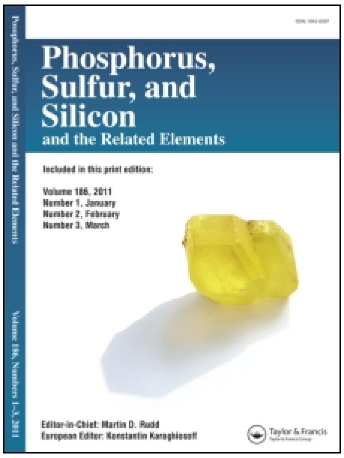

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SYNTHESIS OF HETEROANTHRACYCLINONE INTERMEDIATES: SYNTHESIS OF 6a,7,10,10a-TETRAHYDROBENZOTHIOXANTHEN-6,11,12-TRIONES

Pahup Singh[a]; R. T. Pardasani[a]; Anita Prashant[a]; Bhavna Choudhary[a]
[a] Department of Chemistry, University of Rajasthan, Jaipur, India

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SYNTHESIS OF HETEROANTHRACYCLINONE INTERMEDIATES: SYNTHESIS OF 6a,7,10,10a-TETRAHYDROBENZOTHIOXANTHEN-6,11,12-TRIONES

PAHUP SINGH, R. T. PARDASANI, ANITA PRASHANT
and BHAVNA CHOUDHARY
Department of Chemistry, University of Rajasthan, Jaipur-302004, India

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The synthesis of some benzothioxanthentriones related to heteroanthracyclinones is reported. 1,4-Dimethoxythioxanthen-9-one was prepared by condensation of 2,2'-dithiosalicylic acid and 1,4-dimethoxybenzene which was demethylated with borontribromide to give the corresponding hydroquinone. *In situ* oxidation with silver oxide followed by addition of various dienes gave 6a,7,10,10a-tetrahydrobenzothioxanthen-6,11,12-triones. The compounds have been characterised on the basis of elemental and spectral studies.

Key words: 2,2'-Dithiosalicylic acid; hydroquinone; Diels-Alder addition; thioxanthene-9-one; NMR; IR.

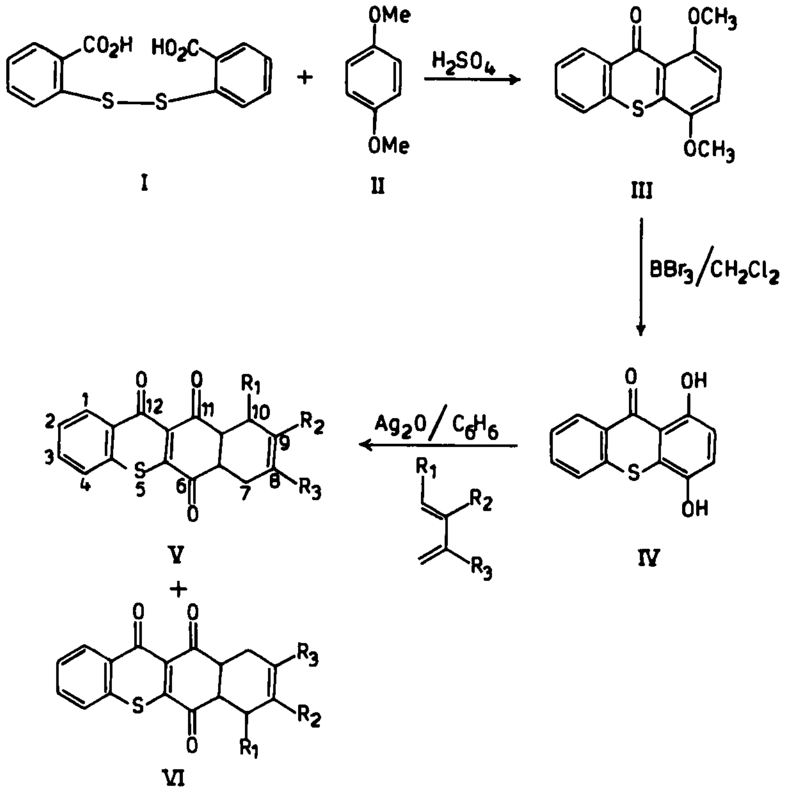
INTRODUCTION

Daunorubicin (daunomycin) and doxorubicin (adriamycin) are two clinically efficacious anticancer compounds which exhibit activity against a wide spectrum of human tumors.[1] The well documented cumulative dose dependent cardiotoxicity[2] of these agents has motivated several efforts[3] to synthesize new derivatives that show decreased side effects and/or increased anticancer activity.

We report the synthesis of some sulfur containing compounds viewed as precursors to the known, tetracyclic anthracyclinone intermediates.

DISCUSSION

Condensation of 2,2'-dithiosalicylic acid (**I**) with 1,4-dimethoxybenzene (**II**) in 1.2:1 ratio in concentrated sulfuric acid at room temperature yielded 1,4-dimethoxythioxanthen-9-one (**III**) (Scheme I) which on demethylation with borontribromide gave 1,4-dihydroxythioxanthen-9-one (**IV**). Oxidation of the hydroquinone (**IV**) with silver oxide/manganese dioxide failed, probably due to the reversible nature of the reaction yielding the hydroquinone. The quinol (**IV**) was thus oxidised by silver oxide in the presence of the reacting diene as reported by Kraus *et al.*[4] in the case of sensitive quinones. The reaction was carried out in absence of light and without isolation of the intermediate quinone. The various dienes used were isoprene, *trans*-piperylene, 2,3-dimethyl-1,3-butadiene, 1-methoxy-1,3-butadiene and Danishefsky's diene. A regioisomeric mixture of benzothioxanthenetriones (**V**/**VI**)



Compd.	R_1	R_2	R_3
a	H	CH_3	H
b	CH_3	H	H
c	H	CH_3	CH_3
d	OCH_3	H	H
e	OCH_3	H	OTMS

SCHEME - I

was obtained in each case which could not be separated by a combination of chromatographic techniques. The addition of the diene took place at the external double bond as indicated by the absence of quinonoid protons in ^{1}H NMR spectra. Such an addition on the terminal double bond has been previously reported by Lee,[5] Kelly,[6] Kende[7] and co-workers. In the case of Danishefsky's diene a fully aromatised product along with a host of other compounds was obtained.

The structures of the synthesised compounds were established by analytical and spectral studies. Elemental and physical data are given in Table I.

TABLE I

Physical and analytical data of compounds

S. No.	% Yield	M.P. (°C)	M.F.	Anals % Found (Calc.)		
				C	H	S
III	60	211	$C_{15}H_{12}O_3S$	66.00	4.28	11.69
				(66.17)	(4.41)	(11.76)
IV	75	136	$C_{13}H_8O_3S$	63.90	3.27	12.90
				(63.93)	(3.27)	(13.11)
V/VI						
a	48	216	$C_{18}H_{14}O_3S$	69.70	4.51	10.33
				(69.67)	(4.51)	(10.32)
b	65	248	$C_{18}H_{14}O_3S$	69.70	4.48	10.10
				(69.67)	(4.51)	(10.32)
c	52	274	$C_{19}H_{16}O_3S$	70.30	4.95	9.60
				(70.37)	(4.93)	(9.87)
d	60	210	$C_{18}H_{14}O_4S$	66.14	4.30	9.88
				(66.25)	(4.29)	(9.81)

IR Spectra

The IR spectrum of compound **III** showed an absorption band at 1710 cm^{-1} due to C=O stretching vibrations. The —OH absorption in compound **IV** was observed at 3300 cm^{-1} as a broad band while the C=O absorption appeared at 1645 cm^{-1}. Compound **V/VI** showed C=O stretching vibrations at 1670 and 1660 cm^{-1}.

^{1}H NMR Spectra

The ^{1}H NMR spectrum of compound **III** showed the presence of two sharp singlets at δ3.53 and δ3.70 ppm corresponding to two methoxyl groups and the aromatic protons appeard as a multiplet in the range δ7.8–8.02 ppm.

The two hydroxyl protons in **IV** displayed broad singlets at δ5.6 and 13.59 ppm whereas the aromatic protons gave a multiplet in the range δ7.82–8.14 ppm.

The ^{1}H NMR spectral data of the regioisomeric mixture of **V/VI** are tabulated in Table II.

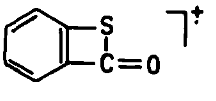
TABLE II

^{1}H NMR spectral data of regioisomeric mixture of **V/VI**

V/VI	$-CH_3/-OCH_3$	6a-H,10a-H	7-H,10-H	8-H,9-H	Ar-H
a	1.63 (s, 3H)	3.40 (m, 2H)	2.32 (brm, 2H)	5.42 (brs, 2H)	7.82-8.30 (m, 4H)
	1.65 (s, 3H)	3.41 (m, 2H)	2.27 (brm, 2H)	5.59 (brs, 2H)	" (m, 4H)
b	0.85 (d, J=7Hz, 3H)	3.25-3.70(brm, 2H)	2.0-3.0(brm,2H)	5.69 (brs, 2H)	7.8-7.85 (dd,J=7.5Hz, 7.5 Hz, 2H) 8.2-8.28 (dd, J=7.5,1.3 Hz,2H)
	0.89 (d,J=7Hz,3H)	3.25-3.70(brm,2H)	"	5.71 (brs, 2H)	"
c.	1.64 (s, 3H)	3.32 (brm, 2H)	2.33 (brm, 2H)	-	7.82-8.01 (m,4H)
	1.65 (s, 3H)	3.33 (brm, 2H)	2.37 (brm, 2H)	-	" (m,4H)
d.	3.15 (s, 3H)	3.48 (m, 2H)	2.40 (brm, 1H) 4.15 (brm, 1H)	6.01 (brs, 2H)	7.88-8.20(m,4H)
	3.32 (s, 3H)	3.27(m, 2H)	"	5.94 (brs, 2H)	" (m,4H)

Mass Spectra

In the mass spectrum of compound **IV** the molecular ion peak appeared at m/z 244 corresponding to the molecular formula $C_{13}H_8O_3S$. Other important peaks were observed at m/z 216, 227, 184, 136 and 108. The base peak appeared at m/z 136 due to the formation of $C_7H_4SO^+$ ion as:



In compounds **Va** and **Vb** the appearance of the parent peaks at m/z 310 confirmed the assigned structures.

EXPERIMENTAL

Melting points, determined on a Toshniwal melting point apparatus (capillary method) are uncorrected. The purity of the synthesized compounds was tested by thin layer chromatography on silica gel in various nonaqueous solvents. IR spectra were recorded in KBr on a Perkin Elmer 577 grating spectrophotometer (ν_{max} in cm^{-1}), PMR spectra in $CDCl_3$ and Jeol FX 90Q (89.55 MHz) using TMS as internal standard. Mass spectra were recorded on a Kratos 30 and 50 Mass spectrometer at 70 eV.

(i) 1,4-Dimethoxythioxanthene-9-one (**III**)[8]: To an ice-cooled stirred conc. H_2SO_4 solution of 2,2'-dithiosalicylic acid (0.025 mol) was added the 1,4-dimethoxybenzene (0.02 mol). The solution was stirred for a period of 6 hr at room temperature and then poured into ice water (750 ml) and extracted exhaustively with ethyl acetate (4 × 200 ml). The combined extracts, washed with water, aqueous $NaHCO_3$ and dried over $MgSO_4$, were evaporated to dryness under reduced pressure to give an orange solid residue, (**III**) along with a small amount of demethylated product. The crude product was purified by prep. tlc to give a crystalline product **III**.

(ii) Synthesis of 1,4-dihydroxythioxanthen-9-one (**IV**): To the solution of 1,4-dimethoxythioxanthen-9-one (0.01 mol) in dry methylene chloride (20 ml) at 0° was added a solution of borontribromide (BBr_3) (0.01 mol) in methylene chloride. The resultant red solution was stirred for 15 hr and then decomposed with water (3 × 25 ml) and dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the yellow crystalline solid **IV**.

(iii) Synthesis of 6a,7,10,10a-tetrahydrobenzothioxanthen-6,11,12-trione (**V** *and* **VI**): The mixture of 1,4-dihydroxythioxanthen-9-one (0.01 mol) and silver oxide (0.06 mol) in dry benzene (10 ml) was stirred for 4 hr at room temperature. The appropriate diene *viz.* (a) *trans*-piperylene; (b) Isoprene; (c) 2,3-dimethyl-1,3-butadiene; (d) 1-methoxy-1,3-butadiene and (e) Danishefsky's diene (0.03 mol) was now added to reaction mixture and stirred for 18 hr in the absence of light. The resulting solution was diluted with dry ether and filtered through celite under nitrogen. The yellow solution obtained was evaporated under reduced pressure to give yellow solid. The compound was purified by tlc to give yellow solids of various shades.

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