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A CAVEAT REGARDING CHIROPTICAL MEASUREMENTS OF CHIRAL ANTHRACYCLINONES

Richard A. RUSSELL[A], Robert W. IRVINE[B] and Adrian S. KRAUSS[A]

[A] Department of Chemistry, Faculty of Military Studies, University of N.S.W., Duntroon, A.C.T. 2600, Australia
[B] Department of Chemistry, The Faculties, The Australian National University, GPO Box 4, Canberra, A.C.T. 2600, Australia

ABSTRACT. The specific rotations of anthracyclinones are shown to exhibit dramatic variation induced by protic solvents. The significance of this finding to the evaluation of optical purity of synthetic anthracyclinones is discussed.

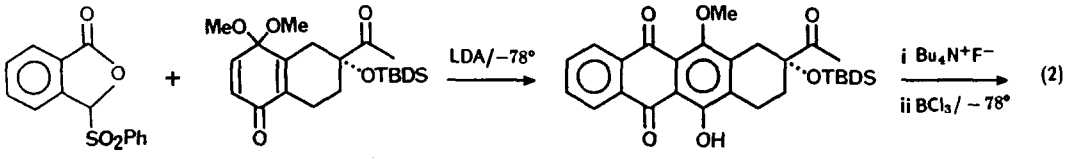
The measurement of specific rotation is a common and well accepted method for evaluating the optical purity of chiral compounds. The success of this method depends entirely on having a reliable rotation for the optically pure material and using this as a standard against which test samples are measured under well defined conditions (e.g. concentration, solvent and temperature).

It was surprising then to find recent reports of purportedly optically pure anthracyclinones having dramatically different reported specific rotations even when measured under seemingly identical conditions. A specific case in point is that of the 4-demethoxydaunomycinone derivative (**1**). The accepted literature value for the specific rotation is $[\alpha]_D = -33.3°$ [1], yet Terashima[2] has reported $[\alpha]_D = -23.3°$ for material which was shown by a separate n.m.r. study, using chiral shift reagents, to be optically pure. Such discrepancies are not confined to (**1**)[3] and throughout our own work[4] on the synthesis of chiral anthracyclinones we frequently encountered specific rotations of optically pure compounds which varied from the literature value. On occasion [e.g. compound (**1**)] these variations were too great to be attributed to experimental error and had it not been for the support of n.m.r.–chiral shift reagent studies[5] totally incorrect conclusions might have been drawn regarding the optical purity of the samples.

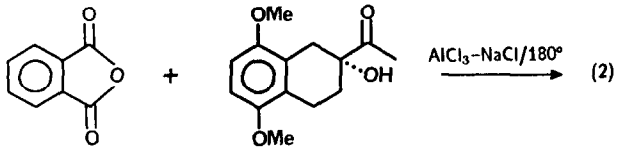
The origin of these previously unexplained variations is now traced to the purity of the solvents used in the determination of specific rotations. We show (Figure 1) that the presence of polar oxygen containing solvents, in particular ethanol and methanol, can dramatically alter the magnitude of specific rotations determined for chloroform solutions of anthracyclinones. Whilst solvent dependence of specific rotations is a well documented phenomenon[6], its relevance to anthracyclines has been largely ignored. The presence of alcohols in chloroform (often present in low concentration as a stabiliser) can shift the specific rotation in either direction (see Table), and the changes are greatest at low concentration of alcohol. In order to clarify results from the literature we have determined[7] the $[\alpha]_D$ values of a number of commonly encountered

anthracyclinone intermediates in absolute chloroform[8]. Whilst this solvent gives consistent results, many anthracyclines tenaciously hold alcohol or water of crystallisation[2,9], which has a significant effect upon the $[\alpha]_D$ value obtained in absolute chloroform. This latter problem can be overcome by determining specific rotations in a 1:1 methanol-chloroform mixture[10] (see Table). Such results are totally insensitive to solvent stabilisers or solvent of crystallisation and are readily reproduced.

The origin of this solvent dependency, which is reflected throughout the visible region of the ORD curve (Figure 2)[11], is associated with the whole anthracycline molecule, since a similar effect on $[\alpha]_D$ is not observed in the bicyclic α-hydroxyketones (10) or their ketals (11). However, it is not yet clear[12] whether the effect originates from conformation changes[6] or molecular aggregation[13].



Scheme 1 Phthalide Annelation Route



Scheme 2 Friedel–Crafts Route

The ability to reproduce $[\alpha]_D$ measurements for pure samples, differing only in origin, enabled us to compare samples of (2) prepared by our phthalide annelation route (Scheme 1) with those obtained from the Friedel–Crafts route (Scheme 2). This latter reaction has been examined by three groups[1,2,14], but only Terashima has recognised and reported[2] racemisation occurring during the reaction. On repeating the work reported by Terashima[2] and subsequently by Rama Rao[14], we obtained a product (2)[15,16] m.p. = 201–206°; $[\alpha]_D$ (1:1 MeOH/$CHCl_3$) = −15.8°, which compared with an $[\alpha]_D$ = −20° recorded for optically pure material obtained by the phthalide route. For the former sample this suggests a degree of racemisation equivalent to 21%, which was further supported by methylation of the Friedel–Crafts product to afford (1). This dimethylether was chemically purified by chromatography to afford material $[\alpha]_D$ (1:1 MeOH/$CHCl_3$) = +26.4° which, when compared with enantiomerically pure material[5]($[\alpha]_D$ = +34.4°), reveals only an enantiomeric excess (ee) of 77%. This figure agrees well with 81% ee obtained using the chiral shift reagent–n.m.r. technique.

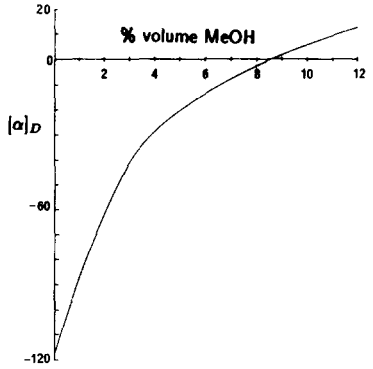


Figure 1. Variation of $[\alpha]_D$ for (5) with increasing concentration of MeOH

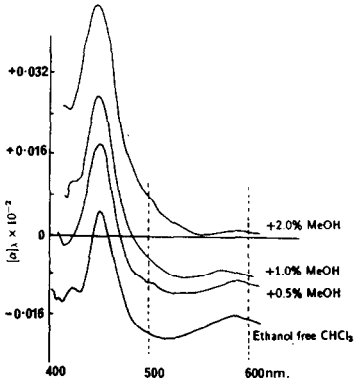
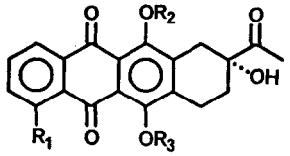


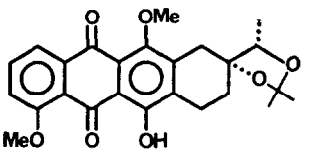
Figure 2. ORD curve for (2)

Table 1

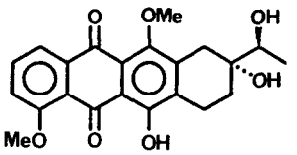
Compound	$[\alpha]_D^\circ$ ($CHCl_3$)(c)	$[\alpha]_D^\circ$ (1:1 MeOH/$CHCl_3$)(c)
(1)	−35.6 (0.87)	+34.4 (0.88)
(2)	−95.2 (0.13)	−20.0 (0.18)
(3)	−109.3 (0.90)	+20.0 (0.49)
(4)	+63.2 (0.82)	+31.1 (0.80)
(5)	−121.1 (0.56)	+24.6 (0.50)
(6)	−52.4 (1.00)	+21.4 (0.89)
(7)	−88.9 (0.086)	−23.7 (0.132)
(8)	−54.2 (0.78)	−36.7 (0.81)
(9)	−81.6 (0.35)	−94.4 (0.28)



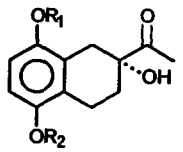
(1) $R_1 = H$, $R_2 = R_3 = Me$
(2) $R_1 = R_2 = R_3 = H$
(3) $R_1 = R_3 = H$, $R_2 = Me$
(4) $R_1 = R_2 = H$, $R_3 = Me$
(5) $R_1 = OMe$, $R_2 = Me$, $R_3 = H$
(6) $R_1 = OMe$, $R_2 = R_3 = Me$
(7) $R_1 = OMe$, $R_2 = R_3 = H$



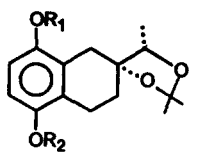
(8)



(9)



(10) a $R_1 = Me$, $R_2 = CH_2Ph$
b $R_1 = CH_2Ph$, $R_2 = Me$



(11) a $R_1 = Me$, $R_2 = CH_2Ph$
b $R_1 = CH_2Ph$, $R_2 = Me$

These results fully support our earlier contention[4] that the phthalide anion route is the method of choice for the synthesis of optically pure anthracyclinones. In contrast the Friedel–Crafts reaction can at best convert enantiomerically pure starting materials into optically enriched products and then only if the reaction time is minimised[17]. Further enhancement of the optical purity of such products can only be attained by wasteful multiple recrystallisations[16].

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REFERENCES AND FOOTNOTES

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[4] Russell, R., Krauss, A., Warrener, R. and Irvine, R., *Tetrahedron Lett.*, 1984, 1517.

[5] Determinations of optical purity were made using a solution of (1) (25 mg) and Eu(hfc)$_3$ (6.3 mg) in $CDCl_3$ (0.35 ml). ^1H n.m.r. spectra (270 MHz) of racemic (1) showed a clean separation of the methylketone resonances for the diastereoisomeric complexes.

[6] *Inter alia*, Coulombeau, C. and Rassat, A., *Bull. Soc. Chim. France*, 1963, 2674; Menger, F. and Boyer, B., *J. Org. Chem.*, 1984, **49**, 1826.

[7] Optical rotations were recorded on a Perkin Elmer–241 polarimeter using a 10 cm path length cell with a volume of approximately 1 ml, and have an accuracy of ±1.0%.

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[10] 1:1 MeOH/$CHCl_3$ is an excellent solvent for many anthracyclinones which frequently are sparingly soluble in either of the single solvents.

[11] Recorded on a Jasco ORD/UV–5 instrument.

[12] ^1H n.m.r. studies have shown no significant effect due to the addition of CD_3OD to $CDCl_3$ solutions of (1).

[13] Barthelemy–Clavey, V., Maurizot, J.-C., Dimicoli, J.-L. and Sicard, P., *FEBS Lett.*, 1974, **46**, 5.

[14] Rama Rao, A., Yadav, J., Bal Reddy, K. and Mehendale, A., *J. Chem. Soc., Chem. Commun.*, 1984, 453.

[15] The reaction time for this experiment was taken as the time to melt the mixture + 2 minutes.

[16] One recrystallisation from benzene afforded material with mp = 212–214°, $[\alpha]_D = -17.8°$, and subsequent recrystallisation slowly improved the optical purity of this product.

[17] Reaction time after melting ($[\alpha]_D$): 6 min (−10°); 40 min (−1.5°); specific rotations recorded in 1:1 MeOH/$CHCl_3$ on material crystallised once from benzene.

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