Tetrahedron Letters,Vol.30,No.38,pp 5173-5176, 1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

DICHLORO QUINONES AS DIENOPHILES: SYNTHESIS OF ALIZARIN DERIVATIVES

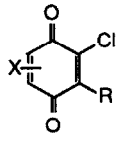
Donald W. Cameron*, (the late) Geoffrey I. Feutrill and Philip L. C. Keep
Department of Organic Chemistry, University of Melbourne, Parkville, Victoria 3052, Australia

Abstract. 2,3-Dichloro quinonoid dienophiles react with 1,3-dioxy butadienes to give cycloadducts, which aromatise with uptake of external nucleophile to give 1,2-disubstitution in the newly formed aromatic ring. With oxy nucleophiles this has led to synthesis of natural alizarin derivatives.

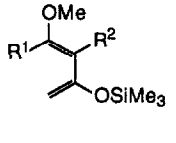
Cycloadducts of 1,3-dioxy butadienes (1)[1] and chloroquinonoid dienophiles (2) undergo aromatisation, generally with the loss of an alcohol, so that the products (3) retain only one oxy substituent in the newly formed ring. Raising the oxidation level of the diene component, *e.g.* by 1,1,3-trioxy substitution, similarly affords aromatic products incorporating the 1,3-dioxy substitution pattern of natural polyketides.[2]

This paper considers alternatively raising the oxidation level of the dienophile, as in 2,3-dichloroquinones (4). After cycloaddition of 1,3-dioxy butadienes (1) and subsequent aromatisation these also have been found to yield dioxy products but with 1,2- rather than 1,3-substitution. This has allowed natural products based on the alizarin system to be synthesised.

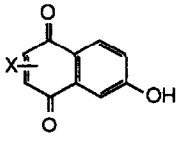
Thus diene (1) reacted at room temperature with the dichloro quinone (5) to give the hydrolysed adduct (6) (77%, m.p.154°). Its structure followed from first order spectroscopic considerations, stereochemistry being assigned by analogy with related cycloadditions.[3] The preferred regiochemistry of addition was expected to be determined by the chelated hydroxy group and this was confirmed by zinc reduction of (6), with concomitant aromatisation, to give the known 1,6-dihydroxyanthraquinone (7).



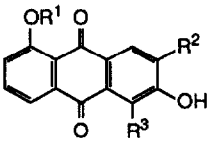
(2) R = H
(4) R = Cl



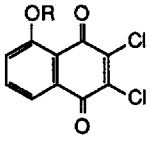
	R^1	R^2
(1)	H	H
(22)	H	Me
(28)	$OSiMe_3$	H
(37)	Me	CO_2Me
(39)	H	OAc
(43)	$OSiMe_3$	Me



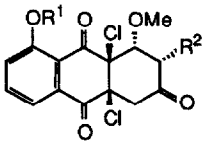
(3)



	R^1	R^2	R^3
(7)	H	H	H
(8)	H	H	OMe
(11)	H	H	OH
(16)	H	Me	OMe
(18)	Me	Me	OH



(5) R = H
(13) R = Me

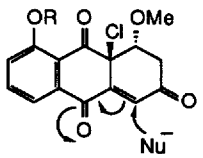


	R^1	R^2
(6)	H	H
(20)	H	Me
(23)	Me	Me

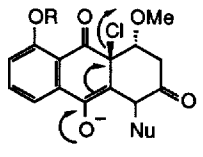
Treatment of adduct (6) with sodium methoxide in methanol proceeded rapidly at room temperature to give the 1,2,5-trioxy anthraquinone (8) (95%, m.p.254°, $\delta_{H3,4}$7.36, 8.15; *J* 8.4 Hz). This also is a natural plant product.[4] Its formation from (6) presumably involved intermediates (9), (10), with elimination of the second chloride as shown and methanol, not necessarily in that order. Potentially competitive 1,2-elimination of HCl from (9), or the analogous elimination from (6) is evidently impeded by *cis* geometry.[5] Treatment of (6) with nucleophiles other than methoxide proceeded similarly. Thus reaction with conc. HCl, HBr, ammonia, or sodium thiophenoxide gave products analogous to (8) in which R^3 was Cl, Br, NH_2, SPh respectively (75-97%), all products showing the characteristic AB resonances in respect of H3,4. Dehalogenation of the chloro product with alkaline dithionite gave (7). Reaction of (6) with hydroxide as the nucleophile proved inefficient and the expected trihydroxy product (11) was best obtained indirectly through aromatisation of (6) with sodium acetate in acetic acid and subsequent mild hydrolysis. Formation of the intermediate acetate (12) (69%, m.p.247-8°, δ_{OH}12.61,12.81) was accompanied by α-β acyl migration.

An analogous series of products, having opposite regiochemistry to those already discussed, was derived from addition of diene (1) to the methoxy quinone (13). Thus the resulting adduct (14) (81%, m.p.163°) underwent aromatisation with methoxide to give the 1,2,8-trioxy anthraquinone (15) (82%).

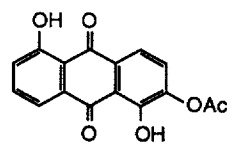
This chemistry allows easy synthesis of anthraquinones based on the alizarin (1,2-dihydroxyanthraquinone) system. Control of such syntheses is usefully further enhanced by the stability of dichloro adducts (6), (14) relative to their monochloro analogues. This allows efficient O-methylation and -demethylation respectively to be carried out, prior to aromatisation. This is exemplified by chemo- and regio-selective synthesis of the four isomeric anthraquinones (16), (17), (18), (19), the first two of which are natural plant products.[6,7,8]



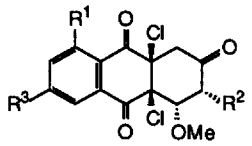
(9)



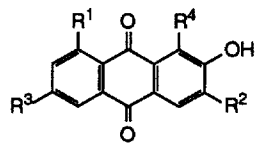
(10)



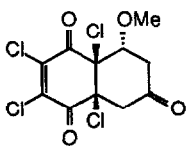
(12)



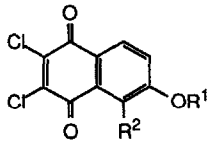
	R^1	R^2	R^3
(14)	OMe	H	H
(21)	OMe	Me	H
(24)	OH	Me	H
(30)	H	Me	H
(33)	H	Me	OMe



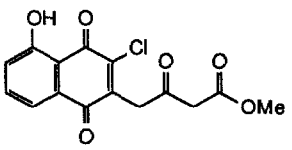
	R^1	R^2	R^3	R^4
(15)	OMe	H	H	OMe
(17)	OH	Me	H	OMe
(19)	OMe	Me	H	OH
(31)	H	Me	H	OMe
(34)	H	Me	OMe	OMe



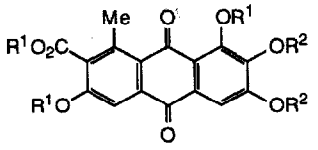
(25)



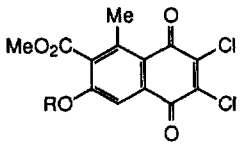
R^1 R^2
(26) H Cl
(27) H H
(32) Me H



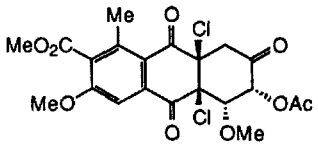
(29)



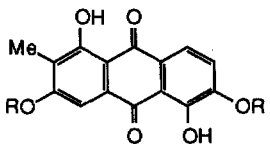
R^1 R^2
(35) H H
(41) Me Ac



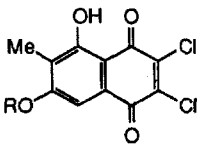
(36) R = Me
(38) R = H



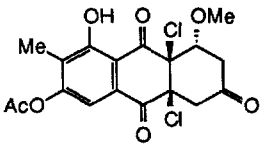
(40)



(42) R = H
(47) R = Ac



(44) R = H
(45) R = Ac



(46)

Thus adducts (20) (81%, m.p.205-7°) and (21) (83%, m.p.164-5°) were prepared from the 2-methyl diene (22) as for formation of (6), (14) respectively. The ^1H n.m.r. spectra of the former pair differed from those of the latter in not showing cross carbonyl coupling ($J_{1\alpha,3\alpha}$1.8 Hz), thereby assigning equatorial orientation to the C-methyl group. Treatment of (20) with methyl iodide/silver(I) oxide gave the O-methyl derivative (23) (95%, m.p.175-8°, δ_{OMe}2.83, 4.03), regioisomeric with (21). Selective demethylation of (21) was similarly effected without appreciable aromatisation by treatment with aluminium trichloride, giving the hydroxy product (24) (84%, m.p.160°, δ_{OH}10.81), regioisomeric with (20). Methoxide aromatisation of this latter pair (20), (24) gave the natural products (16)[6,8] (92%, m.p.240-1°, $\delta_{OMe,\alpha-OH}$4.01, 12.70) and obtusifolin (17)[7,8] (97%, m.p.241-3°, $\delta_{OMe,\alpha-OH}$4.02, 12.83). The isomeric systems (18), (19), which incorporated selective methylation of the other α-oxy substituent, were similarly, though less efficiently, prepared from the methoxy cycloadducts (23), (21) respectively. This involved treatment of the latter pair with sodium acetate followed by mild deacylation, as in the formation of (11). Compounds (18) (m.p. 239-40°, δ_{OMe}[DMSO-d_6]3.92) and (19) (m.p.262-4°, δ_{OMe}[DMSO-d_6]3.96) were thereby obtained, each in overall yield of 50%.

Extending the chemistry to a wider range of systems requires more versatile access to dichloro dienophiles than the extended chlorination/dehydrochlorination, which sufficed for preparing (5) and (13). Approaches involving cycloaddition have been found useful. Thus addition of diene (1) to chloranil gave the adduct (25) (82%, m.p.146°). The latter was converted into dichloro naphthoquinones in two ways: chloride-catalysed aromatisation (conc. HCl) gave (26) (92%, m.p.193°, $\delta_{H7,8}$7.42, 8.17; J 8.8 Hz), however, this could only be employed with weak nucleophiles, because of the reactivity of the dichloroquinonoid system, once

formed. Alternatively zinc dehalogenation of (25) was accompanied by aromatisation to give (27) (43%, m.p.235-6°, $\delta_{H5,7,8}$7.57, 7.20, 8.12), following aerial reoxidation of the intermediate quinol.

A better yield of (27) (95%) was more easily obtained by cycloaddition of diene (1) to trichloro-1,4-benzoquinone, followed by conventional aromatisation. This versatile approach benefited from addition involving exclusively the monosubstituted side of the dienophile. This, in turn, is consistent with the observed lower dienophilicity of dichloroquinones (5), (13) than their monochloro counterparts. Indeed with highly nucleophilic dienes, *e.g.* (28), cycloaddition was not observed at all, reaction of (5) leading instead to the Michael product (29).[9]

Some further natural products have been synthesised by the methodology so far discussed. The simplest example involved reaction of diene (22) with 2,3-dichloronaphthoquinone to give to give the adduct (30) (84%, m.p.188-90°); methoxide-catalysed aromatisation then gave digitolutein (31)[8,10] (92%, m.p.222°). A similar sequence starting from the β-methoxy dienophile (32) gave successively the major adduct (33) (75%, m.p.188-9°) and another *Digitalis* product (34)[8,11] (87%, m.p.227-9°).

The insect pigment ceroalbolinic acid (35)[12,13] represented a more highly substituted target, first requiring synthesis of the dienophile (36). This was obtained by cycloaddition of diene (37)[13] to trichlorobenzoquinone, aromatisation to (38) (87%, m.p.174-5°) and methylation to (36) (95%, m.p.167°). Addition of the acetoxy diene (39)[14] preferentially gave the adduct (40), which underwent methoxide-catalysed aromatisation and acetylation with acetic anhydride to form the isolated product (41) (43% from [36], m.p.218-9°, δ_{OAc}2.35, 2.39; δ_{OMe}3.96, 4.00). Deprotection with aluminium trichloride then gave ceroalbolinic acid (35)[13] (61%).

Finally stucture (42), assigned to a plant anthraquinone,[15] has been synthesised similarly. Addition of diene (43) to trichlorobenzoquinone, aromatisation to (44) (76%, m.p.280-1°, $\delta_{\alpha\text{-}OH}$12.19) and selective β-acetylation gave the dienophile (45) (90%, m.p.167-8°, $\delta_{OAc,OH}$2.38, 12.14). Cycloaddition to diene (1) was controlled by the chelated hydroxy group giving the adduct (46) (92%, m.p.175-6°). This was converted by acetate-catalysed aromatisation into the anthraquinone (47) (73%, m.p.232-4°, $\delta_{OAc,OH}$2.39, 2.40, 12.75, 13.13), deprotection of which gave (42) (78%, m.p.>300°).

Satisfactory analytical data have been obtained on all compounds mentioned in this work. ^{1}H N.m.r. spectra were run in $CDCl_3$ unless stated otherwise. We are grateful to Dr. P. G. Griffiths for discussion and acknowledge financial support from the Australian Research Grants Scheme and an Australian Postgraduate Research Award (to P. L. C. K.).

References

1. Danishefsky, S., and Kitihara, T., *J. Am. Chem. Soc.*, 1974, **96**, 7807.
2. Trost, B. M., and Pearson, W. H., *Tetrahedron Lett.*, 1983, **24**, 269.
3. Bell, S. H., Cameron, D. W., Feutrill, G. I., Skelton, B. W., and White, A. H., *Tetrahedron Lett.*, 1985, **26**, 6519.
4. Thomson, R. H., and Brew, E. J. C., *J. Chem. Soc. (C)*, 1971, 2001.
5. Boeckman, R. K., Delton, M. H., Nagasaka, T., and Watanabe, T., *J. Org. Chem.*, 1977, **42**, 2946.
6. Druva, B. R., Rama Rao, A. V., Srinivasan, R., and Venkataraman, K., *Ind. J. Chem.*, 1972, **10**, 683.
7. Takido, M., *Chem. Pharm. Bull. (Tokyo)*, 1958, **6**, 397 (*Chem. Abstr.* 1959, **53**, 3168f).
8. Cameron, D. W., Feutrill, G. I., Gamble, G. B., and Stavrakis, J., *Tetrahedron Lett.*, 1986, **27**, 4999.
9. Crosby, I. T., Ph. D. Thesis, University of Melbourne, 1987.
10. Burnett, A. R., and Thomson, R. H., *J. Chem. Soc.*, 1959, 4139.
11. Imre, S., and Wagner, H., *Phytochem.*, 1969, **8**, 1601.
12. Rios, T., *Tetrahedron*, 1966, **22**, 1507.
13. Cameron, D. W., Conn, C., and Feutrill, G. I., *Aust. J. Chem.*, 1981, **34**, 1945.
14. Danishefsky, S., and Craig, T. A., *Tetrahedron*, 1981, **37**, 4081.
15. Inoue, K., Nayeshiro, H., Inouye, H., and Zenk, M., *Phytochem.*, 1981, **20**, 1693.

(Received in UK 31 July 1989)