CHEMISTRY LETTERS, pp. 1057-1060, 1982.

ANTHRACYCLINES . CYCLOADDITIONS OF 9-CHLORO-10-HYDROXY-1,4-ANTHRAQUINONE WITH VARIOUS BUTA-1,3-DIENES

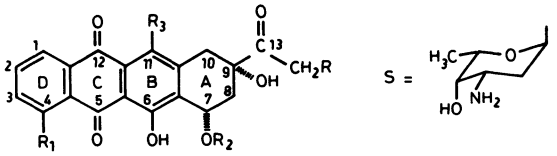
Nand L. AGARWAL and Hans W. SCHEEREN*

Department of Organic Chemistry, Catholic University, Toernooiveld, 6525 ED NIJMEGEN, The Netherlands

Summary: The Diels-Alder type cycloaddition of several substituted buta-1,3-dienes with 9-chloro-10-hydroxy-1,4-anthraquinone (10) affords an efficient, regiospecific access in two steps to tetracyclic ketones (12-14) which have been investigated as intermediates for the synthesis of anthracycline derivatives. Butadienes with a less asymmetric π-electron distribution than 9 give lower regiospecificity in cycloadditions with 10. Depending on the substituents in the used butadiene, the obtained cycloadducts are transformed under the reaction circumstances into the aromatized products (15-20).

The outstanding anticancer properties[1] of anthracyclines like adriamycin 1 and daunorubicin 2, and the awareness of the limited supply and serious side effects of these drugs have prompted the search for new synthesis of these and analogous compounds[2]. As 4-demethoxydaunorubicin and 4-demethoxy-adriamycin were found to be markedly more active and less toxic[3-6] many chemists have been encouraged to develop efficient syntheses of the 4-demethoxyaglycone derivatives[7]. The recent isolation and reported activity[8] of the 11-deoxy-derivatives 3 and 4 further demonstrate that aglycone modification is important to enhance the therapeutic index of these drugs. The reported syntheses of aglycones[7,9] are, however, still lengthy and tedious, with low overall yield, or involve expensive starting materials.

Scheme I

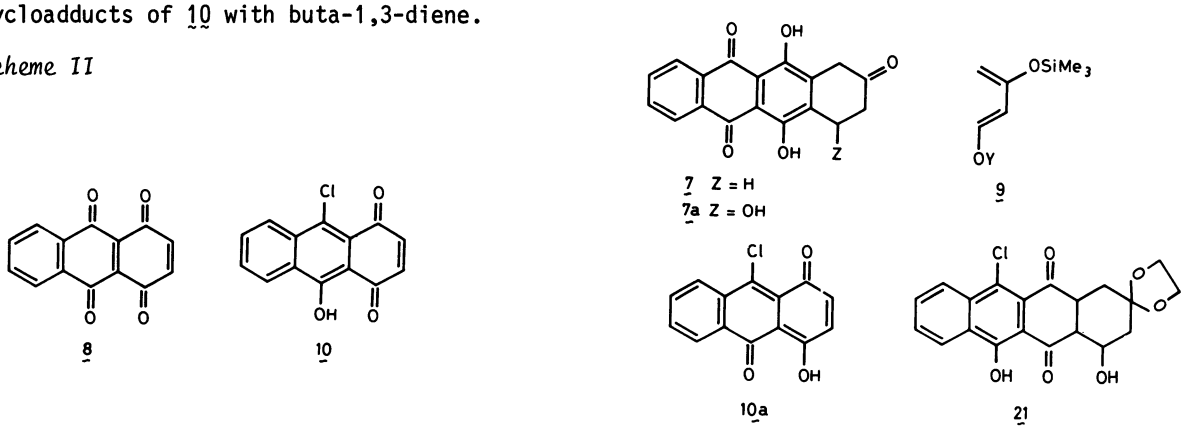


1: adriamycin R_1=OCH_3, R_2=S, R_3=OH, R=OH
2: daunorubicin R_1=OCH_3, R_2=S, R_3=OH, R=H
3: 11-deoxyadriamycin R_1=OCH_3, R_2=S, R_3=H, R=OH
4: 11-deoxydaunorubicin R_1=OCH_3, R_2=S, R_3=H, R=H
5: 4-demethoxyadriamycinone R_1=H, R_2=H, R_3=OH, R=OH
6: 4-demethoxydaunomycinone R_1=H, R_2=H, R_3=OH, R=H

Easily available starting materials containing three rings have already extensively been investigated[7] in Diels-Alder reactions. Generally the synthetic route leads to 7 which can be transformed into 6 in four steps. For example 8 has successfully been converted into 7 *via* a reaction with 2-acetoxybuta-1,3-diene[10]. Furthermore, it is well known that dienes of type 9 (Y=$SiMe_3$) and naphthoquinones give adducts which after mild hydrolysis contain[11,12] the ring A of the tetracyclic ketone 7a. Unfortunately, the reaction of 9 with 8 gives exclusive addition to the internal double bond[13,14],

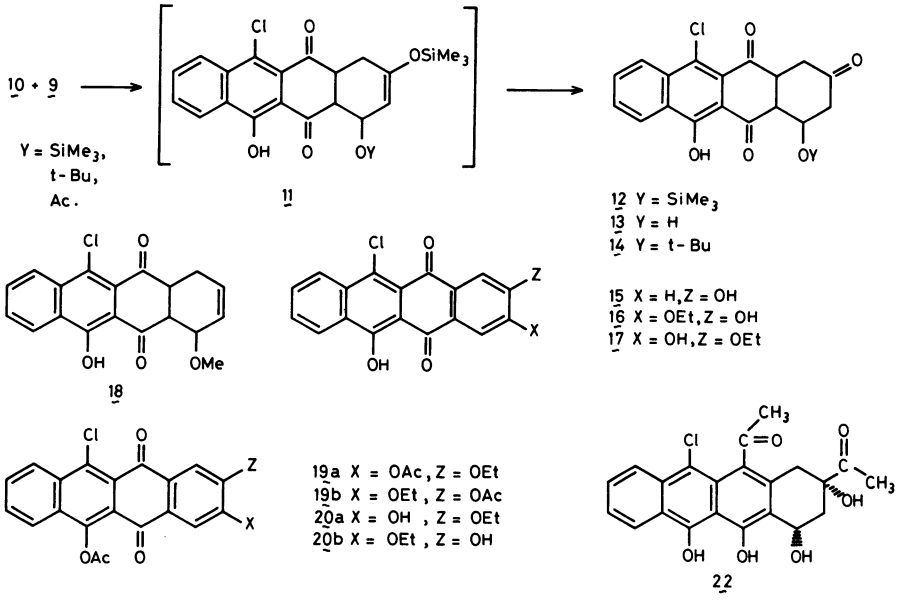
so that the expected 7a, which might give 6 in two steps, cannot be obtained in this way. Winkler[15] and Hodge[16] *et al.* reported the reaction of 9-chloro-10-hydroxy-1,4-anthraquinone[17,18] (10) with some dienes. The latter workers were unable to develop a simple and efficient route for 7 from the cycloadducts of 10 with buta-1,3-diene.

Scheme II



In this communication we disclose a simple, efficient, regiospecific approach to 13, an important analogue of anthracyclinones. The key step is the cycloaddition of the inexpensive and easily prepared 10 with suitable butadienes: 1,3-bis (trimethylsilyloxy)butadiene[19] in CH_2Cl_2 gave the unstable adduct 11 after 20 h at room temperature. After mild hydrolysis (0.1N HCl) 11[20a] yielded the tetracyclic ketone 12 (yield 84%, crystallized from acetone-hexane, m.p. 202-210°) which on controlled hydrolysis with 3N HCl in MeOH-CH_2Cl_2, at -5° overnight, afforded a mixture of 13 (80%, m.p. >260°, from acetone-hexane) and 15 (12%, m.p. >260° from acetone-hexane). The replacement of Cl in 13 by OH could provide directly a key intermediate for the anthracyclinones 5 and 6. Cycloaddition of 10 with 1-*tert.* butoxy-3-trimethylsilyloxybutadiene[21] under the same conditions proceeds also regiospecific; mild hydrolysis (0.1N HCl) of the adduct gave 14 (75%, from CH_2Cl_2-hexane, m.p. 232-234°[20b]). The cycloaddition of 10 with 1-acetoxy-3-trimethylsilyloxybutadiene[14], followed by mild hydrolysis, led to aromatization of the primary formed adduct, yielding 15 (80%). Apparently the acetoxy group is more liable to elimination than the trimethylsilyloxy group. Reflux of 10 and 1-methoxybutadiene in CH_2Cl_2 for 18 h yielded 18 (82%, m.p. 200° from $CHCl_3$-hexane). Under the same conditions 1-acetoxybutadiene gave no cycloadduct with 10.

Scheme III



The cycloaddition of 10 with the highly electron-rich 1,2-diethoxy-3-trimethylsilyloxybutadiene (CH_2Cl_2, 2 days, 20°), followed by mild hydrolysis, afforded directly a mixture of the regioisomers 16 and 17 (76%, m.p. >260°) as appeared from the ^1H NMR spectrum. The aromatization can be due to the stabilizing effect of the ethoxy group on the double bond. Analogous results were observed in the cycloaddition of this diene with naphthoquinone[21]. The isomers could not be separated by TLC. Acetylation of the mixture with acetic anhydride-pyridine gave a reaction mixture, which could be separated by TLC into mono[22b] and diacetylated products (main product). ^1H NMR of the latter[22a] indicated the presence of two isomers, which could not be separated (19a and 19b).

The absence of regioselectivity has also been reported[15,16] for the cycloaddition of 10 with simple, alkyl substituted butadienes. These results demonstrate that a high regioselectivity in [4+2]-cycloadditions of 10 can only be expected with electron-rich butadienes having a strongly asymmetric π-electron distribution.

The purity of all end products was ascertained by TLC in several solvents; the structures were supported by elemental analyses, mass spectroscopy, NMR and IR[23-25].

Treatment of 12 and 13 with sodium methoxide or sodium hydroxide under various conditions in order to replace the chlorine yielded 15. Ketalization of 13 with ethylene glycol, PTS, in benzene or CH_2Cl_2 afforded 21[24] (75%, m.p. 165-170° (dec) from CH_2Cl_2-hexane), in which the chlorine could also not be replaced by treatment with sodium methoxide or sodium hydroxide. Compound 13 has shown an interesting way for the synthesis of aglycones having new substituents in ring B, because one of the carbonyl group at ring B has enhanced reactivity. Treatment of 13 with excess of ethynyl magnesium bromide followed by hydrolysis with mercuric oxide in dilute sulphuric acid afforded 22[25] (16%, m.p. 192-194°, after chromatographic separation and crystallized from CH_2Cl_2-hexane) confirming two acetyl functions in the molecule. The oxidation of 21 and 22 with various oxidizing agents are under way.

REFERENCES

1. F. Arcamone, *Lloydia* 40, 45 (1977); D.W. Henry in "Cancer Chemotherapy", A.C. Sartorelli, Ed., Amer. Chem. Soc., Washington D.C., 1976, Chapter 2.
2. W.A. Remers in "The Chemistry of Antitumor Antibiotics", Vol. 1, Wiley, N.Y., 1979, Chapter 2.
3. F. Arcamone, L. Bernardi, P. Giardino, B. Patelli, A. DiMarco, A.M. Casazza, G. Pratesi, P. Reggiani, *Cancer Treatm. Rep.* 60, 829 (1976).
4. A. DiMarco, A.M. Casazza, F. Guiliani, G. Pratesi, F. Arcamone, L. Bernardi, G. Franchi, P. Giardino, B. Patelli, S. Penco, *Cancer Treatm. Rep.* 62, 375 (1978).
5. F. Arcamone in "Advances in Medical Oncology", Vol. 3, B.W. Fox, Ed., Pergamon Press, Oxford-New York, 1979, p. 21-32.
6. A.M. Casazza *et al.* in "Anthracyclines, Current Status and New Developments", S.T. Crooke and S.D. Reich, Eds., Acad. Press, N.Y., 1980, Chapter 23.
7. T.R. Kelly in "Annual Reports in Medicinal Chemistry", Vol. 14, H.J. Hess, Ed., Acad. Press, N.Y., 1979, Chapter 28 and references cited therein.
8. F. Arcamone, C. Cassinelli, F. DiMatteo, S. Forenza, M.C. Ripamonti, G. Rivola, A. Vigevani, J. Clardy, T. McCabe, *J. Am. Chem. Soc.* 102, 1462 (1980).
9. T.R. Kelly, J. Vaya, L. Ananthasubramanian, *J. Am. Chem. Soc.* 102, 5983 (1980) and references cited therein.
10. A.S. Kende, Y. Tsay, J.E. Mills, *J. Am. Chem. Soc.* 98, 1967 (1976); A.S. Kende, D.P. Curran, V. Tsay and J.E. Mills, *Tetrahedron Lett.* 1977, 3537.
11. R.W. Aben, H.W. Scheeren, *J.C.S. Perkin I* 1979, 3132.

12. K. Krohn, K. Tolkiehn, *Chem. Ber.* 112, 3453 (1979).

13. T.R. Kelly. R.N. Goerner, Jr., J.W. Gillard, B.K. Prazak, *Tetrahedron Lett.* 1976, 3869.

14. J.W. Scheeren *et al.*, to be published.

15. R.E. Winkler, *Helv. Chim. Acta* 50, 2497 (1967).

16. D.N. Gupta, P. Hodge, N. Khan, *J.C.S. Perkin I* 1981, 689.

17. Two structures, 10 (ref. 16, C.W. Greenhalgh, *Endeavour*, 35, 134 (1976); A.M. Birch, A.J.H. Mercer, C.W. Greenhalgh, *Heterocycles*, 12, 757 (1979) and 10a (ref. 15,18) have been mentioned in the literature of this compound, neither of them being based on conclusive evidence. This difference is small by strong hydrogen bonding between the hydroxyl group and neighbouring carbonyl oxygen, which causes the high regioselectivity in the cycloadditions given in Scheme III (cf. A.J. Birch, W.H. Powell, *Tetrahedron Lett.* 1970, 3467). X-ray analyses of 10 and 14 are underway to establish the crystal structure of these compounds.

18. A. Green, *J. Chem. Soc.* 1926, 1428.

19. T. Ibuka, Y. Mori, Y. Inbushi, *Tetrahedron Lett.* 1976, 3169.

20a 11 decomposes at melting solidifies again, and does not melt then up to 260°.
b 14 melts at 232-234° after discoloration at 210°, solidifies again and does not melt up to 260°.

21. R.W. Aben, J.W. Scheeren (unpublished results).

22a The NMR-spectrum ($CDCl_3$, δ1.39 (t, 3H, OCH_2CH_3), 2.35 (s, 3H, 5-OAc), 2.62 and 2.63 (s, 3H, 8- and 9-OAc), 4.25 and 4.26 (q, 2H, 8- or 9-OCH_2), 7.25-8.74 (m, 6H, aromatic protons), points to structures 19a and 19b.
b The product contains two compounds. The assignment of structures 20a and 20b was based on a comparison of the NMR spectrum with those of the diacetylated product (19a and 19b) and of 2-acetoxy-3-ethoxy-9,10-anthraquinone.

23. The ^1H NMR and IR(KBr) data of the compounds 12-18 are:

12: ^1H NMR ($CDCl_3$): δ-0.301 (s, 9H), 2.16-2.79 (m, 3H), 3.37-3.70 (m, 3H), 4.71-4.80 (m, 1H), 7.63-7.97 (m, 2H), 8.52-8.64 (m, 2H), 14.62 (s, 1H, OH, D_2O exchangeable; IR(KBr): 3390, 1710,1628,1575 cm^{-1}

13: ^1H NMR (DMSO-d_6): δ2.18-3.2 (m, 3H), 3.60-3.99 (m, 3H), 4.54-4.57 (m, 1H), 7.82-8.01 (m, 2H), 8.43-8.54 (m, 2H), 14.73 (s, 1H, OH, D_2O exchangeable); IR(KBr): 3490,1720,1618, 1586 cm^{-1}

14: ^1H NMR ($CDCl_3$): δ0.79 (s, 9H, $C(CH_3)_3$), 2.17-2.83 (m, 3H), 3.40-3.74 (m, 3H), 4.60-4.66 (m, 1H), 7.64-7.97 (m, 2H), 8.55-8.63 (m, 2H), 14.64 (s, 1H, OH, D_2O exchangeable); IR(KBr): 3382,3080,1709,1624,1575 cm^{-1}

15: ^1H NMR (DMSO-d_6): δ7.15-8.65 (m, 7H), OH protons not visible; IR(KBr): 3400,1656,1620,1595, 1572 cm^{-1}

16 and 17: ^1H NMR (DMSO-d_6): δ1.42 (t, 3H, J=7 Hz, $-CH_3$), 4.26 and 4.27 (q, 2H, $-OCH_2$), 7.43-8.56 (m, 6H), OH protons not visible; IR(KBr): 3420,1660,1608,1580,1515 cm^{-1}

18: ^1H NMR ($CDCl_3$): δ1.26-2.75 (m, 2H), 3.05 (s, 3H, OCH_3), 3.28-3.49 (m, 2H), 3.84-4.15 (m, 1H), 5.92-6.22 (m, 2H), 7.36-8.06 (m, 2H), 8.20-8.89 (m, 2H), 14.47 (s, 1H, OH, D_2O exchangeable); IR(KBr): 3060,3020,2860,1725,1625,1570 cm^{-1}

24a The structure of 20 was tentatively assigned on ^1H NMR and IR data. The alternative glycosidation at quinonoid carbonyl adjacent to chlorine was ruled out because 18 under similar glycosidation conditions have no reaction.
^1H NMR ($CDCl_3$): δ1.13-3.29 (m, 6H), 3.5-4.73 (m, 2H), 3.95 (s, 4H, $-OCH_2CH_2O-$), 7.4-8.73 (m, 4H), 14.8 (s, 1H, 11OH, D_2O exchangeable); IR(KBr): 3390,2960,1700,1642,1590 cm^{-1}.
b It starts to change the color at 135° and dec 165-170 °C.

25a The structure of 21 was assigned on basis of high resolution MS, ^1H NMR and IR data and was a mixture of stereoisomers. The possibility of having the acetyl group on the other side appears to be less probable because the attack of ethynyl magnesium bromide on the hydrogen bonded quinonoid carbonyl group has never reported[7].
^1H NMR ($CDCl_3$): δ1.22-2.24 (m, 2H), 2.64-3.24 (m, 2H), 2.33 (s, 3H, $COCH_3$), 2.40 (s, 3H, $COCH_3$), 4.24-4.6 (m, 1H), 3.71-5.15 (m, 2H, OH protons, D_2O exchangeable), 7.65-7.83 (m, 2H), 8.27-8.61 (m, 2H), 14.89 (s, 1H, OH proton, D_2O exchangeable); IR(KBr): 3260,1718,1625,1612 cm^{-1}; MS, found: m/e 414.2022 Calcd for $C_{22}H_{19}ClO_6$: M, 414.2042.
b It starts to shrink at 174° and melts at 192-194 °C.

(Received May 18, 1982)