SYNTHESIS AND RING A CONFORMATION OF NEW ANTHRACYCLINES

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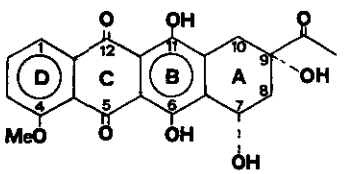
Abstract — Our continuing interest in the development of new anticancer agents structurally related to daunorubicin and doxorubicin has led us to synthesize analogues modified in the sugar or in the aglycone moieties. Among the latter, 4-demethoxy analogues, obtained by total synthesis, display outstanding antitumor activity and potency. Recently new synthetic procedures have been developed aiming to new classes of analogues characterized by the presence of only one phenolic group on ring B. Such new approaches have allowed the synthesis of 6-deoxy and 11-deoxy derivatives of the antitumor anthracyclines. Interestingly, the absence of the 6-hydroxyl results in an increased conformational flexibility of ring A as shown by nmr measurements on 4-demethoxy-6-deoxydaunorubicin and its derivatives. Changes in ring A conformation had also been recorded in derivatives substituted on ring A including 10-(S)-methoxydaunorubicin [S. Penco et al., Heterocycles 13, 281 (1979)]. Correlations between ring A conformation and structure of a number of derivatives will be discussed.

The successful development of doxorubicin (Adriamycin) as a major chemotherapic agent for the treatment of a range of human cancers has aroused great interest in the total synthetic approaches to doxorubicin-related anthracyclines. Several studies were concerned with elaborate syntheses of daunomycinone (1), the aglycone of daunorubicin , itself a key precursor for the manufacture of doxorubicin (for reviews see ref. 1 and 2). A major challenge of the synthetic approaches to daunomycinone is in fact the regiospecific construction of the tetracyclic chromophore with the correct relative positions of the C-4 methoxyl and the C-9 acetyl side chain.



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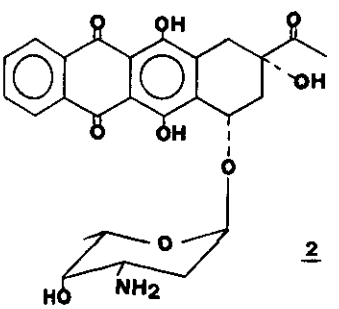

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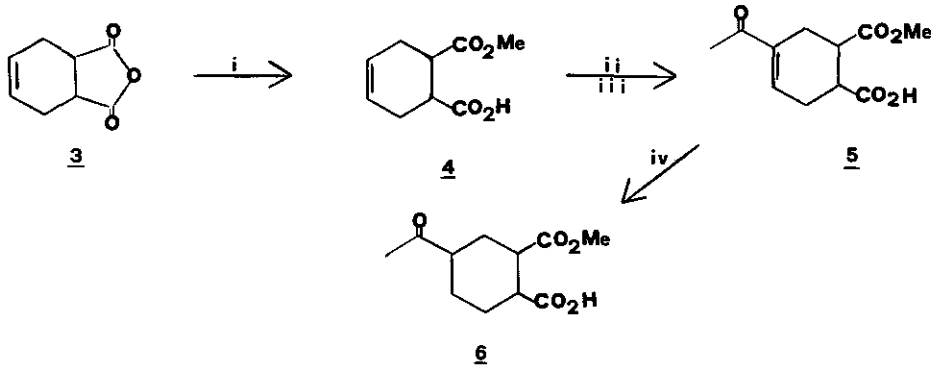
On the other hand, the outstanding biological activity of daunorubicin and doxorubicin derivatives bearing identical substitution at, respectively, position 1,4 and 2,3[3] has prompted the development of practical total synthetic procedures leading to anthracycline glycosides representing new structural varieties in respect to those available by chemical manipulation of the biosynthetic products. The new glycoside, 4-demethoxydaunorubicin (idarubicin, 2) has been selected for extended clinical trials because of its high efficacy against experimental mouse leukemias, activity after oral administration and lower cardiotoxicity[1,4]. For this reason the total synthesis of 4-demethoxydaunomycinone has received considerable attention by different researchers[1,5,6,7]. An extension of this work is represented by the synthesis of new aminoglycosides of 4-demethoxydaunomycinone, namely the 4'-epi, 4'-O-methyl and 4'-deoxy derivatives of 4-demethoxydaunorubicin and-doxorubicin[8].

The intercalation complex of the antitumor anthracyclines with double-stranded cell DNA is stabilized by π-π interaction of the base pairs with the drug planar chromophore moiety. The phenolic groups of the latter appear also to take part in the intercalation process as deduced by spectroscopic evidence[9,10]. Both x-ray diffraction and nmr studies indicate rings B and C to be in the interior of the shielding region of the DNA base pairs[11,12]. For these reasons, there is current interest in the relationships between the phenolic substitution on ring B and affinity for double-stranded DNA or antitumor activity in different series of daunorubicin or doxorubicin analogues. The 11-deoxy analogues of daunorubicin, doxorubicin and carminomycin retaining substantially the same antitumor properties of the 11-hydroxylated compound although at higher dosages, have been isolated in our laboratory[13-15]. Totally synthetic 4-demethoxy-11-deoxydoxorubicin was shown to be endowed with outstanding biological potency, practically equivalent to that of doxorubicin itself, by Umezawa et al [16]. These findings had already indicated the potential pharmacological importance of analogues characterized by the presence of only one phenolic group on ring B. Our studies aimed at the regioselective synthesis of the 6-deoxy and 11-deoxy analogues were based on a new chemical approach for the construction of the aglycone moiety.

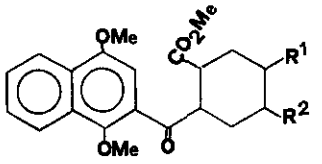
The corresponding synthetic route involved intermediate 6, prepared from 3, the Diels-Alder adduct of maleic anhydride and butadiene in three steps (scheme 1).

SCHEME 1

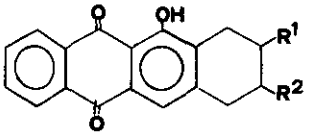


Reagents: i, MeOH; ii, AcCl, $AlCl_3$; iii, Na_2CO_3; iv, H_2, Pd/C.

It is noteworthy to point out the regioselective course of acylation of 4 giving rise in 65% yield to compound 5 (after crystallization). Acylation of 1,4-dimethoxynaphthalene with 6 in the presence of trifluoroacetic anhydride and trifluoroacetic acid afforded, non regioselectively, a mixture of 7a and b, whose benzylic catalytic reduction and cyclization-oxidation in concentrated sulfuric acid gave isomers 8a and b. The isomeric mixture was submitted to tertiary hydroxylation via epoxidation of the corresponding enolacetate followed by an alkaline and an acid treatment.



7a,b

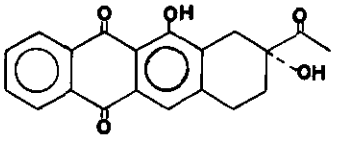


8a,b

a : R^1 = H; R^2 = $COCH_3$

b : R^1 = $COCH_3$; R^2 = H

The resulting regioisomers 9 and 10 ,respectively 4-demethoxy-6,7-dideoxy- and 4-demethoxy-7,11-dideoxydaunomycinone, could be separated by silica gel chromatography.



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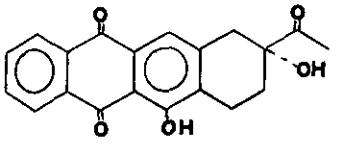

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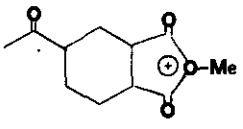
The non-regioselective course of the Friedel-Crafts acylation should be attributed to the intermediate formation of oxonium species 11. It appeared therefore



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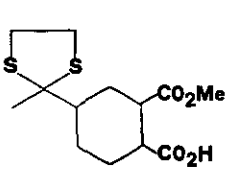

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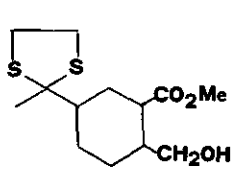
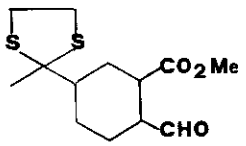


13

necessary to develop a modified procedure in order to obtain the desired regioselectivity. A possible solution was the conversion of the acid function to a formyl group followed by nucleophilic attack by a suitable metalated naphthalene derivative.

Protection of the methyl ketone group in 6 as in 12, followed by formation of the mixed anhydride with ethyl chloroformate and treatment of the latter with sodium borohydride at -75° gave 13 as an oil prone to lactonization. Nevertheless, careful recovery of 13 and oxidation with pyridinium chlorochromate afforded the key intermediate 14 in 45% overall yield starting from 6.



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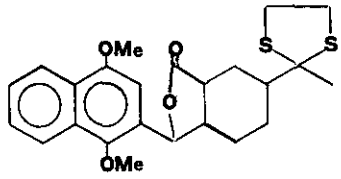
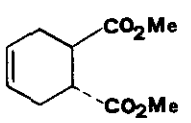


15

Reaction of 2-bromo-1,4-dimethoxynaphthalene with n-butyl lithium at -70° and subsequent addition of 14 gave 15 which, without isolation, was treated with concentrated sulfuric acid. This treatment allowed, in a single reaction step, cyclization, oxidation to the anthraquinone system and removal of the protecting group to give 8b in 10% yield from 14. Introduction of the tertiary hydroxyl group, performed following the procedure outlined above for the mixture 8a + 8b, gave 9 in 60% yield (4 steps)[17].

An improved procedure for the synthesis of 9 has been developed more recently. Starting material was the Diels-Alder adduct of dimethyl fumarate and butadiene 16 whose acetylation (acetic anhydride and tin tetrachloride followed by an acid treatment) gave 17 in 75% yield. Conversion of 17 into exocyclic olefin 18 was car-



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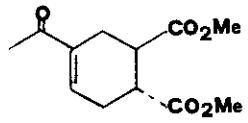

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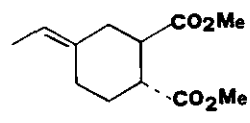
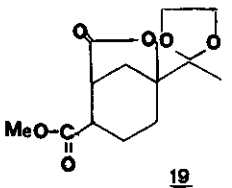


18

ried out by reduction of tosylhydrazone of 17 with catechol borane (yield 80%). Permanganate oxidation of 18 in acetic acid and treatment of the resulting hydroxy-

ketone with ethylene glycol and a trace of p-toluenesulfonic acid gave 19 in good yield. Reaction of 19 with 2-lithium-1,4-dimethoxynaphthalene afforded regioselec-



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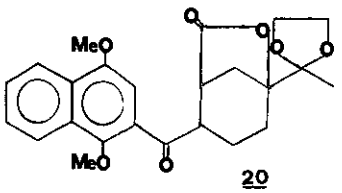

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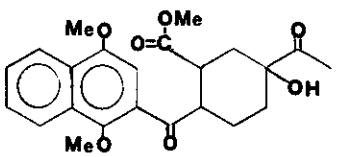
tively up to 70% yield. Compound 20, in turn, converted into methyl esther 21 with dry hydrogen chloride in methanol. Reduction of 21 with the pyridine-borane complex followed by alkaline hydrolysis and esterification with phenyldiazomethane



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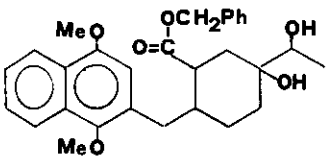
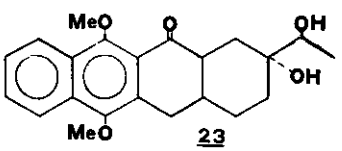


22

afforded 22 in 63% overall yield. O-Acetylation of both alcoholic groups was then carried out in order to avoid formation of the lactone during the cyclization step. The latter was performed after hydrogenolysis of the benzyl ester (cyclohexane, Pd/C) with trifluoroacetic anhydride and trifluoroacetic acid to give 23, subsequently oxidized to 24 with silver carbonate. Finally, transformation of 24 to 9 was readily accomplished upon treatment with aluminum chloride in nitrobenzene.



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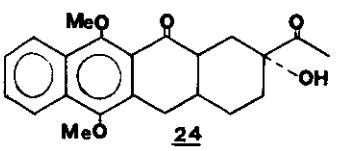

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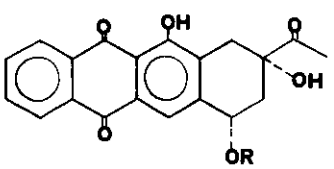
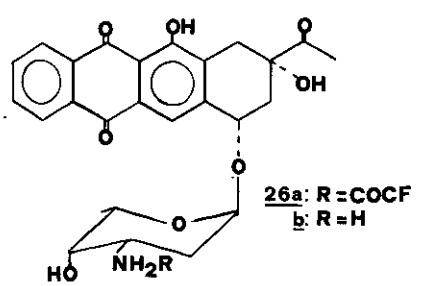


25a: R = H
b: R = Ac



26a: R = COCF
b: R = H

Further reaction steps for the synthesis of the final glycosides were those allowing the introduction of the benzylic hydroxyl at C-7 and the final glycosidation with the amino sugar, daunosamine. Compound 9, after ketalization at C-13, was brominated with bromine or with N-bromosuccinimide and a radical initiator, then treated with alkalis and deblocked with acid to give 25a in 26% overall yield from 9. Alternatively the bromo derivative was treated with silver acetate to give 25b whose methanolysis and acid hydrolysis afforded 25a in 32% yield from 9.
Silver triflate-catalyzed coupling of 25a with N,O-ditrifluoroacetyldaunosaminyl chloride followed by chromatographic separation afforded 26a and the corresponding 7(R)9(R) diastereomer. Stereochemical assignment in 26a at C-7 and C-9 was based on circular dichroism measurements[17]. Deblocking of the amino group in dilute alkalis gave the desired aminoglycoside 26b.
Following substantially similar procedures, 10 was converted into 4-demethyl-11-deoxydaunorubicin showing physico-chemical properties identical to those reported in the literature[16].
The absence of the C-6 phenolic hydroxyl in ring B affects the conformation of the acyclic ring A, as indicated by ^{1}H NMR studies in $CDCl_3$ and in DMSO-d_6 solutions. In fact 4-demethoxy-11-deoxydaunomycinone displays the α half-chair conformation as shown by the spin couplings values in both solvents. The values, reported in Table 1, are identical to those of daunomycinone. On the contrary the 6-deoxy isomer, which in $CDCl_3$ solution prefers the α half-chair conformation, in DMSO-d_6 changes to β half-chair, as shown by the high values of J_{H7-H8} together with the evidence of a long-range coupling between H-8_{eq} and H-10_{eq}.

TABLE I PMR data

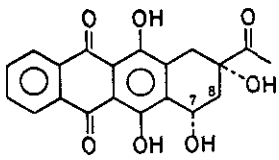
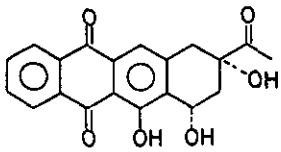
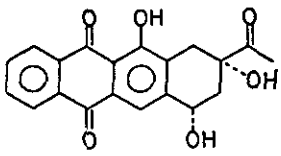
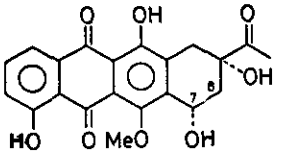
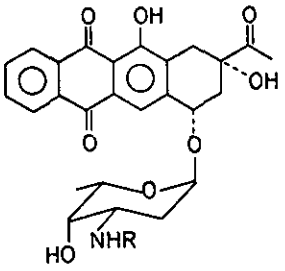
Compound	Solvent	$J_{H7-H8eq}$ (Hz)	$J_{H7-H8ax}$ (Hz)	$J_{H8eq-H10eq}$ (Hz)
	$CDCl_3$	2.0	4.8	2.2
	DMSO-d_6	2.8	4.6	1.0
	$CDCl_3$	2.2	4.9	2.2
	DMSO-d_6	2.0	4.6	1.0
	$CDCl_3$	1.7	4.5	1.7
	DMSO-d_6	5.8	9.7	1.2

TABLE I PMR data (follows)

Compound	Solvent	$J_{H7-H8eq}$ (Hz)	$J_{H7-H8ax}$ (Hz)	$J_{H8eq-H10eq}$ (Hz)
	$CDCl_3$	2.2	4.8	2.0
	DMSO-d_6	2.9	4.4	1.1
	R=$COCF_3$ $CDCl_3$	3.7	3.7	1.1
	R=$COCF_3$ DMSO-d_6	4.1	8.6	1.0
	R=H DMSO-d_6	6.2	8.8	0.7

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