous oxidations with Frémy's salt.

All new compounds gave satisfactory analyses.

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