# Hydrogenolytic Transformations of 5a,11a-Epoxyhexahydronaphthacene-5,6,11,12-tetrones. Implications for the Synthesis of 6- and 11-Deoxyanthracyclinones

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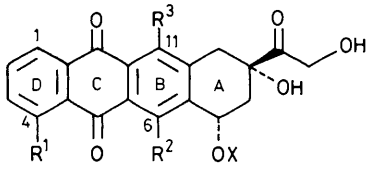
Catalytic hydrogenation ($H_2$, Pd–C) of the epoxide (**5a**) gives the dione derivative (**6**); an analogous procedure (**5d**)→(**7**) has been used in a sequence (**5b**)→(**5c**)→(**5d**)→(**7**)→(**2d**)→(**2b**) to give a valuable intermediate (**2b**) for the synthesis of 4,11-dideoxyanthracyclinones: implications for interconversions in the anthracyclinone series are described.

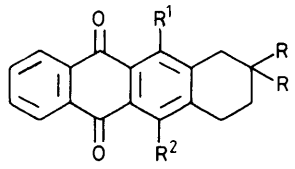
There is considerable interest in the total synthesis of the anthracycline derivative, adriamycin (**1a**)[1] and in related compounds such as 4-demethoxy- (**1b**),[2] 11-deoxy- (**1c**),[3] and 6-deoxy-adriamycin (**1d**). The preparation of intermediates (**2a,b**) relating to 4,6-[4] and 4,11-dideoxyanthracyclinones[5] has recently been achieved in a DC→DCBA Diels–Alder approach using naphthoquinone and ring A 1,3-diene synthons.

Our synthetic approach to 6- and/or 11-deoxyanthracylinone intermediates [*cf.* (**2a,b**)] is based on an overall transformation [(**2c**) (equivalent)→(**2a**) and/or (**2b**)] and is modelled on the known hydrogenolysis–oxidation sequence (**3a**)→(**4**)→(**3b**)[6] recently elaborated in our studies.[7]



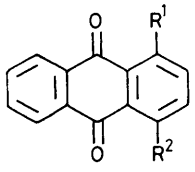
(**1**; X = daunosaminyl)

| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| **a**; | OMe | OH | OH |
| **b**; | H | OH | OH |
| **c**; | OMe | OH | H |
| **d**; | OMe | H | OH |



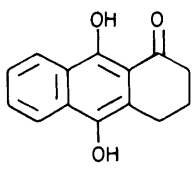
(**2**)

| | $R^1$ | $R^2$ | RR |
|---|---|---|---|
| **a**; | OH | H | =O |
| **b**; | H | OH | =O |
| **c**; | OH | OH | =O |
| **d**; | H | OH | $-O[CH_2]_2O-$ |



(**3**)

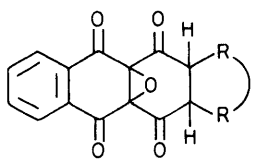
| | $R^1$ | $R^2$ |
|---|---|---|
| **a**; | OH | OH |
| **b**; | OH | H |



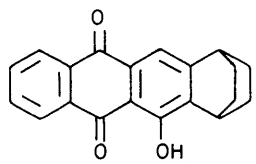
(**4**)

Compounds related to (**2c**) are available from epoxy tetrones† [*cf.* (**5**)] and the latter were selected as (**2c**) equivalents suitable for hydrogenolysis. Thus the model compound (**5a**) was reduced catalytically [$H_2$ (40 atm.), 5% Pd–C, $HCONMe_2$, 80 °C, 15 h] and after work-up in air gave directly (**6**)‡ (m.p. 242—244 °C, 51%). In the series relating to (**2a**) and/or (**2b**) synthesis, the sequence (**5b**)→(**5c**)→(**5d**)→(**7**)→(**2d**)→(**2b**) was successfully accomplished.§

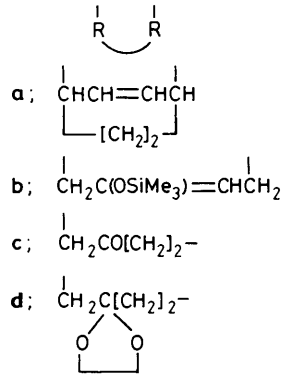
The regiochemical outcome of the hydrogenolysis step¶ (**5d**)→(**7**) could not be ascertained from spectral data but became clear from subsequent conversion (**7**)→(**2d**)→(**2b**) into a product (**2b**) of known structure.



(**5**)



(**6**)



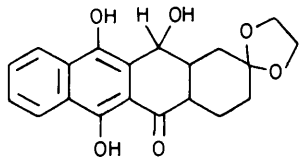
**a**; $CHCH{=}CHCH[CH_2]_2$

**b**; $CH_2C(OSiMe_3){=}CHCH_2$

**c**; $CH_2CO[CH_2]_2-$

**d**;





(**7**)

† Regioselective annulation of 1,3-dienes to quinizarin quinone can be effected by protection of the 4a,9a-double bond as the epoxide (see ref. 8).

‡ Satisfactory analytical and spectral data were obtained for all new compounds.

§ (**5b**) (90%, m.p. 205—207 °C) was prepared by a modification of the method of ref. 8 using $CH_2{=}C(OSiMe_3)CH{=}CH_2$, $CH_2Cl_2$, 25 °C, 3 days. (**5c**) [96%, m.p. 200—220 °C (dec.)] was prepared from (**5b**), 7% HCl, tetrahydrofuran, 0.5 h, 25 °C. (**5d**) [78% m.p. 185—200 °C (dec.)] was prepared from (**5c**), $HO[CH_2]_2OH$, *p*-$MeC_6H_4SO_3H$, $CH_2Cl_2$, 40 °C, 2 h. (**7**) (28%, m.p. 186—188 °C) was prepared from (**5d**), $H_2$ (40 atm.), 5% Pd–C, $HCONMe_2$, 80 °C, 15 h. (**2d**) (85%, m.p. 255—227 °C) was prepared from (**7**), $K_2CO_3$, MeOH, 65 °C, 0.5 h. (**2b**) (92%) was prepared from (**2d**), 36% HCl, tetrahydrofuran, 68 °C, 0.5 h. The sample of (**2b**) was identical (m.p., i.r., n.m.r., u.v.) with an authentic sample.

¶ The hydrogenolysis product from (**5d**) is complex and (**7**) could only be isolated in 28% yield. It is unlikely that this process is regioselective.

In addition to providing an inexpensive route to 4,11-dideoxyanthracyclinone intermediates, these results provide encouragement to extend hydrogenolyses of this type to epoxide intermediates in the 4-methoxy-6,11-dihydroxy series, and ultimately, to effect the direct interconversion of suitably protected 6,11-dihydroxyanthracyclinones into 6- and/or 11-deoxy analogues.

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## References

1 F. Arcamone, 'Doxorubicin: Anticancer Antibiotics,' Academic Press, New York, 1981; T. R. Kelly, *Annu. Rep. Med. Chem.*, 1979, **14**, 288; 'Anthracycline Antibiotics,' ed. H. S. El Khadem, Academic Press, New York, 1982.
2 F. Arcamone, L. Bernadi, P. Giardino, and A. Di Marco, German Patent 2,652,391,1977; *Chem. Abstr.*, **87**, 152522.
3 F. Arcamone, G. Cassinelli, F. Di Matteo, S. Forenza, M. C. Ripamonte, G. Rivola, A. Vigevani, J. Clardy, and T. McCabe, *J. Am. Chem. Soc.*, 1980, **102**, 1462.
4 J. P. Gesson, J. C. Jacquesy, and M. Mondon, *Tetrahedron Lett.*, 1981, **22**, 1337.
5 J. P. Gesson, J. C. Jacquesy, and M. Mondon, *Tetrahedron Lett.*, 1980, **21**, 3351.
6 K. Zahn and H. Koch, *Ber.*, 1938, **71**, 172.
7 P. N. Preston, S. G. Will, T. Winwick, and J. O. Morley, *J. Chem. Soc., Perkin Trans.* 1, 1983, 1001.
8 M. Chandler and R. J. Stoodley, *J. Chem. Soc., Perkin Trans.* 1, 1980, 1007.