Tetrahedron Letters Vol. 22, pp 701 - 702 0040-4039/81/0208-0701$02.00/0

REGIOSPECIFIC SYNTHESIS OF QUINIZARIN DERIVATIVES BY CYCLOADDITION

Donald W. Cameron*, Geoffrey I. Feutrill and Peter G. McKay
Department of Organic Chemistry, University of Melbourne, Parkville, Vic. 3052, Australia.

Summary. Cycloaddition of (E)-1,1,4-trimethoxy-1,3-butadiene (1) to naphthoquinones affords regiospecific syntheses of derivatives of 1,4-dihydroxyanthraquinone including the mould metabolites helminthosporin (21) and cynodontin (22).

This communication reports a simple regiospecific approach to unsymmetrical derivatives of 1,4-dihydroxyanthraquinone (quinizarin), a system commonly encountered in nature[1]. This involves Diels Alder cycloaddition. Whilst this process has facilitated the synthesis of other hydroxy quinones[2] it has not generally been applied to introduction of 1,4-dioxy substitution, adducts from 1,4-dioxy dienes undergoing easy elimination of the oxy substituents[3].

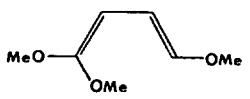
The readily available (E)-1,1,4-trimethoxy-1,3-butadiene (1)[4] reacted with each of the chloronaphthoquinones (2), (3), (4) at room temperature to give single crystalline adducts (5), (6), (7) respectively (76-100%). The orientation was consistent with attack of the more nucleophilic end of the diene occurring adjacent to the chloro carbon, as observed for other cycloadditions[2]. It was confirmed by first order ^{1}H n.m.r. spectra which showed vicinal coupling (J 5-6Hz) of the angular asterisked proton.

These adducts were aromatized by boiling in pyridine to give the quinizarin derivatives (8)[5], (9) m.p. 104-5°, (10)[6] (64-100%). Alternatively treatment with dilute sulphuric acid followed by sodium acetate afforded the demethyl analogues (11)[7], (12) m.p. 234-5°, (13) m.p. 248-50°. For these latter products the position of hydrolysis was related to the position of the acetal group in each adduct and thence to the position of chlorination in the naphthoquinone from which each was derived. Addition of (1) to the chloro napththoquinone (14) isomeric with (3), and aromatization of the adduct with dilute acid, gave the anthraquinone (15), m.p. 236-7° (34% overall), isomeric with (12).

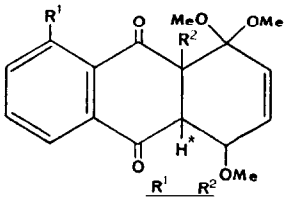
Addition of (1) to non-halogenated naphthoquinones was usually slow. However 5-hydroxy-1,4-naphthoquinone (juglone) at room temperature gave a single adduct (16) (76%), m.p. 130° (decomp.), orientation being controlled by the H-bonded hydroxy group[8]. This orientation was confirmed by aromatization. Sublimation in vacuum at 130° quantitatively gave 1-hydroxy-8-methoxyanthraquinone while treatment with aqueous sulphuric acid gave its 1,8-dihydroxy analogue (67%). Since the adduct (16) was one oxidation level lower than the chloro adducts (5)-(7) retention of 1,4-dioxy substitution necessitated an oxidation step. Accordingly reaction with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in boiling benzene gave (9) (80%).

Reaction of (1) with benzoquinones proceeded similarly to naphthoquinones except that yields were generally lower. The approach is thus also applicable to derivatives of 5,8-dihydroxy-1,4-naphthoquinone (naphthazarin)[1].

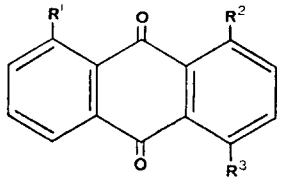
Cycloaddition of (1) to appropriate quinones followed by aromatization of the adduct by elimination, hydrolysis and/or oxidation thus affords a mild, versatile and specific procedure. With the controlled syntheses of compounds (9), (12), (13), and (15) described here,



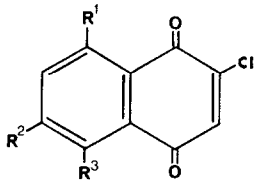
1



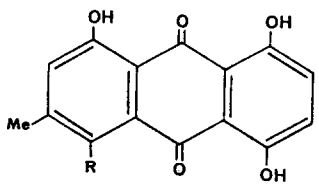
	R^1	R^2
5	H	Cl
6	OH	Cl
7	OMe	Cl
16	OH	H



	R^1	R^2	R^3
8	H	OMe	OMe
9	OH	OMe	OMe
10	OMe	OMe	OMe
11	H	OH	OMe
12	OH	OH	OMe
13	OMe	OH	OMe
15	OH	OMe	OH
17	OMe	OMe	OH
18	OMe	OH	OH



	R^1	R^2	R^3
2	H	H	H
3	OH	H	H
4	OMe	H	H
14	H	H	OH
19	OH	Me	H
20	OH	Me	OH



21 R = H

22 R = OH

added to the known compounds (17)[9] and (18)[10], all possible mono- and di-methyl ethers of 1,4,5-trihydroxyanthraquinone have now been obtained.

Addition of (1) to the chloro quinones (19)[11] and (20)[12] proceeded as for compounds (2)-(4). Aromatization in pyridine and subsequent demethylation gave the mould metabolites helminthosporin (21) and cynodontin (22), identical with authentic materials[1], in overall yields of 55 and 16% respectively.

Satisfactory elemental analyses and spectra have been obtained for all new compounds reported in this work. We are grateful to Professor Lord Todd for samples of helminthosporin and cynodontin and acknowledge an Australian Postgraduate Research Award (to P.G.McK).

References

1. R.H. Thomson, "Naturally Occurring Quinones", 2nd Edn. (Academic Press: London 1971).
2. e.g., D.W. Cameron, G.I. Feutrill, P.G. Griffiths, and D.J. Hodder, J.Chem.Soc.Chem.Commun., 1978, 688; J. Savard and P. Brassard, Tetrahedron Lett., 1979, 4911.
3. e.g., J.F.W. Keana and P.E. Eckler, J.Org.Chem., 1976, 41, 2625.
4. J.W. Scheeren, A.T.M. Marcelis, R.W. Aben, and R.J.F. Nivard, Recl Trav.Chim.Pays-Bas., 1975, 94, 196.
5. T.R. Criswell and B.H. Klanderman, J.Org.Chem., 1974, 39, 770.
6. L.A. Wiles and L.C. Thomas, J.Chem.Soc., 1956, 4811.
7. H. Waldmann, J.Prakt.Chem., 1931, [2] 130, 92.
8. R.K. Boeckman, T.M. Dolak, and K.O. Culos, J.Am.Chem.Soc., 1978, 100, 7098.
9. A.S. Kende, J.L. Belletire and E.L. Hume, Tetrahedron Lett., 1973, 2935.
10. K. Krohn and K. Tolkiehn, Chem.Ber., 1979, 112, 3453.
11. T.J. Lillie and O.C. Musgrave, J.Chem.Soc.Perkin Trans. I., 1977, 355.
12. P.C. Arora and P. Brassard, Can.J.Chem., 1967, 45, 67.

(Received in UK 24 November 1980)