Synthesis and Characterisation of Compounds related to Daunomycin

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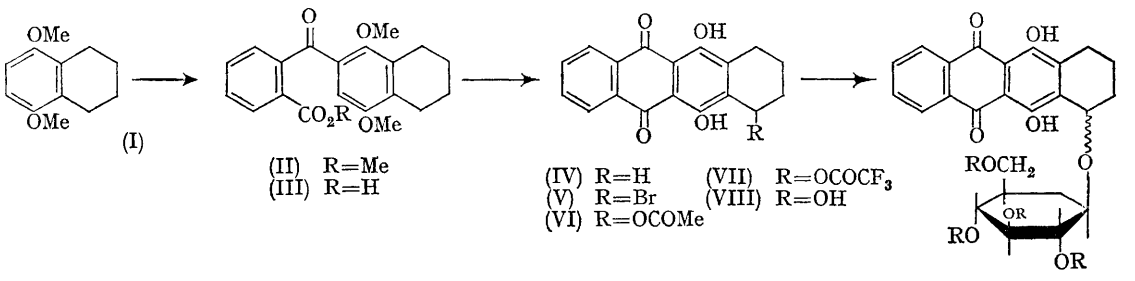
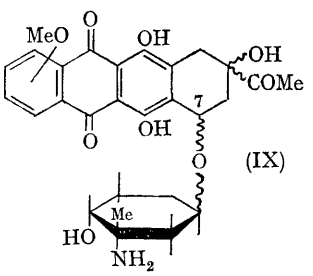
THE cytotoxic antibiotic, daunomycin (IX)[1a,b] has useful antitumour activity.[2] We have prepared compounds closely related to (IX) in an attempt to explore structure-activity relationships in this system. Here is described the synthesis of a tetracyclic analogue (VIII) of daunomycinone[1a] [the aglycone of (IX)] and its conversion to the D-glucoside (XI). The tetra-acetate (X) has been separated into its two diastereoisomers which have been related to daunomycin (IX) by c.d. studies.



Scheme



The dimethoxytetralin (I)[3a,b] was condensed with the mixed anhydride of methyl hydrogen phthalate and trifluoroacetic acid to give an excellent yield of the keto-ester (II) which was saponified to (III).† Ring closure with sulphuric acid was accompanied by the loss of one of the *O*-methyl groups; complete demethylation to (IV) was accomplished with aluminium chloride. Bromination with tetramethylammonium tribromide[4] gave a mixture of the unstable bromide (V), some dibromide, and unchanged (IV) which was treated with silver acetate to give a mixture of (IV), (VI), and some diacetate that could be separated chromatographically. Attempts to convert (VI) to the model aglycone (VIII) with methanolic sodium methoxide were unsatisfactory, but it was found that (VI), dissolved in trifluoroacetic acid, was converted essentially quantitatively to (VII), which was readily methanolysed to (VIII), m.p. 292—294° (decomp.).

Reaction of (VIII) with acetobromoglucose in the presence of mercuric cyanide gave a good yield of (X)‡ as a mixture of diastereoisomers, m.p. 235—242° (decomp.). Treatment of (X) with methanolic sodium methoxide in the cold afforded (XI), m.p. >300°. Preparative t.l.c. on silicic acid caused the separation of (X) giving a faster-moving glucoside (A), m.p. 235° (decomp.), $[\alpha]_D$ + 106° (dioxan), and the slower-moving component (B), m.p. 268° (decomp.), $[\alpha]_D$ − 216° (dioxan). The c.d. spectra of the diasterio-isomers (Figure c)§ clearly demonstrate that diasterioisomer A has the same configuration at the benzylic carbon as do daunomycin (Figure a) and daunomycinone (Figure a). The c.d. curve of 7-deoxydaunomycinone (Figure a) defines that part of the spectrum that is largely contributed by the benzylic optical centre. As additional confirmation

† Satisfactory analytical and spectral data were obtained for all the compounds in the scheme, except (V).

‡ Compound (X) is assumed to be the β-anomer since α-acetobromoglucose should give the β-anomer, either by S_N2 reaction or by way of the *ortho*-ester ion.[5]

§ The c.d. spectra were run in dioxan on a Durrum JASCO Spectropolarimeter, Model ORD/UV/CD-5. We thank Mr. Donald P. Sproul of Durrum Instrument Co. for help in obtaining these spectra.

for the relationship between diasterioisomer A and daunomycin, the pattern of the acetate methyl ^1H n.m.r. resonances was essentially identical with that of the condensation product of daunomycinone and acetobromoglucose and completely different from that of diasterioisomer B.

Condensation of other sugars, including daunosamine,[1b,6] with (VIII) and with daunomycinone is being studied.

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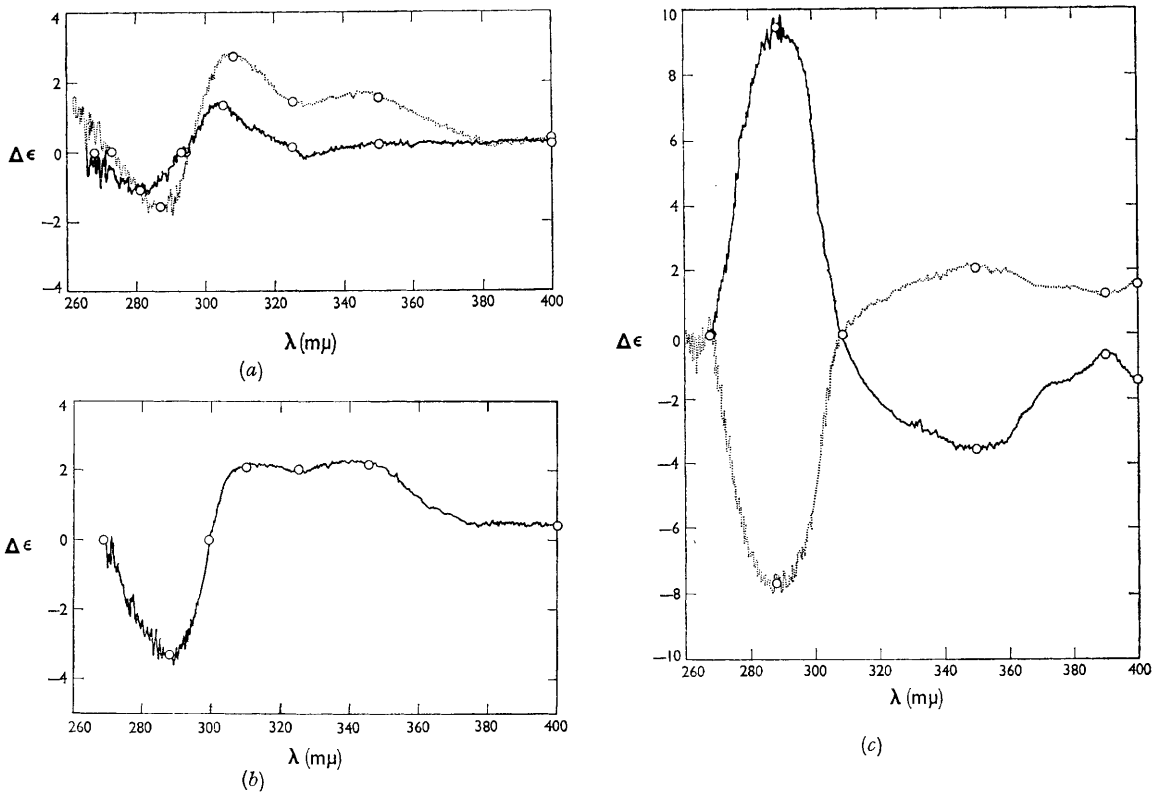

FIGURE. *Circular dichroism curves.*

(*a*) —7-*Deoxydaunomycinone*, – – – *daunomycinone*; (*b*) *Daunomycin*; (*c*) *Diastereoisomer B*, – – – *diastereoisomer A*.

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