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FORMATION OF A p-QUINONE METHIDE IN THE PRESENCE OF METHANOL✦

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(±)-4β-Acetoxythaliporphine (IV) reacted readily with methanol to give (±)-4β-methoxythaliporphine (V). Consequently, a facile formation of p-quinone methide (XI) as a key intermediate was deduced.

Quinone methides$^{1)}$ (I, II), which are highly reactive towards conjugate addition, are readily available from phenols having structural features of para- or ortho-hydroxybenzyl halide or alcohol by thermolysis or treatment with acid or base.

However, little is known about the formation or intermediacy of a quinone methide from an appropriate precursor by use of a weak acid such as alcohol, except an instance$^{2)}$, where 2-benzoyl-4,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline is transformed to 2-benzoyl-4-ethoxy-6,7-dimethoxy-1,2,3,4-

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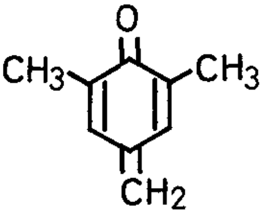
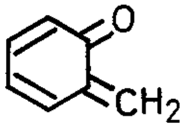
✦ Dedicated to Dr. K. Takeda on the occasion of his seventieth birthday.



I



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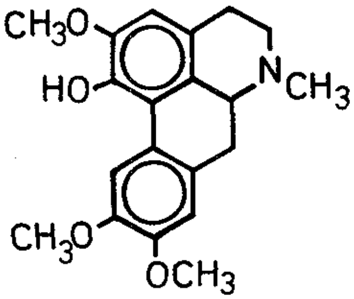

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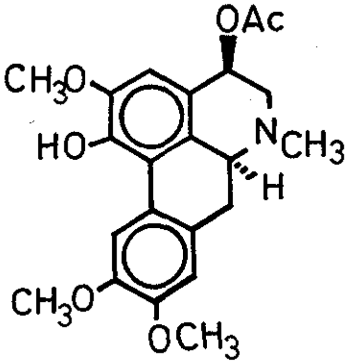

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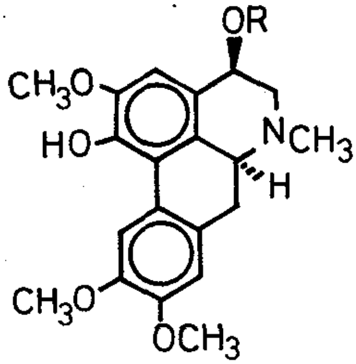
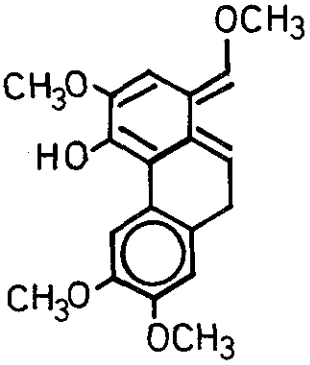
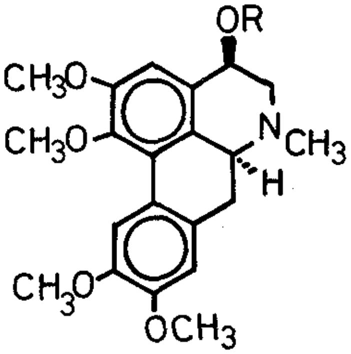


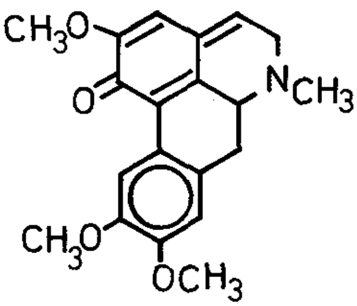
V : $R = CH_3$
VIII : $R = H$
X : $R = CH_2CH_3$



VI



VII : $R = H$
IX : $R = Ac$



XI

tetrahydroisoquinoline on mere reflux in ethanol (EtOH).

The present communication described the generation of a p-quinone methide by methanol (CH_3OH).

The oxidation with lead tetraacetate (156 mg) of (±)-thaliporphine (III) (100 mg) gave an amorphous mass (IV)[3] (122 mg), which without purification, was dissolved in MeOH (30 ml) and stirred at room temperature for 1 hr. Usual work-up afforded brown crystals (V)[4] (94 mg, 86%), mp 198-199° (dec.) (benzene-n-hexane). N.m.r.[5] δ: 2.53 (3H, s, NCH_3), 3.47 (3H, s, aliphatic OCH_3), 3.86 (9H, s, aromatic OCH_3), 4.12 (1H, b.t., w/2 = 5Hz, 4-H), 6.24, 6.26 (each 1H, s, 2 x aromatic H), 8.06 (1H, s, 11-H); i.r.[6] ν_{max}^{KBr} cm^{-1}: 3450 (OH); m.s.[7] m/e: 371 (M^+), 337, 327 (base peak), 322, 297. The base peak [VI: $M^+ - 43$][8] in mass spectrum and the signal due to aliphatic methoxyl protons (δ: 3.47) in n.m.r. spectrum assigned 4-methoxyaporphine to this compound. Furthermore the n.m.r. signal of C-4 proton (δ: 4.17) showed a broad triplet exactly similar to that of (±)-cataline[3,8b] (VII), IV and (±)-4β-hydroxythaliporphine (VIII)[3], in which the configuration of their 4-protons was α. On the basis of the above results and elemental analysis the structure of V was proved to be (±)-4β-methoxythaliporphine.

No reaction occured when (±)-diol (VIII) or (±)-O-acetylcataline (IX) was dissolved in MeOH and IV did not react at room temperature with other alcohols such as EtOH, isopropanol, and benzylalcohol. On the other hand, IV underwent a smooth reaction with a mixture of MeOH and EtOH (1:1) at room temperature for 1 hr to give a mixture of V and (±)-4β-ethoxythaliporphine (X) in a ratio of 1:1 (measured on the n.m.r. spectral chart). The structure of the latter was confirmed by the spectral (i.r., n.m.r.) comparison with authentic sample, mp 171-172° (dec.) [n.m.r. δ: 4.21 (1H), bt, w/2 = 5.0Hz, 4-H], which was prepared from IV and EtOH using boron trifluoride etherate.

Thus, it was evident that the reaction was specifically dependent on both IV and MeOH. Since a key intermediate for the reaction was most probably the p-quinone methide (XI) and MeOH is well known to be much more acidic than any other alcohols, MeOH must have played a dual roll; that is, MeOH behaved as an acid generating XI and a nucleophile adding to it.

Consequently, the present communication constituted an unprecedented example that MeOH possessed enough acidity to create a p-quinone methide.

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2. B. Jaques, R.H.L. Deeks, and P.K.J. Shak, Chem. Commun., 1969, 1283.
3. O. Hoshino, H. Hara, M. Ogawa, and B. Umezawa, J. Chem. Soc. Chem. Commun., 1975, 306; Idem, Chem. Pharm. Bull. (Tokyo), 1975, **23**, 2578.

4. All new compounds gave satisfactory analytical data.

5. N.m.r. spectra were taken with a Japan Electron Optics Labs. Model JNR-4H-100 Spectrometer in deuteriochloroform solution (5-10%) by using tetramethylsilane as internal standard.

6. I.r. spectra were run on a Hitachi 225 spectrometer.

7. Mass spectrum was measured with a Hitachi Model RMU-6E mass spectrometer.

8. a) J. Kunitomo, Y. Okamoto, E. Yuge, and Y. Nagai, Tetrahedron Letters, 1969, 3287; b) I. Ribas, J. Sueiras, and L. Castedo, ibid, 1972, 2033.

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