Benzylic substitution in ring A of daunomycinone. Conversion of daunomycinone into thiodaunomycinone and related deoxy analogs[1]

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Catalytic hydrogenolysis of daunomycinone (**4**) over palladium–carbon or palladium – barium sulfate afforded a mixture of 7-deoxydaunomycinone (**5**) and 7,11-dideoxydaunomycinone (**6**). 7-Deoxy-7-thioacetyldaunomycinone (**8**) and its 7-epimer (**9**) were prepared from **5** via the intermediate 7-deoxy-7-bromo derivative **7** in 33% yield. Compound **8** was prepared from **4** in a one-step reaction by treatment with thioacetic acid (THAA) and trifluoroacetic acid (TFAA), in 13% yield. Refluxing **4** in a mixture of THAA and glacial acetic acid (GAA) increased the yield of **8** and **9** to 83%. Epimerization of **9** with TFAA afforded **8**. Hydrolysis of **8** gave a mixture of thiodaunomycinone (**10**), **5**, and bisanhydrodaunomycinone (**11**). Compound **10** converts partially into its dimeric form (**12**) on standing.

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L'hydrogénolyse catalytique de la daunomycinone (**4**) sur des catalyseurs de palladium/charbon ou de palladium/sulfate de baryum conduit à un mélange de déoxy-7 daunomycinone (**5**) et didéoxy-7,11 daunomycinone (**6**). On a aussi préparé la déoxy-7 thioacétyl-7 daunomycinone (**8**) et son épimère en position 7 (**9**) avec un rendement de 33% en utilisant **5** comme produit de départ et en procédant par l'intermédiaire du dérivé déoxy-7 bromo-7 (**7**). Le traitement de **4** par de l'acide thioacétique (ATHA) et de l'acide trifluoroacétique (ATFA) conduit en une étape au composé **8**, avec un rendement de 13%. Si l'on porte le composé **4** au reflux dans un mélange d'ATHA et d'acide acétique glacial (AAG), on augmente le rendement de **8** et de **9** à 83%. L'épimérisation de **9** par de l'ATFA conduit à **8**. L'hydrolyse de **8** conduit à un mélange de thiodaunomycinone (**10**), de **5** et de bisanhydrodaunomycinone (**11**). Si on le laisse à la température ambiante, le composé **10** se transforme partiellement en sa forme dimère **12**.

[Traduit par le journal]

The anthracycline antibiotics, daunorubicin (**1**, $R^1 = CH_3$, $R^2 = H$) (2, 3), doxorubicin (adriamycin; **1**, $R^1 = CH_3$, $R^2 = OH$) (3, 4), and carminomycin (**1**, $R^1 = R^2 = H$) (5) are potent and clinically useful antitumor agents, with adriamycin having an especially broad spectrum of activity, extending to certain solid tumors that are normally resistant to most modes of chemotherapy. However, the clinical use of these drugs is hampered by a number of undesirable side effects, common to many antitumor drugs, such as severe alopecia, and dose-limiting and irreversible cardiotoxicity (6) (congestive heart failure), which have limited their optimum utilization in chemotherapy. The possible covalent bindings between C-7 and various biological nucleophiles have been suggested (7) as a basis for the toxic side effects of daunorubicin and adriamycin. Major efforts have been made to modify the anthracycline molecule with the objective of developing analogs with a wider spectrum of activity and reduced toxicity (8, 9). The synthesis of anthracycline analogs with various leaving groups (10) at C-7, and displacement of the 7-OH with O- and S-nucleophiles (11), have been described.

Rapid deactivation of these useful anticancer drugs takes place by hydrolytic or reductive cleavage of the glycosidic oxygen at position 7. The *C*-glycosyl analog **2**, in which the glycosidic oxygen atom is replaced by CH_2, was suggested to be more resistant (12) to rapid metabolic deactivation than the glycosidic oxygen-linked analog **1**. It might be incapable of generating alkylating activity at the 7-position, one mechanism of action proposed (10) as following ejection of the sugar from **1**. On the other hand, **2** should retain the DNA-binding properties (13) of the anthracyclines and the free-radical generating properties from cyclic reduction and reoxidation of the quinone (14, 15). The *C*-glycosyl analog **2** might also show favored biological effect upon testing and is expected to be a superior drug. *C*-Daunosaminyl intermediates required for the elaboration of the carbon-bridged anthracyclines have been reported (12).

The sulfur-bridged glycoside **3** is also expected to be considerably more stable (16) to reductive cleavage and hydrolysis in vivo than the glycosidic oxygen bond in **1**. In addition, replacement of the glycosidic oxygen by sulfur might possibly display or exhibit biological properties markedly different from the glycosidic oxygen analog, as expected for the carbon bridged analog **2**. In this work, replacement of the oxygen atom at C-7 of daunomycinone **4** by sulfur was explored to provide the aglycon part required for the elaboration of the sulfur-bridged analog **3**.

Catalytic hydrogenolysis of daunomycinone **4** with hydrogen over palladium – barium sulfate afforded a mixture of 7-deoxydaunomycinone (**5**) and 7,11-dideoxydaunomycinone (**6**) (Scheme 1). Reported (17) catalytic hydrogenolysis of the glycoside daunomycin or the aglycone **4** afforded only com-

[1] For a preliminary account of part of this work, see ref. 1.
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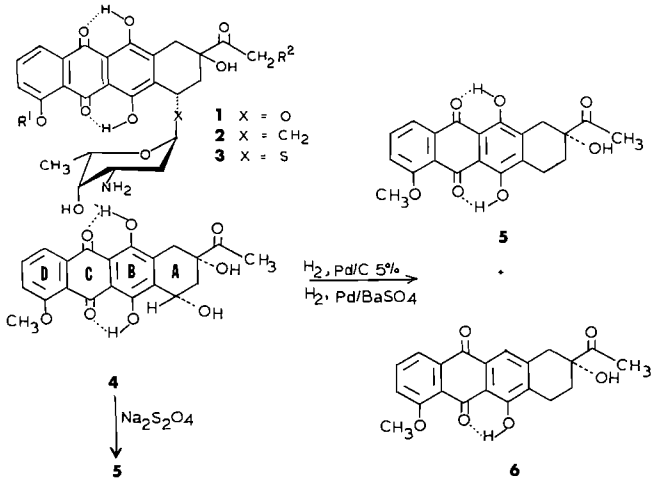
TABLE 1. ^{1}H nuclear magnetic resonance spectra[a] of compounds **4–6** and **8–10**

Proton (coupling constant)	Compound 4	5	6	8	9	10
H-1	8.011 s	8.028 d	8.028 d	7.984 d	7.985 d	7.934 d
($J_{1,2}$)	(7.5)	(7.5)	(8.4)	(7.4)	(7.7)	(7.5)
($J_{1,3}$)	(~1)					(~1)
H-2	7.763 t	7.761 t	7.595 t	7.753 t	7.745 t	7.736 t
H-3	7.385 d	7.374 d	7.016 d	7.368 m	7.358 d	7.355 d
($J_{2,3}$)	(8.4)	(8.5)	(7.8)	(8.0)	(8.3)	(8.3)
H-7	5.306 sbs	2.951 m	2.786 m	5.447 sbs	5.077 m	5.057 bs
	$\nu_{1/2}$ 5			$\nu_{1/2}$ 4.7	$\nu_{1/2}$ 15.9	$\nu_{1/2}$ 5
9-OH	3.776 sbs	3.771s	3.813 s	3.664 s	3.586 s	3.897 s
(J)	(4.7)					
H-10e	3.160 d	3.151 dd	3.044 dd	3.114 d	3.186 d	2.940 d
H-10a	2.901 d	3.061 d	2.951 d	2.990 d	3.093 d	2.825 d
($J_{10e,10a}$)	(19.5)	(18.6)		(18.5)	(16.5)	(19.0)
H-8e	2.321 d			2.625 dd		2.694 d
($J_{8e,8a}$)	(15.3)			(14.5)		(15.3)
		2.814–	1.899–		2.431–	
H-8a	2.150 dd	2.982 m	1.942 m	2.164 d	2.540 m	2.489 dd
($J_{7,8a}$)	(3.7)					(4.8)
7-OH	4.615 s					
6-OH	13.890 s	13.844 s	13.827 s	13.889 s	13.957 s	14.096 s
11-OH	13.202 s	13.449 s	—	13.302 s	13.306 s	12.929 s
H-11	—	—	8.580 s	—	—	—
4-OMe	4.084 s	4.088 s	4.039 s	4.063 s	4.064 s	4.058 s
9-Ac	2.438 s	2.391 s	2.371 s	2.386 s	2.406 s	2.355 s
7-SAc	—	—	—	2.368 s	2.341 s	—

[a]Spectra recorded at 470 MHz in chloroform-*d*. Spin couplings (Hz) are given in parentheses. Signal multiplicities: b, broadened; d, doublet; m, multiplet; s, singlet; sbs, split broad singlet; t, triplet.



SCHEME 1

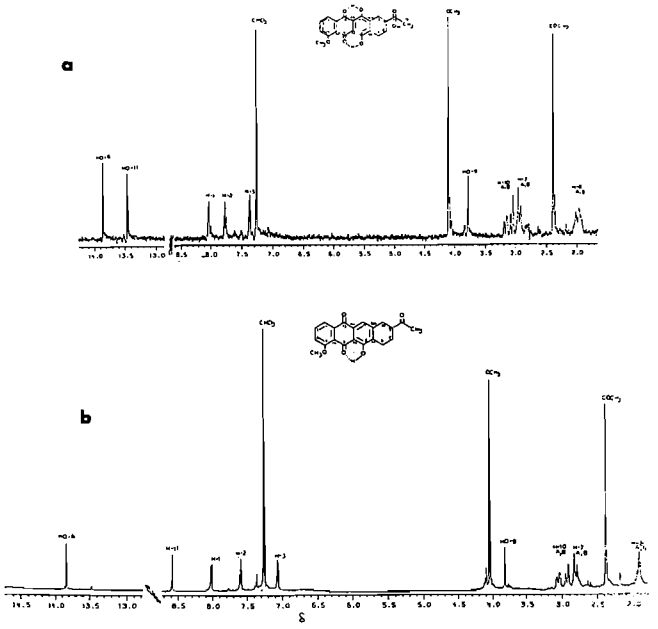
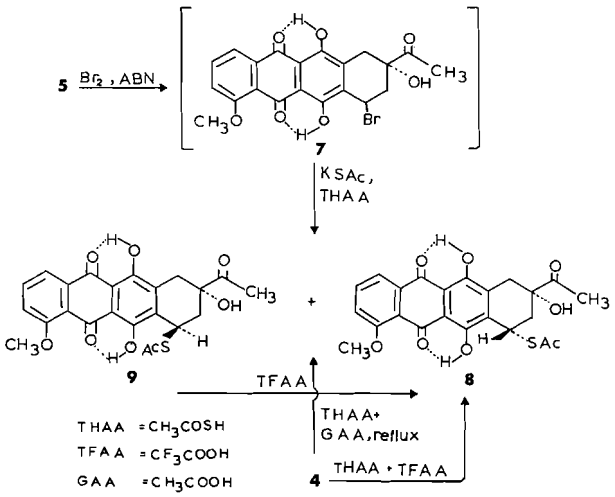


FIG. 1. The 470-MHz nmr spectra of (a) 7-deoxydaunomycinone **5** and (b) 7,11-dideoxydaunomycinone **6**.

pound **5**. The nmr spectrum of compound **6** (Fig. 1) showed the absence of the singlet corresponding to the chelated phenolic 11-OH which is present at δ 13.449 for compound **5**, and the appearance of a down-field singlet corresponding to the aromatic H-11 at δ 8.580, instead (Table 1). The further down-field shift for the chelated phenolic 6-OH at δ 13.844 and δ 13.827 for compounds **5** and **6**, respectively, can be rationalized based on extended resonance (18) with the C-4 methoxy that can occur only for the 6-OH. The nmr spectral data for compound **6** are similar to those reported for the compound obtained by catalytic hydrogenolysis of the biologically active 11-deoxydaunoribicin or 11-deoxydaunomycinone (19).

Chemical reduction of compound **4** with sodium dithionite (19–21) gives compound **5**.

Several attempts were made to introduce sulfur as a thioacetyl group at the 7-position of 7-deoxydaunomycinone in a reasonable yield. Treatment of compound **5** with bromine and a catalytic amount of 2,2′-azobisisobutyronitrile (ABN) in refluxing CCl_4 gave the unstable intermediate 7-bromo-



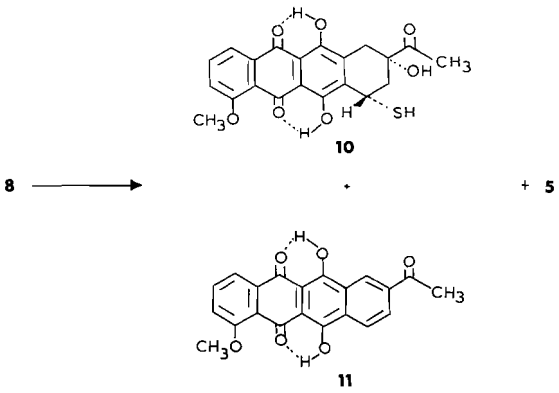
SCHEME 2

daunomycinone **7**. Wong *et al.* (22) postulated that steric hindrance about the 10-position allowed benzylic bromination to proceed regiospecifically at the 7-position. The bromine derivative **7** was treated with potassium thioacetate in a solution of thioacetic acid, giving a mixture of 7-thioacetyldaunomycinone **8** and 7-epithioacetyldaunomycinone **9** in 33% yield (Scheme 2).

In a one-step reaction, the 7-thioacetate **8** was prepared in 13% yield from **4**, by treatment with a mixture of thioacetic acid (THAA) and trifluoroacetic acid (TFAA) in the ratio of 5:2 at room temperature. This reaction mixture favors the formation of compound **8** with the stereochemistry of the natural 7,9-*cis* configuration at C-7. Replacement of TFAA with glacial acetic acid (GAA) and refluxing, gave a mixture of the thioacetate **8** and its epimer **9** in a ratio of 5:1 and in a total yield of 83%. The major isomer **8** was purified by recrystallization, and the minor isomer was separated from the mother liquor by chromatography. The reaction is assisted by the unusual reactivity of the benzylic hydroxyl group at the 7-position, which undergoes nucleophilic substitution by the thioacetate anion. The formation of two isomeric thioacetates can be explained by racemization through the formation of the carbocation at C-7 and subsequent attack of the thioacetate anion, rather than an S_N2 process which would produce the epimer. An identical benzylic carbocation was postulated (23).

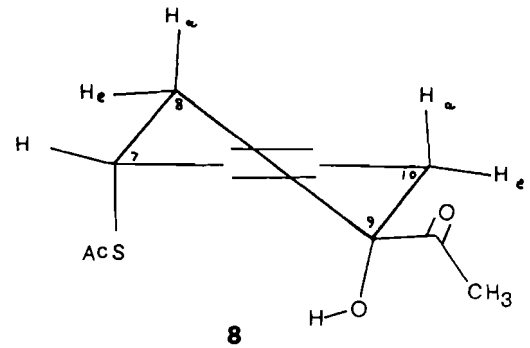
The nmr spectrum of compound **8** showed two signals at δ 2.388 and δ 2.368, each of three-proton intensity corresponding to the 9-acetyl and 7-thioacetyl groups, respectively. The 7*S* configuration of **8** was determined according to a previous method of assignment (20, 21, 24–27) based on the peak widths ($\nu_{1/2}$) for the benzylic proton (H-7). Compound **8** showed H-7 as a doublet at δ 5.447 having a coupling constant of 4.7 Hz, thus assigning the natural 7*S* configuration to **8** (see Table 1).

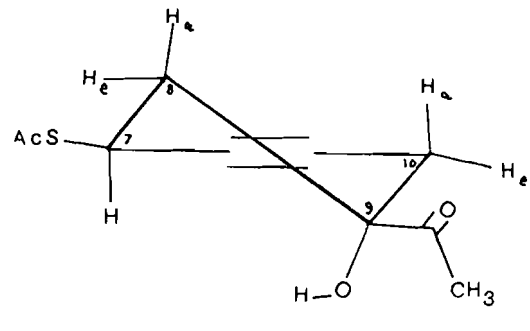
The nmr spectrum of compound **9** also showed the three-proton signals at δ 2.406 and 2.341, characteristic for the acetyl groups. The 7*R* configuration of **9** was determined from the benzylic proton (H-7) which was shown as a multiplet at δ 5.077 having $\nu_{1/2}$ 15.9 Hz, in agreement with an axial orientation of H-7. The stereochemistry at position 7 for compounds **8** and **9** can be ascertained on the basis of the chemical shifts in pyranoid rings (28–30); equatorial protons resonate at lower field than constitutionally similar axial protons. The benzylic proton H-7 for compound **8** was shown at relatively lower field



SCHEME 3

(δ 5.447) than that for compound **9** (δ 5.077). In addition, the protons associated with the methyl groups in axial acetoxy groups resonate at lower field than the corresponding protons in equatorial acetoxy groups (29). However, the appearance of the 7-thioacetyl signal at relatively lower field (δ 2.368) for compound **8** than that for compound **9** (δ 2.341) is in agreement with the axial orientation of the 7-thioacetyl group for compound **8** and the equatorial orientation for compound **9**.





Half-chair conformation of ring A for compounds **8** and **9**

The mass spectrum of compound **8** showed a weak molecular ion at *m/z* 456, and a base peak at *m/z* 43 corresponding to the CH_3CO group. The mass spectrum of compound **9** did not show a molecular ion; however, its C.I. mass spectrum showed the protonated molecular ion at *m/z* 457. It showed a fragmentation pattern identical to that of compound **8**.

Anthracyclines having an axial proton at C-7 have been

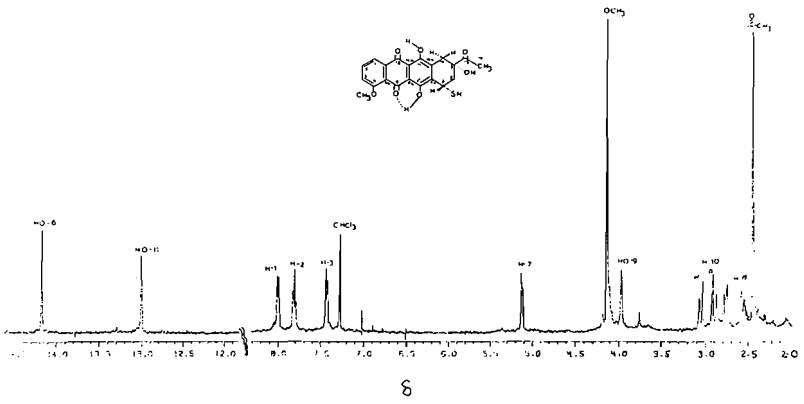
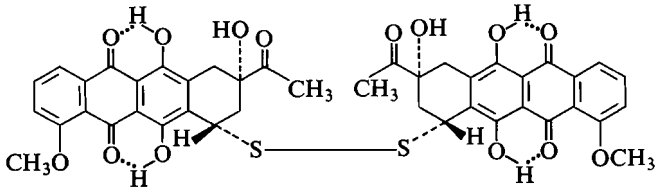


FIG. 2. The 470-MHz nmr spectrum of thiodaunomycinone **10**.

epimerized with acid (24). Treatment of compound **9** with TFAA afforded compound **8**.

Hydrolysis of compound **8** with sodium methoxide or potassium carbonate (Scheme 3) afforded a mixture of 7-deoxy-7-thiodaunomycinone **10**, **5**, and bisanhydrodaunomycinone **11** (31). The yield of **10** was low (37%) because of the concomitant formation of compound **5**, by ring-sulfur cleavage, and compound **11** by aromatization of ring A. Numerous repetitions and variation of the reaction conditions failed to give only one product. Compounds **5** and **10** were separated on preparative tlc and identified. Further purification of **11** by multiple development chromatography produced resolution into two components having very close R_f values, by partial dimerization of compound **10** into the dimer **12**.



12

The nmr spectrum of compound **10** (Fig. 2) showed a singlet of three-proton intensity at δ 2.355 corresponding to the 9-acetyl group, with the disappearance of the singlet corresponding to the thioacetyl group. The signal corresponding to the 9-hydroxyl group for compound **10** was shown as a singlet shifted to lower field (δ 3.897) than that for daunomycinone (δ 3.776). In addition, the peaks corresponding to the 8-CH_2 group were shifted to lower field than that for daunomycinone (Table 1). The benzylic proton for compound **10** was shown as a broad singlet at δ 5.057, shifted to higher field than that for compound **8** (δ 5.447) due to the removal of the acetyl group, and shifted to higher field than that for compound **4** (δ 5.306) because of the shielding effect of the sulfur compared to oxygen. The shielding of the benzylic proton of **10** compared to that of **8** and **4**, confirms the substitution at position 7.

The stereochemistry at the 7-position of anthracyclines is important for the expression of biological activity (32) and of DNA binding properties (33). The signal corresponding to H-7 for compound **10** showed $\nu_{1/2}$ ($J_{7,8a} + J_{7,8e}$) = 5 Hz, indicating (20, 21, 24–27) a quasiequatorial orientation for this proton. The new substituent at C-7 for compound **10** therefore has the same 7*S* configuration as the precursor acetate **8** and the natural daunomycinone, i.e., the quasiaxial configuration.

Compound **10** was further identified by mass spectroscopy. Its C.I. or E.I. mass spectrum did not show a molecular ion. The C.I. mass spectrum showed the highest mass peak at m/z 383 corresponding to the ion ($M + 1 - S$). The base peak was shown at m/z 363 corresponding to the ion ($M + 1 - H_2S - H_2O$). The E.I. mass spectrum showed the highest mass fragment at m/z 396 corresponding to the ion ($M - H_2O$), which was followed at the lower masses by the peaks at m/z 382 corresponding to ($M - S$), and m/z 362 corresponding to the ion ($M - H_2S - H_2O$). The base peak was shown at m/z 43 corresponding to the CH_3CO group. However, the field desorption mass spectrum of compound **10** showed the molecular ion peak (M) as the most intense peak at m/z 414, followed at the lower masses by the fragments at m/z 380 ($M - H_2S$), 362 ($M - H_2S - H_2O$), and 337 ($M - H_2S - CH_3CO$). Partial dimerization of **10** into **12** was shown by the peak at m/z 826 corresponding to $M_2 - 2H$ at the high mass spectrum region.

This synthetic route represents the method for replacement of the benzylic oxygen atom of daunomycinone by a sulfur atom. The synthetic availability of the 7-thioanalog **10** provides the versatile aglycon portion required for further elaboration of the sulfur-bridged anthracyclines **3**.

Experimental

Melting points are uncorrected, infrared spectra (ir) were recorded with a Perkin Elmer 467 grating spectrometer. The ^1H nmr spectra were recorded with a Nicolet 470-MHz instrument, using internal tetramethylsilane as the reference. Mass spectra were recorded with a Finnigan 6100 Data System gas chromatograph/E.I.–C.I. spectrometer. Combustion analyses were performed in the Department of Chemistry, Purdue University.

Thin-layer chromatograms (tlc) were obtained on 200 μm silica gel G plates. Preparative layer chromatograms (plc) were obtained on 20 × 20 × 0.2 silica gel 60 F plates (E. Merck) with solvent A, 9:1 benzene–acetone and solvent B, 97:2 methylene chloride – methanol.

Reduction of daunomycinone

(a) *With hydrogen over palladium–carbon 5%*

Daunomycinone (**4**, 200 mg) was dissolved in ethanol (300 mL), and shaken under hydrogen atmosphere with palladium–carbon 5% for 3 h. Thin-layer chromatography indicated the disappearance of the starting material and formation of two more mobile spots in the ratio of 1:1; R_f 0.36 and 0.29 (solvent A). The solution was filtered off and the catalyst washed with ethanol. The filtrate and washings were combined and evaporated to dryness, yield 160 mg (83%). The solution was green in color and turned pink upon exposure to the air. The two components were separated by plc (solvent A) and recrystallized

from benzene. The slower-migrating spot (orange), R_f 0.29, showed mp 234–235°C, identical to that of 7-deoxydaunomycinone **5** (lit. (17) mp 229–231°C); ir: 3480 (OH), 1720 (C=O), 1610, 1575 (H-bonded quinone) cm^{-1}; mass spectral data (E.I., selected ions): *m/z* 384 (1, *M* + 2), 383 (4, *M* + 1), 382 (16, *M*), 364 (7, *M* − H_2O), 340 (22), and 339 (100, *M* − CH_3CO). For nmr spectral data see Table 1.

The faster-migrating spot (pink), R_f 0.36, mp 190–192°C, (lit. (19) mp for 7,11-dideoxydaunomycinone **6**, 186–189°C); E.I. mass spectral data (selected ions): *m/z* 368 (1, *M* + 2), 367 (7, *M* + 1), 366 (28, *M*), 348 (23, *M* − H_2O), 339 (3), 324 (21), and 323 (100, *M* − CH_3CO). For nmr spectral data see Table 1. *Anal.* calcd. for $C_{21}H_{18}O_6$: C 68.85, H 4.95; found: C 68.66, H 5.16.

(b) *Reduction with hydrogen over palladium – barium sulfate*

Compound **4** (50 mg) was dissolved in ethanol (200 mL), treated with a catalytic amount of palladium – barium sulfate (20 mg), and shaken under hydrogen atmosphere for 2 h, and treated as above. Thin-layer chromatography indicated the disappearance of the starting material and formation of two more mobile spots at the same R_f as those of **5** and **6** (solvents A and B).

(c) *Reduction with sodium dithionite*

Compound **4** (100 mg) was dissolved in THF (50 mL), the solution was blanketed with nitrogen, and treated with dropwise addition of sodium dithionite (200 mg) in water (25 mL). After complete addition (15 min), the solution was stirred at room temperature for a further 2 h, evaporated to dryness, the residue extracted with chloroform, and the extract washed with water, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness, yield 75 mg. It was recrystallized from benzene to give chromatographically (tlc) pure red needles, mp and mixture mp (with **5**) 232–233°C, having the same R_f values on tlc (solvents A and B).

7-Thioacetyldaunomycinone (8)

A solution of compound **5** (50 mg) in CCl_4 was refluxed under N_2 for 1 h. Br_2 (3 mL of 0.125 *M* solution in CCl_4) and ABN (4 mg) were added and refluxed for 2 h. The solvent was removed and the residue was dissolved in THAA (10 mL), then CH_3COSK (100 mg) was added and the mixture stirred under N_2 for 17 h. The mixture was evaporated to dryness, the residue extracted with $CHCl_3$, and the organic layer was then washed with water, dried over anhydrous sodium sulfate, and evaporated. The residue was recrystallized from benzene–hexane giving a red amorphous precipitate. Thin-layer chromatography (solvent B) showed two spots, R_f 0.31 and 0.21. Fractional recrystallization of the mixture from benzene gave compound **8** as orange-red needles, yield 18 mg, mp 230–232°C; R_f 0.31, solvent A; ir: 3420 (OH), 1705 (C=O), 1690 (SAc), 1610 and 1580 (chelated quinone) cm^{-1}; mass spectral data (C.I.): *m/z* 459 (7, *M* + 3), 458 (16, *M* + 2), 457 (83, *M* + 1), 425 (9), 383 (41), 363 (52), 321 (22), and 77 (100); (E.I.): *m/z* 456 (1, *M*), 438 (1, *M* − H_2O), 413 (1, *M* − CH_3CO), 382 (1, *M* − CH_3COSH), 362 (*M* − CH_3COSH − H_2O), 338 (1), 77 (2, Ph), 76 (2, CH_3COSH), 75 (1, CH_3COS), and 43 (100, CH_3CO); for nmr spectral data see Table 1. *Anal.* calcd. for $C_{23}H_{20}O_8S$: C 60.39, H 4.63, S 7.01; found: C 60.45, H 4.81, S 6.81.

7-Epithioacetyldaunomycinone (9)

The mother liquor of **8** showed two spots on tlc which were separated by plc (solvent A) and the slow migrating spot, R_f 0.21, was recrystallized from methanol giving red needles, mp 207–209°C; ir: 3440 (OH), 1705 (C=O), 1690 (SAc), 1610 and 1580 (chelated quinone) cm^{-1}; mass spectral data (C.I.): *m/z* 457 (1, *M* + 1), 385 (3), 383 (39), 363 (17), 91 (29), 85 (42), and 76 (100); (E.I.): *m/z* 362 (10, *M* − CH_3COSH − H_2O), 339 (9, *M* − CH_3COSH − CH_3CO), 337 (13), and 43 (100, CH_3CO). For nmr spectral data see Table 1. *Anal.* calcd. for $C_{23}H_{20}O_8S$: C 60.39, H 4.63, S 7.01; found: C 60.14, H 4.84, S 6.94.

Conversion of daunomycinone into 7-thioacetyldaunomycinone

Method "A", by treatment of 4 with a mixture of THAA and TFAA

Compound **4** (50 mg) was treated with THAA (5 mL) and TFAA (2 mL) and kept at room temperature for 6 h. Thin-layer chromatography indicated the disappearance of the starting material and formation of three spots; the slow migrating one was shown at the same R_f value as for compound **8**. It was isolated by plc and recrystallized from benzene, yield 6.5 mg, mp and mixture mp 232–234°C. Its nmr spectrum was identical to that of **8**. No spot corresponding to compound **9** was detected by tlc.

Method "B", by refluxing compound 4 with THAA and GAA

Compound **4** (100 mg) was treated with THAA (10 mL) and GAA (4 mL) and the mixture refluxed for 21 h. Monitoring of the reaction by tlc indicated disappearance of the starting material and formation of two more mobile spots at the R_f values for compounds **8** and **9**. The reaction was complete after 21 h. The mixture was evaporated to dryness and traces of acids were removed by repeated evaporation with CH_2Cl_2. The dry residue was recrystallized from benzene giving orange red needles of compound **8**, mp and mixture mp 228–230°C. The mother liquor, containing **8** and **9**, was separated with plc (solvent B); yield of **8**, 80 mg, and **9**, 15 mg; total yield 83% from **4**.

Epimerization of compound 9 into 8

Compound **9** (5 mg) was treated with TFAA (1 mL) and kept for 20 h at 20°C. The acid was removed by repeated evaporation with CH_2Cl_2. Thin-layer chromatography indicated complete conversion of **9** into **8**. Similar treatment of **8** with TFAA did not give **9** by epimerization under the same conditions.

Hydrolysis of 7-thioacetyldaunomycinone

Method "i", with 0.01 N *sodium methoxide solution*

A solution of **8** (30 mg) in THF (4 mL) was blanketed with argon and a solution of 0.01 *N* sodium methoxide (2 mL) was added with stirring; the blue-colored solution obtained was stirred at 20°C for 5 h. It was neutralized with glacial acetic acid which turned the solution red. Thin-layer chromatography (solvent B) showed the formation of three spots which were isolated by plc and identified. The slow migrating spot, R_f 0.47 (solvent B), was isolated, dissolved in benzene, and precipitated by hexane as an amorphous powder of thiodaunomycinone **10**; yield 10 mg, mp 195–198°C. Further purification on analytical tlc plates (solvent B) showed splitting into two non-resolvable spots, having close R_f values, probably by air oxidation and formation of the dimer **12**; ir: 3430 (OH), 1705 (C=O), and 1615 and 1580 (hydrogen bonded quinone) cm^{-1}. Mass spectral data (C.I.): *m/z* 383 (9, *M* + 1 − S), 363 (100, *M* + 1 − H_2S − H_2O); (E.I., selected ions): *m/z* 396 (1, *M* − H_2O), 382 (3, *M* − S), 362 (*M* − H_2S − H_2O), 344 (17), 339 (16), 337 (9, *M* − H_2S − CH_3CO), and 43 (100, CH_3CO). Field desorption mass spectrum (F.D.): 826 (31, M_2 − 2H), 414 (91, *M*), 380 (77, *M* − H_2S), 362 (18, *M* − H_2S − H_2O), 337 (18, *M* − H_2S − $COCH_3$). For nmr spectral data see Table 1. *Anal.* calcd. for $C_{21}H_{18}O_7S$: C 60.86, H 4.38, S 7.74; found: C 60.64, H 4.62, S 7.45.

The second hydrolysis product (orange color), R_f 0.59 (solvent B) was isolated by plc and recrystallized from benzene, mp and mixture mp (with **5**) 233–235°C (lit. (20) mp 230–232°C). The faster moving spot (violet color), R_f 0.67 (solvent B), was isolated by plc and recrystallized from benzene–methanol as brown-violet needles, yield 5 mg; mp 229–232°C (lit. (31) mp for bisanhydrodaunomycinone, 225–230°C); mass spectral data (C.I.): *m/z* 363 (100, *M* + 1), 361 (36, *M* + 1); (E.I., selected ions): *m/z* 364 (9, *M* + 2), 363 (40, *M* + 1), 361 (96, *M* + 1), 345 (52), 343 (38), 319 (5, *M* − CH_3CO), and 43 (100, CH_3CO).

Method "ii". Hydrolysis of 8 with saturated solution of potassium carbonate

A solution of compound **8** (30 mg) in THF (5 mL) was blanketed with argon, then a solution of saturated potassium carbonate (0.2 mL) was added with stirring. The solution, which turned blue, was stirred at 20°C for 2 h, then acidified with 5% oxalic acid solution which converted it into a red color; the mixture was then partitioned between water and chloroform, and the organic layer washed with water and dried. The chloroform was removed and tlc (solvent B) of the residue showed three spots at the same R_f values, for compounds **5**, **10**, and **11**, that were obtained by method i.

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