Tetrahedron Letters No. 12, pp. 963-966, 1970. Pergamon Press. Printed in Great Britain.

THE CONSTITUTION OF HERQUEINONE AND ITS RELATIONSHIP TO ISOHERQUEINONE

J.S. Brooks and G.A. Morrison

Department of Organic Chemistry, The University, Leeds, 2.

(Received in UK 26 January 1970; accepted for publication 5 Feburary 1970)

Herqueinone, which is a red pigment present in the mycelium of Penicillium herquei (1), has been shown to possess the same carbon skeleton as atrovenetin (III; R = R' = R" = H) (2) and has been tentatively assigned the structure (I; R = H, R' = Me) or (I; R = Me, R' = H) (3). We now wish to present evidence which establishes that herqueinone is to be represented as (I; R = H, R' = Me). We have also found that herqueinone extracted from the mycelium is contaminated with varying amounts of isoherqueinone, which is now shown to differ only in the configuration of the asymmetric centre in the side chain. Mild base treatment of herqueinone results in epimerisation at the tertiary alcoholic centre to produce enantio-isoherqueinone, possibly through the intermediate diketone (II) [cf. the structure of trimethylherqueinone B (4)]. The crystalline material isolated after treatment of herqueinone with potassium carbonate in refluxing acetone, referred to in the literature simply as isoherqueinone (1), is in fact racemic isoherqueinone arising by admixture of the newly-formed enantio-isoherqueinone with the isoherqueinone already present. Depending on the composition of the original sample of "herqueinone" the mother liquors contain either isoherqueinone or enantio-isoherqueinone, and we have obtained transformation products in both series.

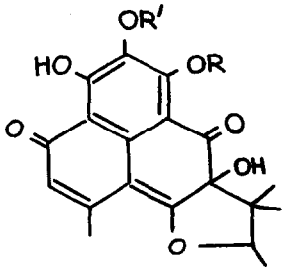
The IR, UV, Mass and NMR spectra of herqueinone are all consistent with structure (I; R = H, R' = Me) and deuterium exchange experiments have revealed the presence of three hydroxyl groups. In particular, the nuclear methyl group and the hydrogen atom on the adjacent carbon atom are coupled (J = 1 Hz.), as required by the quinonoid structure (I). The position of the methoxyl group of herqueinone follows from conversion of its reduction product, deoxyherqueinone (III; R = R' = H, R" = Me), into a mixture of atrovenetin orange (III; R = R' = R" = Me) and yellow (IV; R = R' = R" = Me) trimethyl ethers (cf. ref. 2b), which were separated chromatographically. Since these methylation products are dextrorotatory, as are the same compounds obtained from atrovenetin itself, it follows that herqueinone and atrovenetin have the same absolute configuration at the asymmetric centre in the side chain.

All the specimens of herqueinone obtained by us exhibited in their NMR spectra impurity peaks which corresponded exactly to the spectrum of the racemic isoherqueinone obtained by base-catalysed isomerisation. All the batches of mycelia grown by us, except one, gave on extraction a mixture in which herqueinone predominated. Chromatography and crystallisation failed to produce a sample of herqueinone which was completely free from isoherqueinone.

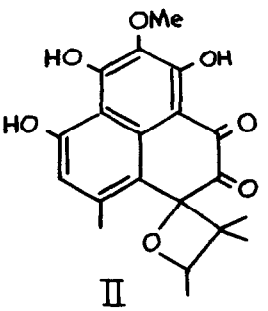
Zinc and acetic acid reduction of racemic isoherqueinone, followed by acetylation, gave deoxyherqueinone diacetate (III or IV; R = R' = Ac, R" = Me) with a residual rotation of only +2·7°. Similar treatment of the best grade of herqueinone gave material of $[\alpha]_D$ +57°. Samples of deoxyherqueinone diacetate with $[\alpha]_D$ values of +54° and -31° were obtained when the mother liquors from the isomerisation respectively of herqueinone-predominant and isoherqueinone-predominant samples of "herqueinone" were reduced and acetylated.

When the herqueinone-isoherqueinone mixture extracted from the mycelium was hydrogenated, and the resulting mixture of dihydroherqueinone and dihydroisoherqueinone was methylated under various conditions, isomeric pairs of mono- (V; R = R" = H, R' = Me), di- (V; R = R' = Me, R" = H) and trimethyl (V; R = R' = R" = Me) ethers were obtained. It was not found possible to separate the isomeric components of any of these pairs of compounds. Racemic modifications of these compounds in the isoherqueinone series have, however, been obtained pure, starting with racemic isoherqueinone. In all these compounds, the free phenolic hydroxyl groups were readily acetylated (acetate C=O at 1765 $cm.^{-1}$); the tertiary aliphatic nature of the remaining hydroxyl group was apparent since forcing conditions were required to acetylate it (acetate C=O band at 1735 $cm.^{-1}$), and comparison of the NMR spectrum of each of the tertiary acetates with its precursor alcohol revealed no downfield proton shift, as would have been the case had the aliphatic hydroxyl been primary or secondary. The placement of the methoxyl groups in the dimethyl ethers follows from the acid-catalysed dehydration of the hydride reduction product (VI), $[\alpha]_D$ +64°, (see below) to afford the phenalenone (VII; R = R' = R" = Me), in which the position of the carbonyl group was revealed by the coupling evident in its NMR spectrum between the nuclear methyl group and the hydrogen atom on the adjacent carbon. The methylation patterns in the mono- and dimethyl ethers are assigned on the basis of their infrared carbonyl stretching frequencies at 1620 $cm.^{-1}$ (H- bonded aryl C=O) and 1670 $cm.^{-1}$ (normal aryl C=O) respectively.

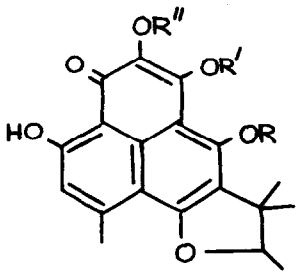
Lithium aluminium hydride reduction of the mixture of dimethyl ethers of dihydroherqueinone and dihydroisoherqueinone gave two products which were separated chromatographically. One of these, $[\alpha]_D$ +43°, was shown by spectral comparison to be an optically active form of the single racemic compound



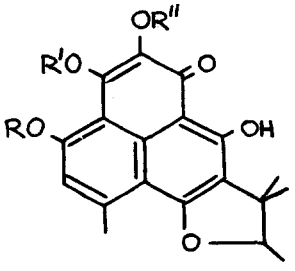
I



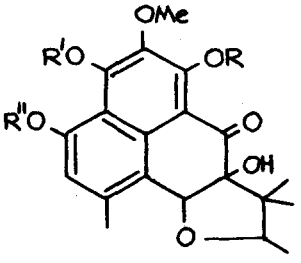
II



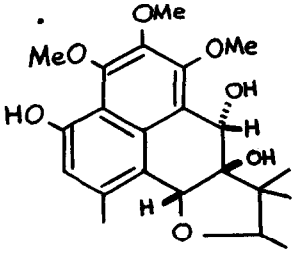
III



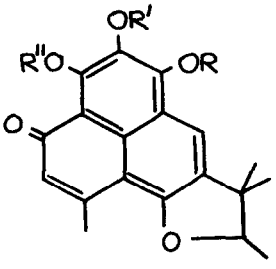
IV



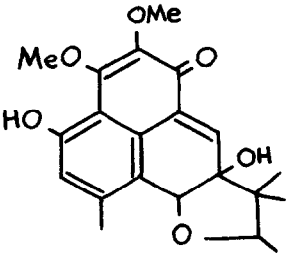
V



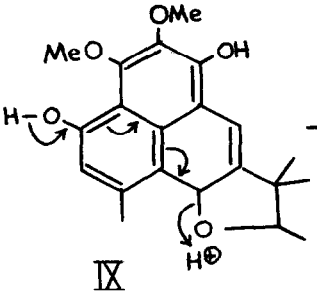
VI



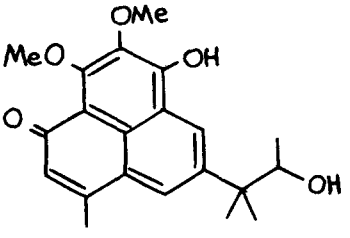
VII



VIII



IX



X

obtained when the same complete reaction sequence was applied to racemic iso-herqueinone; the other enantiomer, less optically pure ($[\alpha]_D$ -32°), was obtained starting from the enantio-isoherqueinone present in the mother liquor from the isomerisation of a herqueinone-predominant sample of "herqueinone". This compound is assigned the structure (VI). The other product was an epimer, $[\alpha]_D$ +64°, of the same gross structure, derived ultimately from herqueinone. An interesting feature of the NMR spectra of these compounds is that they both exhibit long-range coupling (J = 2 Hz.) between the two benzylic protons. If the usual geometric requirement for such coupling (5) is assumed, the two compounds may both be assigned the relative stereochemistry implied in (VI).

The structures and epimeric relationship of these reduction products were shown by treatment of each with hydrochloric acid in aqueous dioxan. The substance of $[\alpha]_D$ +64°, derived from herqueinone, afforded the phenalenone (VII; R = R' = Me, R" = H), $[\alpha]_D$ +137°, and the compound (VIII), $[\alpha]_D$ -476°, while the reduction product derived ultimately from isoherqueinone gave the enantiomer of (VII; R = R' = Me, R" = H), $[\alpha]_D$ -124°, and an epimer of (VIII), $[\alpha]_D$ - 84°. The structures of the enantiomers (VII; R = R' = Me, R" = H) and the epimers (VIII) followed from their spectra; in the case of compound (VIII), $[\alpha]_D$ -476°, its structure was confirmed by its dehydration with p-toluenesulphonic acid to afford the phenalenone (VII; R = H, R' = R" = Me) and by its reduction with zinc and acetic acid to give anotner phenalenone (X), $[\alpha]_D$ -31°, arising presumably by acid-catalysed cleavage of the initially formed phenalene (IX). Compound (X) and its diacetate both had UV, IR, Mass and NMR spectra in full agreement with their assigned structures. Treatment of the epimer (VIII), $[\alpha]_D$ -84°, with zinc and acetic acid gave as expected the enantiomer of (X), $[\alpha]_D$ +28°. The placement of the methoxyl groups in compounds (VII) - (X) is based on a study of the NMR spectra of a range of phenalenones, and will be detailed in our full paper.

Satisfactory analyses and spectra were obtained for all the new compounds described.

We thank Dr. R. Thomas for providing us with a culture of P. herquei, and Professor W. Klyne and Dr. P.M. Scopes for determining the CD curves of some of our compounds.

References

1) J.A. Galarraga, K.G. Neill and H. Raistrick, Biochem. J., 61, 456 (1955).

2) (a) D.H.R. Barton, P. de Mayo, G.A. Morrison and W.H. Schaeppi, Chem. and Ind., 552 (1956); (b) D.H.R. Barton, P. de Mayo, G.A. Morrison and H. Raistrick, Tetrahedron, 6, 48 (1959).

3) I.C. Paul, G.A. Sim and G.A. Morrison, Proc. Chem. Soc., 352 (1962).

4) J. Cason, J.S. Correia, R.B. Hutchison and R.F. Porter, Tetrahedron, 18, 839 (1962).

5) L.M. Jackman and S. Sternhell, Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, Pergamon, London, 1959, p. 334.