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Approaches to the Syntheses of Dimeric Quinolinone Alkaloids

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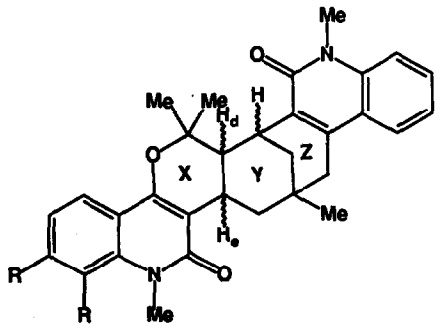
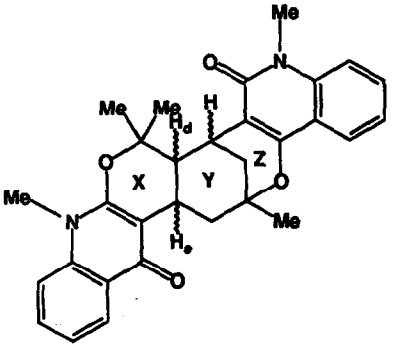
Abstract: A quinolinone allylic alcohol has been synthesised by a palladium-catalysed coupling reaction. Acid-catalysed dehydration of the latter and concomitant Diels-Alder dimerisation, of the resulting diene, afforded dimeric quinolinone derivatives and demonstrated possible approaches to the syntheses of compounds of this type.

Recently we[1] have been studying biomimetic designed methods for the total syntheses of dimeric quinolinone alkaloids, that are apparently derived from the dimerisation of quinolinone monomers to give a characteristic XYZ fused ring system, as exemplified by the paraensidimerins and vepridimerins. The paraensidimerins which constitute a group of five dimers were isolated [2] from the rutaceous species *Euxylophora paraenis*. Four were isomers of the type **1**, with structures consisting of two 2-quinolinone units that differed only in the stereochemistry of the protons H_d and H_e about the XY ring junction. Almost concurrently, the four isomeric dimers, which are referred to as the vepridimerins, were isolated [3] from *Vepris louissi* and *Oricia renieri*. Two of these dimers are tetramethoxy analogues of the paraensidimerins with the structure **2**. The remaining two differ from the dimers **1** and **2**, in that they were apparently derived from a mixture of 2-quinolinone and 4-quinolinone units, as depicted in structure **3**.

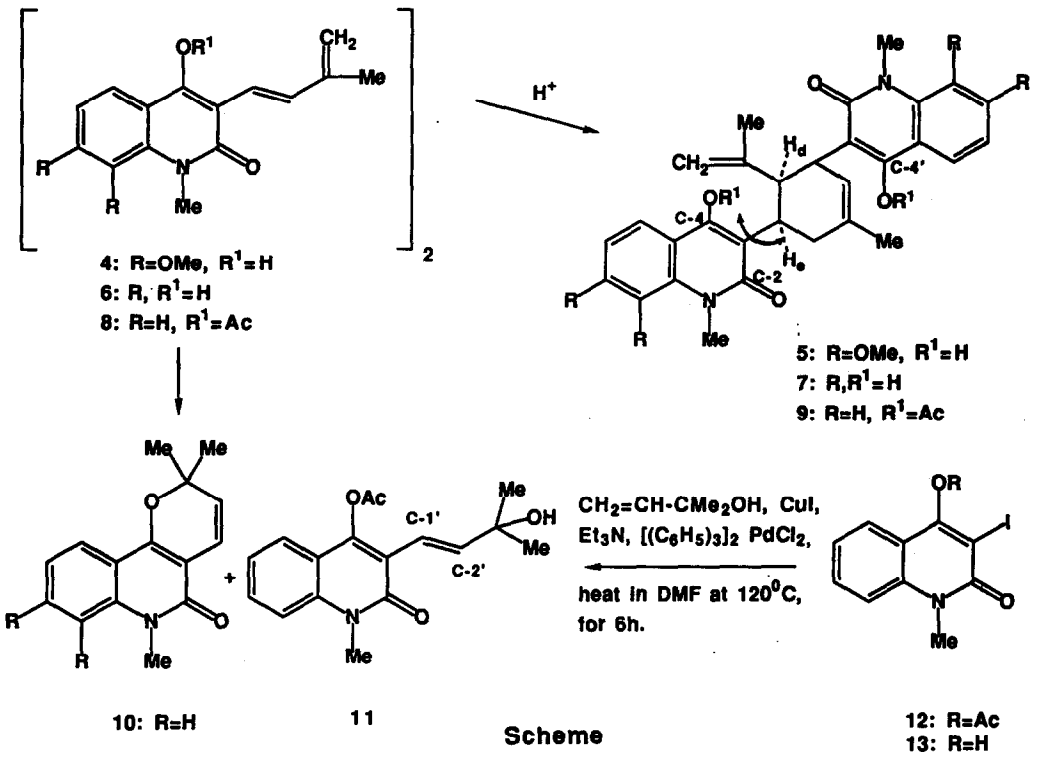


1: R=H
2: R=OMe



3

The biosynthesis of the vepridimerins (Scheme) has been earlier proposed [4] to involve a Diels-Alder type dimerisation of an *ortho*-hydroxydiene **4**. Ring closure of the resulting intermediate **5** *via* the C-4' oxygen and cyclisation involving the residual double bond and the oxygen function at C-4 gave dimers of the type **2**. The dimers **3**, containing a 4-quinolinone unit, apparently arise when the latter cyclisation occurs *via* the oxygen at C-2. We recognised that the paraensidimerins **1** could be derived by similar biosynthetic sequences involving a diene species **6** and an analogous intermediate **7**. We thus attempted a biomimetic designed synthesis of the dimers **1** to check our hypotheses. Our initial approaches were to synthesise a diene with its *ortho*-hydroxyl function suitably protected, that upon dimerisation, would permit isolation of a corresponding intermediate (*cf.* **5** Scheme), which could then be stereospecifically cyclised to the required dimers.

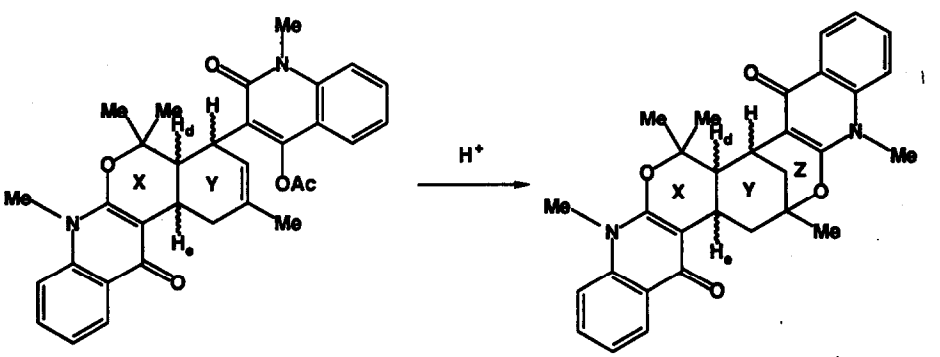


Scheme

In preliminary studies from our laboratories, attempts to synthesise protected dienes were not successful as their purification always proved to be very difficult. We thus desired an alternative approach to these syntheses. Barnes *et al* [5] reported the synthesis of a dimer with a XYZ fused ring system similar to that inherent in **1**-**3**. They proposed that a 2-methylbuta-1,3-diene, formed *in situ* by dehydration of a corresponding 3-hydroxy-3-methyl-1-butenyl derivative, was also implicated in their reaction. We thus reapproached our synthesis using the protected quinolinone alcohol **11** which we hoped would allow, after its dehydration and dimerisation via the diene **8**, isolation of an anticipated diacetate **9**.

Synthesis of 3-methylbut-2-enyl alcohol derivatives can be effected [6] by palladium catalysed Heck reaction of an appropriate aryl halide with 2-methyl-3-buten-2-ol. Treatment of the 4-acetoxy-quinolinone **12**, obtained by acetylation of 4-hydroxy-3-iodo-1-methyl-2-quinolinone [7] **13**, gave three products (Scheme). A strongly fluorescent material was shown by NMR [8] to be the desired quinolinone allylic alcohol **11** (30%). The vinylic protons at C-1' and C-2', appearing as two 1H doublets at δ 7.12 and 6.55 respectively, had coupling constants of J=18Hz which showed that they were occupying a *trans* stereochemistry whilst a 6H singlet at ∂1.44 was typical of a -CMe_2 group. A second less polar product (11%), was identified to be the diene **8**. Its NMR spectrum thus showed only a 3H singlet lower field at δ 1.95 and an additional broad 2H singlet at δ 5.15 which was consistent with a terminal =CH_2 grouping. As previously noted [6] compounds of this type are probably obtained in these reactions due to dehydration of the tertiary allylic alcohol **11** by the Et_3NHI salt byproduct also formed in the reaction mixture. The third product separated was the known alkaloid *N*-methylflindersine **10** since its NMR and TLC behaviour were identical with that of an authentic sample of this pyranoquinolinone. Its formation suggests that the diene **8** is subject to deacetylation and subsequent intramolecular cyclisation during the course of the reaction.

We then proceeded to investigate acid treatment of **11** in an analogous fashion to that described by Barnes *et al.* [5] It was thus dissolved in acetic acid, containing a few drops of concentrated sulphuric acid, and stirred at room temperature for 20 hours. Workup and chromatography resulted in the isolation of several products none of which proved to be an anticipated diacetate **9**. Two products (obtained in yields of 30-35%) were isomeric and were shown by high resolution mass spectroscopy to have the molecular and elemental constitution $C_{32}H_{32}N_2O_5$ which corresponded to the molecular mass of **9** minus C_2H_2O; which denoted loss of an acetate group. Hence their NMR spectra [8] showed only one 3H resonance typical of an acetate group, whilst two 1H doublets in the products occurring at δ 8.47 and δ 8.35 suggested that the structures contained aromatic protons which were being deshielded by an adjacent *peri*-carbonyl group as is typical with 4-quinolinones. Each of the spectra also lacked any 2H broad signal characteristic of a terminal =CH_2 group that occurred at δ 5.15 in the diene **8**, but instead showed two 3H singlets typical of the methyls in a 2,2-dimethylpyran ring system. These spectral properties led us to conclude that these dimeric products arose due to intramolecular cyclisation of **9**, concomitant loss of the acetate group at C-4, and formation of the 2,2-dimethylpyran ring **X** to give isomers with structure **14**.



14 **15**

As Diels-Alder reactions are normally stereospecific, isolation of two isomeric products from our reaction suggest during its cyclisation to form ring **X** , the proton H_e in **9** is prone to epimerisation in the acidic reaction media; analogous with that previously proposed [4] to be occurring during the biogenesis of dimeric quinolinones to account for the isolation of both *cis* and *trans* dimers from plant sources. Other products obtained included the diene **8**, which provided evidence that it had been involved in our dimerisation reaction, and again *N*-methylflindersine **11**. The latter must arise due to the deacetylation and intramolecular cyclisation of **8** and perhaps accounts for the cooccurence of this pyranoquinolinone in plants [2]which contain paraensidimerins that we proposed arise from a diene of the type **8**. When this acid catalysed dehydration and dimerisation was conducted in the presence of additional sulphuric acid, a further product was isolated from the reaction mixture (*ca.* 20% yield). It had the constitution $C_{30}H_{30}N_2O_4$ equivalent to the molecular mass of **14** minus C_2H_2O; again denoting loss of an acetate group. An NMR [8] spectrum thus lacked any resonances typical of acetate residues, but clearly showed the presence of two low-field aromatic protons with chemical shifts of ∂8.35 and 8.38. These latter resonances suggested that this compound contained two 4-quinolinone units; by analogous reasoning as earlier described in the assignment of the structures **14**. COSY ^{1}HNMR and ^{13}C-NMR allowed us to unequivocally assign this further product to have the structure **15**. The protons about the XYZ ring system had chemical shifts compatible with those reported for vepridimerine C (*cf* structure **3**); with the protons H_d and H_e occupying a *cis* stereochemistry. It is obviously derived from the acid-catalysed deacetylation and cyclisation of the *cis* isomer of **14**. The synthesised dimer **15** differs only from vepridimerine C in that it contains no aromatic methoxyl substituents and consists of a mixture of two 4-quinolinone units. This result was however significant since it allowed us to recognise approaches to the syntheses of dimers of this type. More studies are currently in progress and we also plan to check the biological activity of these synthesised dimer derivatives.

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References and Notes

1. Professor Michael F. Grundon; deceased April, 1989.
2. Jurd, L.; Benson, M.J., *J. Chem. Soc. Chem. Commun.*, **1983**, 92 and Jurd, L.; Benson, M.J.; Wong, R.Y. *Aust. J. Chem.*, **1982**, 35, 2505; *ibid.*, **1983**, 36, 759.
3. Ngadjui,T.B.; Ayafor, J.F.; Sondegam, B.L.; Connoly, J.D.;Rycroft, D.S.; Khalid,S.A.;Waterman, P.G.; Brown, N.M.D.; Grundon, M.F.; Ramachandran, V.N. *Tetrahedron Lett.*, **1982**, 23, 2041.
4. Grundon, M.F. in *Chemistry and Chemical Taxonomy of the Rutales* ; Waterman, P.G.; Grundon, M.F. Eds.; London Academic Press: 1983; pp. 9-30.
5. Barnes, C.S; Strong, M.I.; Occolowitz, J.L. *Tetrahedron*, **1963**, 19, 839.
6. Melpolder, J.B.; Heck, R.F. *J. Org.Chem.*, **1976**, 41, 265; and Chalk, A.J.; Magennis, S.A. *ibid.*, **1976**, 41, 273.
7. Gaston, J.L.; Greer, R.J.; Grundon, M.F. *J. Chem. Res. Synop.*, **1985**, 135.
8. A complete account of spectral data of these compounds will be reported later in a full paper.

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