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PREPARATION OF β-HYDROXYHYDROPEROXIDES BY PHOTOOXYGENATION OF ALLYLIC ALCOHOLS AND THEIR ELABORATION INTO 1,2,4-TRIOXANES*

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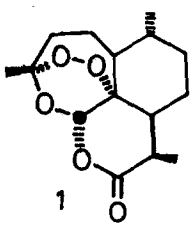
Summary: Dye-sensitized photooxygenation of 3-aryl-2-butenols 2a-e furnishes 3-aryl-1-hydroxy-but-3-en-2-hydroperoxides 3a-e which condense with aldehydes and ketones to give active antimalarial 1,2,4-trioxanes.

Qinghaosu (1) is a naturally occurring 1,2,4-trioxane from Artemisia annua. It is highly effective against both chloroquine-sensitive and resistant malaria[1]. The realization that peroxide moiety is essential for the biological activity of this molecule has created an intense interest in the synthesis of 1,2,4-trioxanes and several new routes for the preparation of this class are now available[2]. Notwithstanding these developments, the preparation and potential of β-hydroxyhydroperoxides in the synthesis of 1,2,4-trioxanes has received only a limited attention. The reaction of epoxides with concentrated H_2O_2 remains the sole method of preparing these hydroperoxides and only a few trioxanes have been made from them[3]. We have explored the regiospecific photooxygenation of allylic alcohols as an alternative and acceptable method of obtaining β-hydroxyhydroperoxides[4]. We reasoned that an aryl group at position 3 of the allylic alcohol would provide the desired regiospecificity to this reaction. Herein, we report the preparation of 3-aryl-1-hydroxy-but-3-en-2-hydroperoxides 3a-e by dye-sensitized photooxygenation of 3-aryl-2-butenols 2a-e and their elaboration into 1,2,4-trioxanes.



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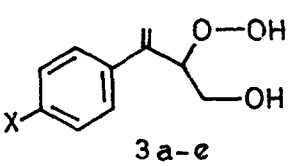
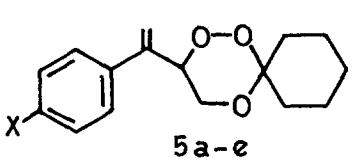
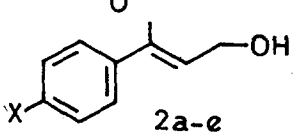


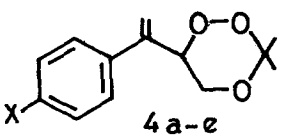
3a-e



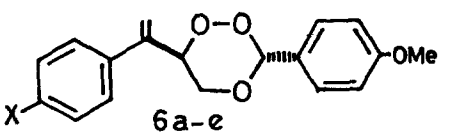
5a-e



2a-e



4a-e



6a-e

a, X=H; b, X=Me; c, X=OMe; d, X=F; e, X=Cl

*CDRI Communication No.4374.

The trans alcohols[5] 2a-e were photooxygenated in EtOH in presence of methylene blue at 0-10°C for 10-16 h to give β-hydroxyhydroperoxides 3a-e in 37-55% yield[6].

These hydroperoxides are stable enough to be handled at room temperature and undergo a facile condensation with various aldehydes and ketones to give 1,2,4-trioxanes. For example, condensation with acetone (H^+/ CH_2Cl_2,,0°C, 12 h) gave 6-(α-arylvinyl)-3,3-dimethyl-1,2,4-trioxanes 4a-e in 38-66% yield[7]. A similar condensation with cyclohexanone gave the spirotrioxanes 5a-e in 43-74% yield; while condensation with p-methoxybenzaldehyde gave trioxanes 6a-e in 34-64% yield.

Most of these compounds have been found to show antimalarial activity (in vitro) against chloroquine-resistant P.falciparum; IC_{50} ranges from 2.86 to 222.46 ng/ml. IC_{50} of Qinghaosu under the same assay is 0.65 ng/ml .

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References and Notes

1. For reviews: (a) D.L.Klayman, Science, 228, 1049 (1985). (b) X.D.Luo and C.C.Shen, Med. Res. Rev., 7, 29 (1987).
2. C.W.Jefford, E.C.McGoran, J.Boukouvalas, G.Richardson, B.L.Robinson and W.Peters, Helvetrica Chimia Acta 71, 1805 (1988) and references cited therein.
3. (a) W.Adam and A.Rios, J.Chem. Soc., Chem. Commun., 822 (1971); (b) V.Subramanyam, C.L.Brizuela and A.H.Soloway, J. Chem. Soc., Chem. Commun. 508 (1976).
4. Photooxygenation of allylic alcohol has earlier been studied but isolation of stable β-hydroxyhydroperoxides has not been reported:
(a) A.Nickon and W.L.Mendelson, J.Am.Chem.Soc., 87, 3921 (1965).
(b) G.Ohloff in "Pure and Applied Chemistry Symposium on Organic Synthesis" (eds.A.Bruylants, L.Ghosez and H.G.Viche), Butterworths, London (1975), pp.481-502.
5. (a)Rene Heilmann and Rene Glinat Bull Soc.Chim.France, 1586 (1955).
(b) E.E.Royals and E.R.Covington J.Am.Chem.Soc., 77,1697 (1955).
6. Products isolated by aqueous work up followed by chromatographic purification on Si gel were crystallized from hexane-methylenechloride. Compound 3a:white solid, m.p.78-82°C, m/e 180 (M^+),162,132; NMR($CDCl_3$) δ H 3.65 (m,2H,1-H_2), 5.0 (dd,1H,J=7Hz,5Hz,2-H), 5.34,5.42 (2s,2H,4-H_2), 7.2-7.5 (m,5H, aromatic).
7. Compound 4a: Oil, m/e 220 (M^+), 188,130; NMR($CDCl_3$) δ H 1.25,1.53 [2s, 6H,3-$(Me)_2$],3.53(dd,1H,J=12Hz,5Hz,5-He),3.75(dd,1H,J=12Hz,10Hz,5-Ha), 5.03(dd,1H,J=10Hz,5Hz,6-H),5.22,5.33(2s,2H, $=CH_2$),7.22(s,5H,aromatic).

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