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PHOTOCHEMICAL SYNTHESIS OF HALLERIDONE, HALLERONE, RENGYOL AND DERIVATIVES

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Abstract - Oxidation of the p-hydroxyphenethyl alcohol with singlet oxygen led to the synthesis of halleridone (4), hallerone (8) and their monoepoxide (9). The cyclohexanols rengyol (5a), isorengyol (5b) and the hydroxyketone form of rengyoxide 6b were also obtained by known procedures.

The existence of natural products with a non-aromatic carbon skeleton and a C_6-C_2 structure -probably derived from the metabolism of prephenic acid- was detected some time ago.[1] However, not many such substances are described in the literature, particularly those with a cyclohexandienone skeleton or their reduction products.[2]

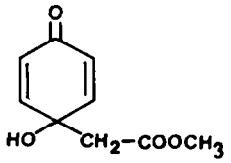
The isolation of compounds with a quinol structure such as jacaranone (1), obtained from Jacaranda caucana Pittier (Bignoniaceae)[3] and other species, was recently reported. These compounds are quite widely distributed since several closely-related products have been observed in other families such as Cornaceae,[4] Scrophulariaceae,[5] Compositae,[6] and Oleaceae.[7] Some members of the series are characterized by exhibiting a varied biological activity that includes cytotoxic[8] and antiulcer[9] properties, induce metamorphosis in larvae of bivalvous molluscs (pecten)[10] and are considered to be phytoalexins.[11]

The recent observation that Digitalis nevadensis produces an enone with the structure 2[12] and the presence of the salidroside 3 in the leaves of Isoplexis chalcantha[13] and of the enone 4 in D. purpurea[5a] led to the investigation of such metabolites in the genus Isoplexis: I. chalcantha and I. canariensis var. tomentosa. The alcohols 1-(2'-hydroxyethyl)-cyclohexan-1,4β-diol and its 4α-epimer 5a,b[5d] have been found in both species as well as in Forsythia suspensa Vahl[7] and Halleria lucida.[5e] Halleridone (4)[7] and 4-hydroxy-4-(2'-hydroxyethyl)-cyclohexanone (6) were also obtained from the latter Isoplexis.

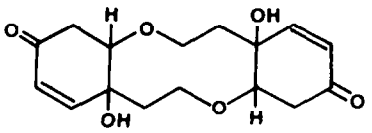
Further studies could not be carried out because of the miniscule amounts and their synthesis was therefore undertaken. The use of oxidation methods of phenols, as an effective procedure for obtaining same, is inadvisable.[14] However, oxidation with singlet oxygen of p-hydroxyphenylethanol[15] led to a substance, the spectral data of which coincided with those reported for 4. This compound was identified by direct comparison with the natural product. The sample obtained by photooxidation was more thoroughly examined by means of bidimensional NMR (^1H-^1H COSY-90 techniques).

The results obtained are presented in Figure 1 where a residual long-range coupling can be observed between C-3 and C-5.

Photooxygenation of the monoacetate 7b, obtained from the diacetate 7c by selective deacylation with Zn powder[16] under the same conditions that led to the formation of 4, afforded a quinol whose spectral data coincided with those reported for 8.[5c] This substance, upon standing, was converted into halleridone acetate (4b), probably by transacetylation and Michael's addition of the primary alcohol to one of the quinonic double bonds. Reduction of 8 with $NaBH_4$ afforded a mixture of alcohols 4a and 4b, and a further compound identified as the alcohol 7a, formed by reduction of the ketone group to an alcohol and by subsequent aromatization. Oxidation of the acetate (5c) with pyridinium dichromate yielded, as expected, the acetate (6b) of a tautomeric form of rengyoxide[1] existing in the more stable hydroxyketone form.



1



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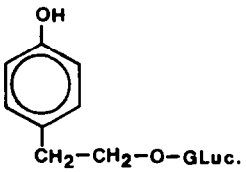

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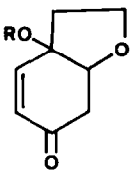
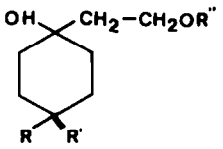


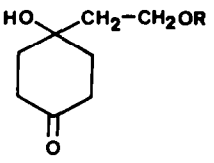
4

a R=H
b R=Ac



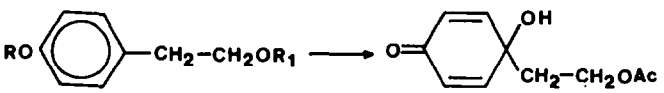
5

a R=OH, R'=R''=H
b R'=OH, R=R''=H
c R=OH, R'=H, R''=Ac



6

a R=H
b R=Ac

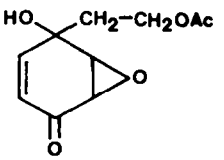


7

a $R=R_1=H$
b $R=H, R_1=Ac$
c $R=R_1=Ac$

8

+



9

The above-mentioned photooxygenation afforded a further substance which was unstable in the atmosphere of the laboratory, and had formula $C_{10}H_{12}O_5$, determined by high resolution mass spectrometry. Its spectral data revealed that this compound, like 8, was an unsaturated α,β-cyclohexenone with the same substituents. However, a noteworthy difference was observed in the ^1H n.m.r. spectrum. The signals assigned to the above-mentioned chromophore were, in this case, two quartets centred at δ6.40 and 5.81 (1H each, J = 10.5 and 2 Hz); moreover, in the absorption region corresponding to protons geminal to the oxygen atom, two new quartets appeared at δ3.65 and 3.34 (1H each, J = 3.65 and 2Hz), suggesting the existence of an oxirane ring. A more complete study of this spectrum, using ^1H-^1H

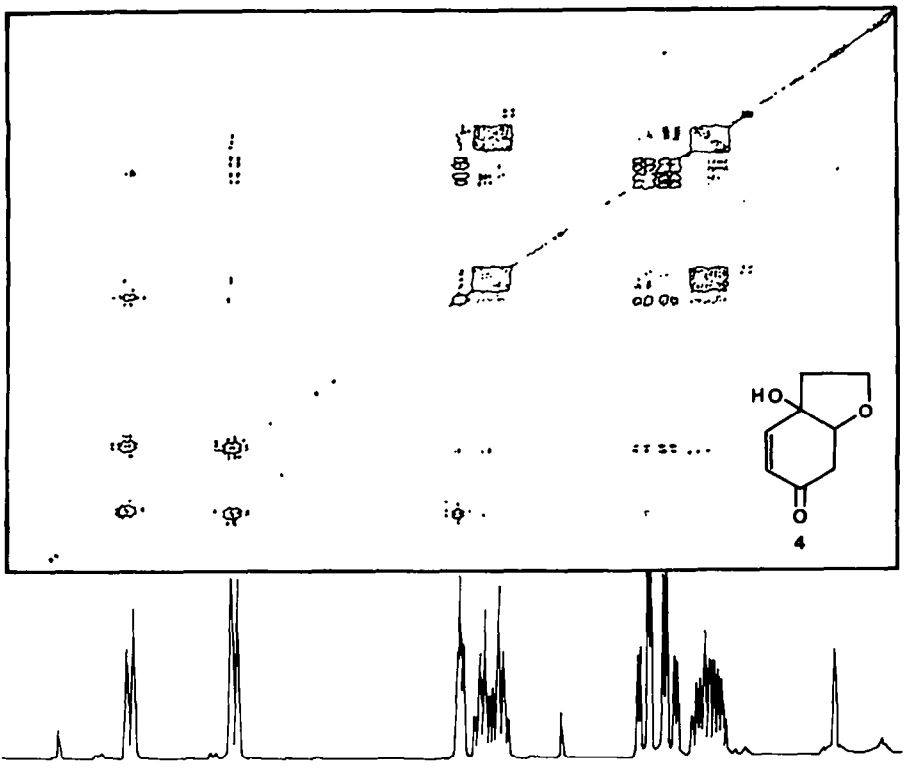


Figure 1

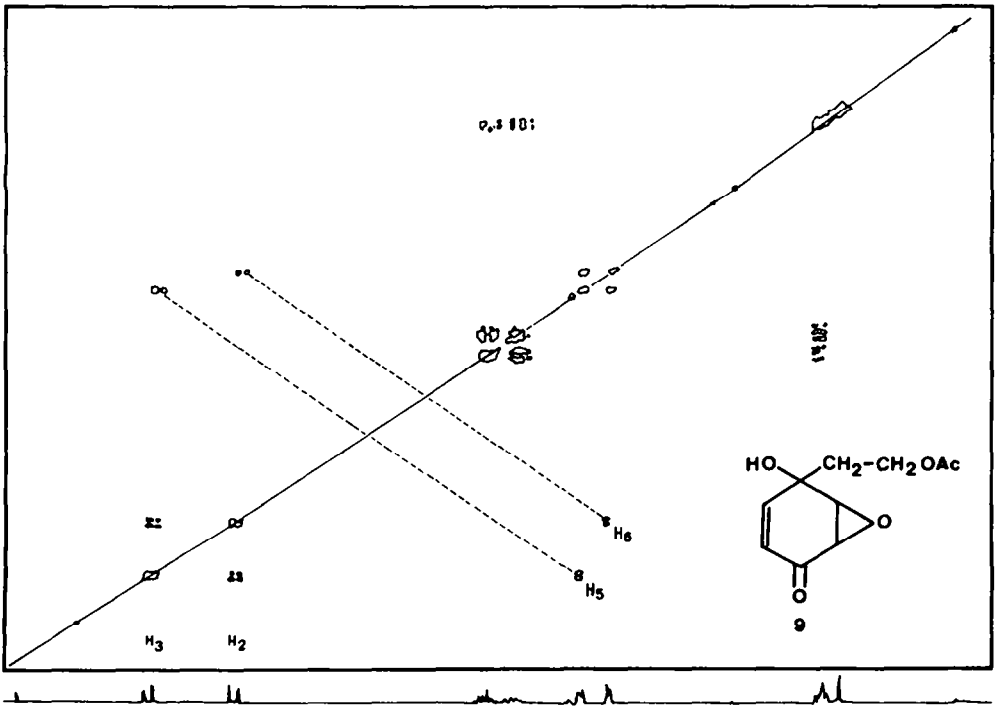


Figure 2

COSY-90 bidimensional n.m.r. techniques (Figure 2) confirmed the existence of a W coupling between C-2H,C-6H and C-3H,C-5H and hence the almost equatorial disposition of the H atoms involved. An examination of the data summarized in the Table revealed the presence of 6 carbon atoms bonded to 5 oxygens, 4 of them with sp^3 hybridation, that appeared between 54 and 70 ppm. Two of these signals were characteristic of trisubstituted carbons. Again, chemical shift arguments suggested assignment of the functionality as an epoxide ring and it was therefore formulated as 9. These results were unexpected because there are relatively few examples of the successful oxidation, by this procedure, of alkenes that are substituted with electron withdrawing groups. The reactivity of α,β-unsaturated ketones towards singlet oxygen is strongly dependent on the conformation of the unsaturated system. Carbonyl systems with S-cis conformation are rapidly oxidized by singlet oxygen, whereas systems in S-trans conformation react slowly or not at all.[17]

Table. ^{13}C NMR Chemical shift assignments for photooxygenation substances (4, 8, 9). Multiplicities.

C	4	8	9
1	197.55s	185.58s	193.21s
2	127.50d	127.30d	124.82d
3	148.93d	151.41d	148.19d
4	74.46s	67.86s	70.12s
5	80.60d	151.40d	58.49s
6	38.97t	127.30d	54.37s
1'	39.40t	38.54t	37.60t
2'	65.48t	59.44t	59.31t
$COCH_3$	---	170.76s	170.78s
CH_3	---	20.48q	20.91q

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. N.m.r. spectra were taken on a Bruker AC-80 or a WP-200SY spectrometer. The homonuclear ^1H-^1H shift correlated 2D-n.m.r. spectra (COSY-90) were performed using the Bruker WP-200SY upgraded with an Aspect 2000 computer. The spectral width was 1000 x 512. Mass spectra were recorded on a VG Micromass ZAB-2F spectrometer at 70eV, 200°C. Infrared spectra were measured on a Perkin Elmer 681 spectrophotometer. Ultraviolet absorption spectra were recorded on a Perkin Elmer 550 SE instrument, in methanol. Gas chromatography was performed on a Hewlett Packard 5790 instrument, with an OV-1 capillary column, and helium as carrier gas, 1ml/min, 150° isotherm. Irradiation was performed with a Philips 500 watt halogen lamp in a reactor refrigerated by running water. During irradiation, a stream of oxygen was bubbled vigorously through the solution. The reaction products were extracted, the solvent dried and evaporated in vacuo, the residue chromatographed on a column of silica gel (Merck, 0.063 mesh), under pressure. Elution was performed with the solvent and mixtures indicated in each case.

Photooxygenation of the p-hydroxyphenethyl alcohol

A solution of the alcohol (1.5 g, 10.9 mmol) in 500 ml of a buffer of potassium phosphate at pH 7 and methanol -in a different amount to obtain a clear solution- containing 300 mg of bengal rose, was irradiated with bubbling for several hours. The reaction mixture was extracted in countercurrent with ethyl acetate. The residue obtained (700 mg) after removal of the solvent was chromatographed (chloroform-acetone 95/1) to afford 4a as a light orange-coloured oil: UV λ_{max}^{MeOH} 223 nm, IR $\nu_{max}^{CHCl_3}$ 3400, 1670 cm^{-1}. ^1H n.m.r. δ 6.76 (1H, dd, J= 10.8Hz), 6.01 (1H, dd, J= 10.8Hz and 1.5Hz), 4.24 (2H, m), 4.02 (1H, t, J= 1.5Hz), 2.69 (2H, dq, J= 16 and 5Hz), 2.27 (2H, m), IR and n.m.r. spectra superimposable with those of an authentic sample of halleridone.

p-Hydroxyphenethyl alcohol acetate (7c)

The alcohol (2 g) was acetylated with acetic anhydride and pyridine in the usual manner. The product obtained, 7c (1.90 g), was dissolved in methanol (150 ml), adding activated Zn.[15] The reaction mixture was kept with stirring for 24 h, filtered, the solvent removed and the residue chromatographed (n-hexane/acetone, 8/2) to afford the target monoacetate (1.4 g): ^1H n.m.r. ($CDCl_3$) δ 7.05 (2H, d, J= 8.7Hz), 6.78 (2H, d, J= 8.7Hz), arom. H, 4.2 (2H, t, J=7.0Hz, CH_2OAc), 2.85 (2H, t, J= 7.0Hz, CH_2), 2.04 (3H, s, CH_3CO).

Photooxygenation of 7b

The monoacetate 7b (1.4 g, 7.7 mmol) dissolved in 100 ml of phosphate buffer at pH 7 in methanol (10 ml) containing bengal rose (200 mg) was irradiated as above.

After 2 hours the transformation had ended. The solvent was concd in vacuo and the residue chromatographed (dichloromethane/acetone, 97/3) to give two compounds, one of which was identified as hallerone (8, 580 mg), colourless liquid, UV λ_{max}^{EtOH} 231 nm, log ε 3.92. IR δ_{max}^{KBr} 3390, 1730, 1660, 1620 cm^{-1}, ^1H NMR ($CDCl_3$) δ6.95 (2H, d, J= 10.8Hz), 6.11 (2H, d, J= 10.8Hz), 4.11 (2H, t, J= 6.6Hz, CH_2OAc), 2.08 (2H, t, J= 6.6Hz, CH_2), 1.93 (3H, s, CH_3-CO). MS m/z M^+ 196 (0.32), 154 (5.8), M^+-C_2H_2O, 136 (53), M^+-60, 110 (48), 109 (91), 43 (100). A high-resolution measurement could not be obtained. M^+-AcOH gave 136.0521. $C_8H_8O_2$ requires 136.0524.

A second photooxygenation product (9, 120 mg) was then isolated, colourless liquid, UV λ_{max}^{EtOH} 212 nm. IR ν_{max}^{KBr} 3420, 1730, 1680, 1620 cm^{-1}. ^1H NMR is discussed in the text. M^+ 212.0646. $C_{10}H_{12}O_5$ requires 212.0685; 170 (2.8), M^+-42, 152 (8.2), M^+-60, 136 (2.3), 97 (96), 43 (100).

Reduction of 8

To a solution of 8 (180 mg) in methanol was added $NaBH_4$ (15 mg) and the mixture was kept overnight at room temperature, then poured into water, acidified with dilute HCl and extracted until exhaustion with EtOAc. The residue was chromatographed (dichloromethane/acetone, 1/1) and, in order of elution, the following pure alcohols were obtained: 5a (15 mg), 5b (11 mg) and 7a (25 mg), identified, respectively, with rengyol, isorengyol and p-hydroxyphenethyl alcohol; IR and NMR spectra were superimposbale and the chromatographic behaviour identical.

Formation of 6b

Rengyol (5 mg) was partially acetylated in the usual manner at a low temperature (-25°C) and was separated from a small amount of diacetate which was also formed. The monoacetate obtained was suspended in CH_2Cl_2 (5 ml) and pyridinium dichromate (15 mg) added dropwise with shaking. After 3 days, the reaction product was obtained in the usual way, colourless oil, identified by comparison of its spectroscopic data with those reported in the literature for 6b. IR ν_{max} 1735 and 1710 cm^{-1}; ^1H NMR ($CDCl_3$) 4.30 (2H, t, H-2, J= 8Hz), 2.73 (2H, m), 2.25 (2H, m), 2.07 (3H, s), 2.00 (2H, m), 1.93 (2H, t, H-1', J= 8Hz), 1.77 (2H, m). MS m/z M^+ 140 (19), 122 (11), 113 (9), 112 (8), 85 (24), 43 (100).

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Note - When this work was completed (December, 1986), it became known that Professor Endo (personal communication), Pharmaceutical Institute, Tohoku University, Aoba-yama, Sendai, Japan, had synthesized hallerone and halleridone by a procedure similar to that described herein.